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Original Research

ANTi-Vax: a novel Twitter dataset for COVID-19 vaccine misinformation detection

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ABSTRACT

Objectives: COVID-19 (SARS-CoV-2) pandemic has infected hundreds of millions and inflicted millions of deaths around the globe. Fortunately, the introduction of COVID-19 vaccines provided a glimmer of hope and a pathway to recovery. However, owing to misinformation being spread on social media and other platforms, there has been a rise in vaccine hesitancy which can lead to a negative impact on vaccine uptake in the population. The goal of this research is to introduce a novel machine learning–based COVID-19 vaccine misinformation detection framework.
Study design: We collected and annotated COVID-19 vaccine tweets and trained machine learning algorithms to classify vaccine misinformation.
Methods: More than 15,000 tweets were annotated as misinformation or general vaccine tweets using reliable sources and validated by medical experts. The classification models explored were XGBoost, LSTM, and BERT transformer model.
Results: The best classification performance was obtained using BERT, resulting in 0.98 F1-score on the test set. The precision and recall scores were 0.97 and 0.98, respectively.
Conclusion: Machine learning–based models are effective in detecting misinformation regarding COVID-19 vaccines on social media platforms.

Introduction

As of July 26, 2021, more than 194 million infections and more than 4 million deaths are attributed to the SARS-CoV-2, commonly referred to as the COVID-19 pandemic.[1] Since the outbreak emerged in Wuhan, Hubei province in China and spread worldwide, lockdown measures and social distancing methods were introduced in most parts of the globe. The impacts were significant on various sectors including the economy,[2] education,[3] and the mental health of the population.[4] The emergence of various safe and effective vaccines[5] provided a potential solution by increasing population immunity and rising as an effective method to control the outbreak. Most vaccines authorization and distribution began during December 2020.[6]

Despite the vaccine introduction, increasing hesitancy on vaccine uptake can be observed among significant parts of the population in various countries.[7] The vaccine hesitancy can be explained in part by the spread of misinformation regarding vaccines that are spread in person.[8] However, with wide social media access and usage, the spread of vaccine misinformation can be significantly increased, potentially leading to a further decline in vaccine uptake. Misinformation can be spread on social media by human users as well as social bots.[9,10] Social bots are programmed to automatically spread false information in disguise. Therefore, it is essential for algorithms to automatically detect the content of the misinformation regardless of the source being a human or a social bot. More specifically, the focus of this research is on Twitter and detecting misinformation in tweets related to vaccines. To the best of our knowledge, there are no existing datasets for detecting vaccine misinformation tweets and this is the first proposed approach on detecting COVID-19 vaccine misinformation.

Machine learning–based algorithms have been widely and effectively utilized for various COVID-19–related applications including screening, contact tracing, and forecasting.[11] CoAID dataset introduced by Cui and Lee[12] contains misinformation related to COVID-19. The authors utilized several machine learning models to

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classify fake news with the best performance of 0.58 F1-score being obtained using a hierarchical attention network–based model. A COVID-19 vaccine misinformation tweets dataset was introduced by Memon and Carley.[13] This dataset characterizes both users who are actively posting misinformation and those who are calling out misinformation or spreading true information. It was concluded that informed users tend to use more narratives in their tweets than misinformed ones. The ReCOVery dataset proposed by Zhou et al.[14] contains more than 2000 news articles and their credibility. Furthermore, it also includes more than 140,000 tweets that reveal the way these news articles are spread on Twitter. A F1-score of 0.83 was obtained for predicting reliable news and 0.67 was obtained for predicting unreliable news using a neural network model. A billion-scale COVID-19 Twitter dataset covering 268 countries with more than 100 languages was collected by Abdul-Mageed et al.[15] Two predictive models were proposed for classifying whether a tweet was related to the pandemic (COVID relevance) and detecting whether a tweet was COVID-19 misinformation. The misinformation detection models were trained using the aforementioned CoAID and ReCOVery datasets, and combining them resulted in the best F1-score of 0.92 using a bidirectional encoder representations from transformers (BERT)-based model. Abdelminaam et al.[16] combined four existing datasets including CoAID and used several machine learning algorithms to classify COVID-19 misinformation. The best F1-score of 0.985 was obtained using a two-layer long short-term memory (LSTM) network. The ArCOV19-Rumors dataset was presented by Haouari et al.[17] to detect COVID-19 misinformation in Arabic tweets. Two Arabic BERT-based models were used for classification, obtaining a highest F1-score of 0.74. A bilingual Arabic and English dataset for detecting COVID-19 misleading tweets was presented in the study by Elhadad et al.[18] Several machine learning models were used to annotate the unlabeled tweets. However, the authors did not quantify the evaluation of the predictive models. Finally, a Chinese microblogging dataset for detecting COVID-19 fake news was presented by Yang et al.[19] Various deep learning models were explored, and the best F1-score of 0.94 was obtained using the TextCNN model.

More recently, several research works have focused on analyzing tweets related to COVID-19 vaccines. Muric et al.[20] presented a dataset containing tweets that indicate a strong anti-vaccine stance. Descriptive analysis of the tweets as well as geographical distribution of the tweets across the United States (US) were presented. Similarly, Sharma et al.[21] utilized tweets to investigate any hidden coordinated efforts promoting misinformation about vaccines and obtain insights into conspiracy communities. A dataset called Covaxxy[22] containing one week of vaccine tweets was introduced to perform a statistical analysis of COVID-19 vaccine tweets. Moreover, the authors also introduced a dashboard for visualizing the relationship between vaccine adoption and US geolocated posts. Malagoli et al.[23] focused on vaccine sentiment on Twitter by analyzing vaccine-related tweets collected between December 2020 and January 2021. The analysis included the usage of emojis as well as the psycholinguistic properties of these tweets. Finally, Hu et al.[24] examined the public sentiment of COVID-19 vaccines in the US by investigating the spatiotemporal patterns of public perception and emotion at national and state levels. No predictive models were introduced by the existing works in the context of the COVID-19 vaccine, and therefore, the proposed work to the best of our knowledge is the first to perform vaccine misinformation detection. Table 1 summarizes the existing works in COVID-19 misinformation detection and COVID-19 vaccine–related tweet datasets.

Methods

This section describes the methodology of the proposed application. The details of the implementation are presented next chronologically.

Table 1
Existing works in COVID-19 misinformation and COVID-19 vaccine tweets.

Source	Application	Dataset	Available online	Prediction results
12	Misinformation dataset, analysis, and classification	Social media and website misinformation regarding COVID-19	✓	F1-score: 0.58 using hierarchical attention network–based model
13	Misinformation dataset and analysis	Annotated COVID-19 misinformation tweets	✓	N/A
14	Reliable and unreliable news dataset, analysis, and prediction	News articles and their credibility level as well as tweets related to their spread	✓	F1-scores: 0.83 and 0.67 for reliable and unreliable news detection, respectively, using neural networks
15	Large COVID-19 tweets dataset, analysis, and classification	Tweets related to COVID-19 in more than 100 languages from 268 countries	✓	F1-score: 0.98 for COVID-relevant tweets using the transformer-based masked language model F1-score: 0.92 for detecting misinformation tweets using BERT-based model
16	COVID-19 misinformation detection	Combination of various existing tweets datasets related to COVID-19, disasters, news, and gossip	×	F1-score: 0.985 using LSTM
17	COVID-19 misinformation detection in Arabic	Arabic tweets related to COVID-19	✓	F1-score: 0.74 using MARABERT
18	COVID-19 misinformation detection in English and Arabic	English and Arabic tweets related to COVID-19	✓	Not presented
19	COVID-19 fake news detection in Chinese	Chinese microblog posts from Weibo	✓	F1-score: 0.94 using TextCNN
20	COVID-19 anti-vaccine tweets dataset and analysis	Tweets exhibiting anti-vaccine stance collected using keywords	✓	N/A
21	COVID-19 anti-vaccine tweets analysis	COVID-19 vaccine tweets collected using keywords	×	N/A
22	COVID-19 vaccine tweets analysis	COVID-19 vaccine tweets collected using keywords	✓	N/A
23	COVID-19 vaccine tweets sentiment analysis	COVID-19 vaccine tweets collected using keywords	✓	N/A
24	COVID-19 vaccine tweets sentiment analysis	COVID-19 vaccine tweets collected using keywords	×	N/A

Dataset collection

Twitter is one of the most popular social media platforms with 353 million active users, and more than 500 million tweets are being posted every day.[25] Twitter API allows the extraction of public tweets including the tweet text, user information, retweets, and mentions in JSON format. A Python library called *Twarc* was utilized to access the Twitter API.

To obtain the relevant tweets about COVID-19 vaccines, we followed the approach in some of the existing works in the literature and collected the tweets using keywords. The following keywords (case insensitive) were used: 'vaccine,' 'pfizer,' 'moderna,' 'astrazeneca,' 'sputnik,' and 'sinopharm.' Additionally, we only considered tweets in the English language. Replies to tweets, retweets, and quote tweets were not considered. Overall, the vaccine-related tweets from December 1, 2020, until July 31, 2021, were collected. In total, 15,465,687 tweets were collected.

Fig. 1 illustrates the total number of tweets per month from December 2020 until July 2021. As vaccines started gaining approval for administration during December 2020, we notice a high volume of tweets with people sharing their initial sentiments regarding the vaccine. In the next couple of months, there is a natural decline as the topic becomes outdated. However, the volume of tweets goes up again from March 2021 and reaches a peak during April 2021. During this time, the rate of vaccination was going up particularly in the UK and the US where a large percentage of Twitter users are from. This led to many expressing their feelings after receiving their vaccines.

Data annotation

In supervised learning, a labeled dataset is required before model training. Because no existing labeled dataset is available for vaccine misinformation, manual annotation of tweets was performed. Unlike the single verification approach by many existing works, we used an additional validation step by medical experts. To label the misinformation, some common myths regarding the COVID-19 vaccines were obtained from reliable sources including *Public Health*,[26] Healthline,[27] the Centers for Disease Control and Prevention (CDC),[28] and the University of Missouri Health Care.[29] This approach is similar to several of the existing works in misinformation detection including the studies by Cui and Lee[12] and Elhadad et al.[18] Some of the common myths and misinformation include 'The vaccine can alter DNA,' 'The vaccine can cause infertility,' 'The vaccine contains dangerous toxins,' and 'The vaccine contains tracking device.' In this process, tweets containing this common misinformation were manually read and labeled/flagged. This ensured the context of the tweets was considered and tweets that were sarcastic and humorous were not included as misinformation. Tweets other than these common myths were considered not misinformation and included general opinions regarding the vaccine, official news, and appointment details of vaccination centers. Finally, once the dataset was accurately annotated using verified sources, we invited medical experts in public health to validate the annotation process. This approach helped in ensuring the manual annotation of data was accurate and the quality of the dataset was of high standard.

Consequently, a total of 15,073 tweets were labeled, 5751 of which were misinformation and 9322 were general vaccine-related tweets. Word clouds are a simple but effective tool for text visualization. They are created by collecting words in a corpus and presenting them in different sizes. The larger and bolder a word appears, the more frequent and relevant is its presence in the corpus. Figs. 2 and 3 illustrate the world cloud for misinformation and general tweets, respectively. The vaccine misinformation tweets include several conspiracy terms such as 'gene therapy,' 'untested vaccine,' and 'depopulation.' Meanwhile, the general vaccine tweets include terms related to people sharing their vaccine experience including 'first dose' and 'grateful.'

Data preprocessing

Preprocessing the contents of the tweets is significant for efficient model training. First, external links, punctuations, and text in brackets were removed. All text contents were also converted to lower case. Common words such as 'the,' 'and,' 'in,' and 'for,' are referred to as stop words. Removing these low-information words that provide little contextual information can reduce the complexity of training. To perform this step, *NLTK*[30] library in Python was utilized. Stemming is a common preprocessing step that reduces derivationally linked forms of a word to a common base form. For example, both 'walking' and 'walked' will be converted to the stem 'walk.' In this step, snowball[31] stemmer from the *NLTK* library was used.

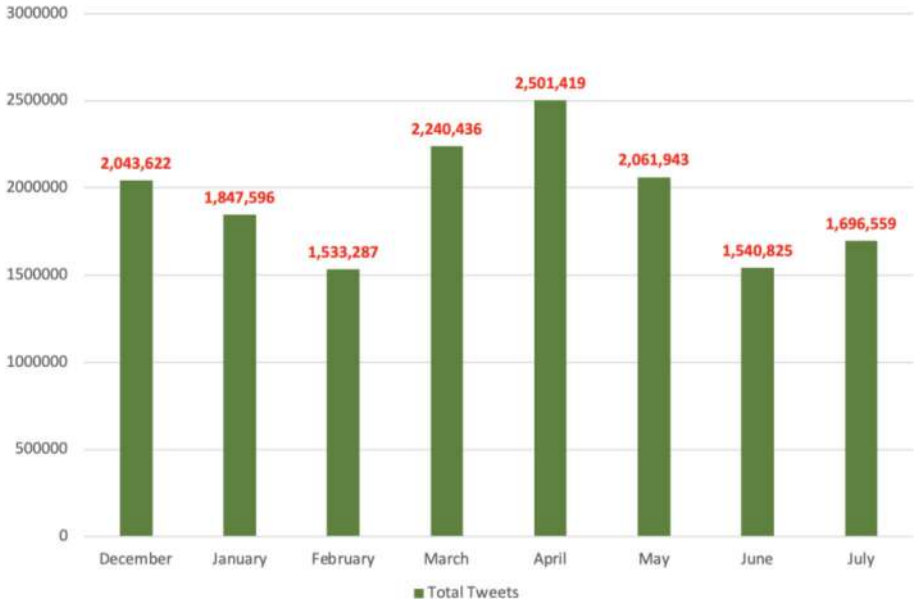

Fig. 1. Number of vaccine tweets by month.

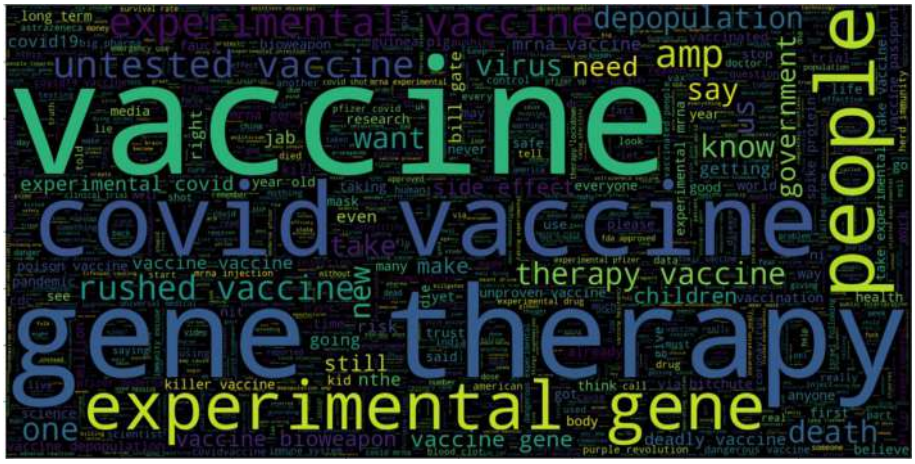

Fig. 2. Word cloud visualization for vaccine misinformation tweets.

Models architecture and implementation

Machine learning enables computer systems to learn from experience using data, without requiring explicit programming. Feature extraction is required to identify relevant features in the dataset before training the models. However, this process is labor-intensive and predictive performance depends to a large extent on the quality of feature engineering. Deep learning[32] models on the other hand can automatically learn the necessary and useful input features and optimize them. Nevertheless, the computational complexity is higher, and consequently, a much longer training time is required. To provide a more comparative evaluation, three models were explored belonging to different categories of machine learning models. From the traditional machine learning, XGBoost was utilized; from the deep learning models, LSTM was utilized; and from the transformer models, BERT was utilized. A description of the models and their implementation are presented next.

XGBoost[33] is considered one of the most competitive and frequently used traditional machine learning models. It is a type of ensemble learning model that uses multiple decision trees which reduces overfitting and maintains complexity at the same time. Term frequency-inverse document frequency (tf-idf) was used to identify the most relevant features. Tf-idf computes values for each word in the corpus by the inverse proportion of the frequency of the word in a specific document to the percentage of documents the word appears in the study by Ramos et al.[34] *XGBoost* library in Python was used for this implementation.

LSTM[35] is a popular deep learning architecture for text and sequential data. These networks are composed of cyclic connections as well as specialized memory cells for storing the temporal state of the network.[36] Glove,[37] a popular unsupervised approach for obtaining vector representations of words, was used with the LSTM network. The obtained word embeddings using Glove represent the semantic similarity between words in a corpus by transforming the words into an n-dimensional space. After the embedding layer, a Bidirectional LSTM layer with 45 units was used followed by a GlobalMaxPool1D. Next, two dense layers of 128 and 32 units, respectively, with ReLU activation[38] were used. A dropout layer[39] with 0.5 rate was used after all the previous three layers. Finally, the classification layer consisted of a sigmoid activation, and the model was optimized using Adam optimizer[40] on binary cross-entropy loss. The implementation was done in Python using *Keras*.

The last approach utilized the transformer-based BERT model. The unconventional training approach used in BERT by looking at a text sequence from both directions provides a comprehensive sense of language context. BERT is pretrained on a large corpus of English texts from Wikipedia and BookCorpus. In this work, the *bert-large-uncased* version was used. It consists of 24 layers (1024 hidden dimensions), 16 attention heads, and a total of 340M parameters.[41] *Transformers*[42] library in Python was used to implement this approach.

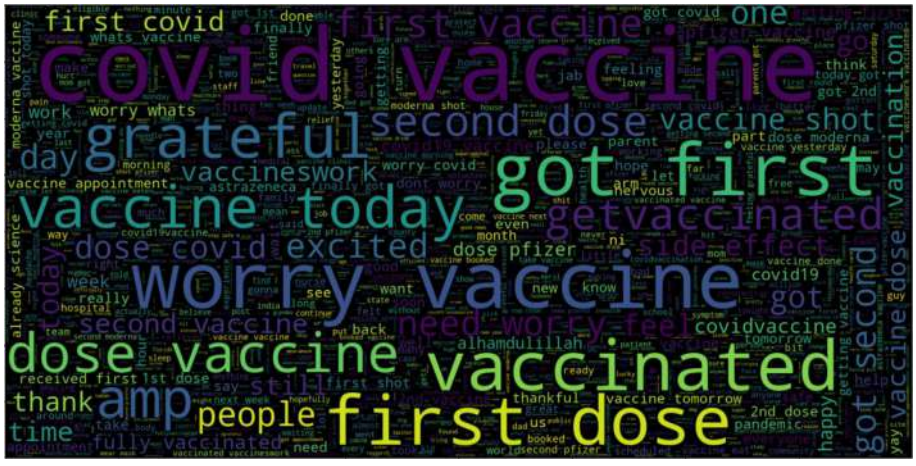

Fig. 3. Word cloud visualization for general vaccine-related tweets.

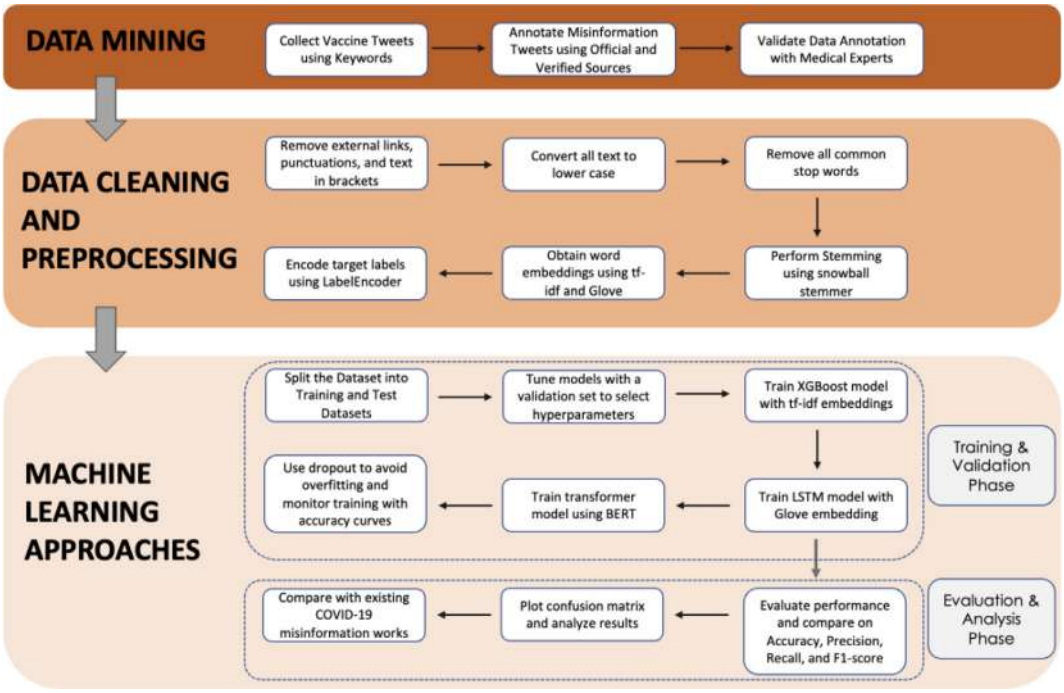

Fig. 4. Research framework. tf-idf, term frequency-inverse document frequency.

Overfitting is considered a major obstacle in training machine learning algorithms. When a specific model performs outstandingly well during the training phase, by using unnecessary input features, but fails to make generalized predictions on the test set, it is 'overfitting' to the training dataset. To avoid the overfitting problem for the two deep learning models, dropout technique was used. Also, training and validation accuracy curves were monitored to ensure no overfitting occurred during training.

The research framework for COVID-19 vaccine misinformation classification is summarized in Fig. 4. The COVID-19 vaccine–related tweets were first collected and then annotated for misinformation or regular tweets using reliable sources. After necessary preprocessing and feature extraction, machine learning and deep learning models were trained to classify vaccine misinformation. Finally, the performance of the models was evaluated on the test set.

Classification algorithms can be evaluated using several metrics including accuracy, precision, recall, and F1-score, as defined in the following equations.(1–4) [43]

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \quad (1)$$

$$Precision = \frac{TP}{TP + FP} \quad (2)$$

$$Recall(TPR) = \frac{TP}{FN + TP} \quad (3)$$

$$F1\ Score = \frac{2 * Precision * TPR}{Precision + TPR} \quad (4)$$

Results

The results from the XGBoost model as well as the two deep learning models are presented next. All models were first trained and validated on 75% of the dataset and then evaluated on the remaining 25% of the dataset.

Performance comparison

The training time for XGBoost as expected was much quicker than the other two deep learning models. The training accuracy obtained was 96.9%, and the accuracy on the test set was 95.6%. The precision, recall, and F1-score on the test were 0.96, 0.95, and 0.95, respectively. Fig. 5 presents the confusion matrix on the test set

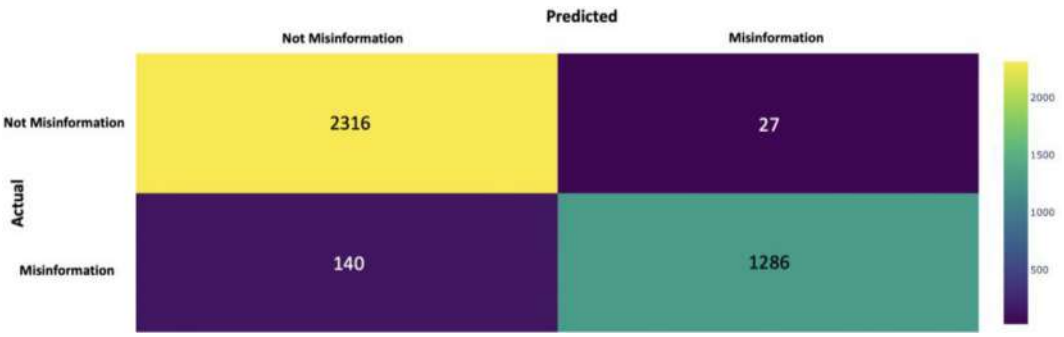

Fig. 5. Confusion matrix on the test set using XGBoost.

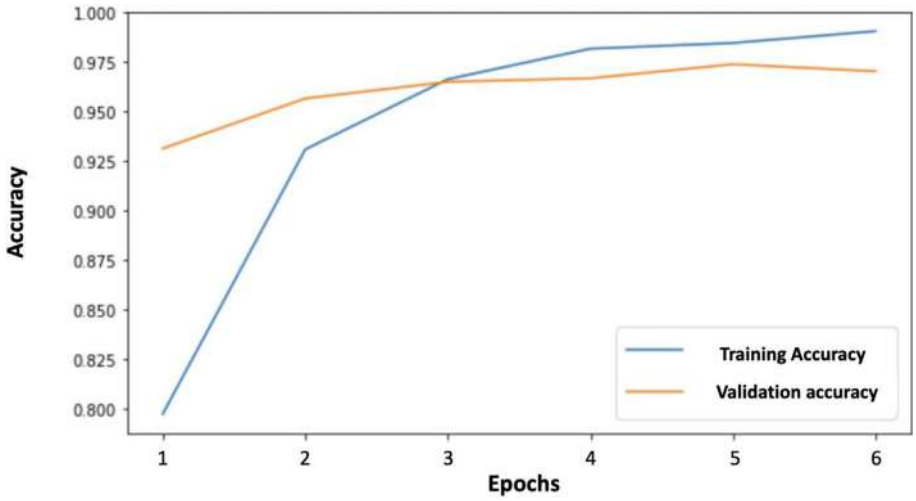

Fig. 6. Training and validation accuracies using LSTM.

using XGBoost. The majority of the error (84%) resulted from misinformation being classified as otherwise, whereas very few of the non-misinformation tweets were wrongly classified.

The LSTM model was trained for six iterations with 20% of the data from the training set used for validation. Fig. 6 displays the training and validation accuracy curves. Because both the curves are very close to each other, there is no indication of overfitting.

The maximum training accuracy using LSTM was 99%, and the accuracy on the test set was 96%. The precision, recall, and F1-score on the test were 0.97, 0.96, and 0.96, respectively. Overall, there was a slight improvement compared with XGBoost. The confusion matrix on the test set using this approach is presented in Fig. 7. Compared with XGBoost, there was a decrease in misinformation being misclassified (68%). However, more non-misinformation tweets were being classified as misinformation.

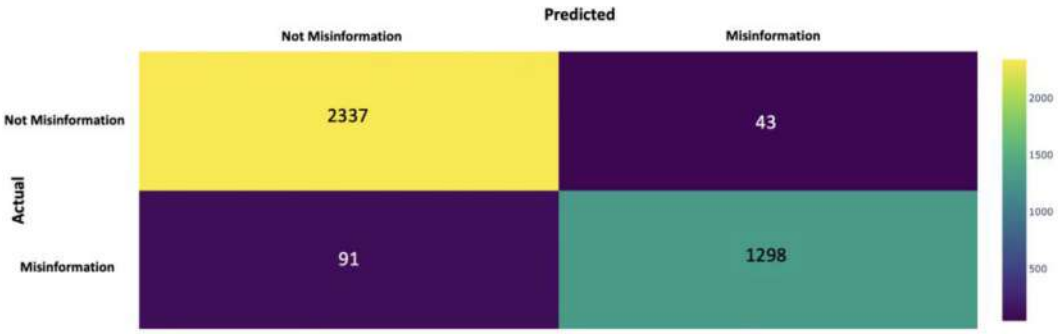

Fig. 7. Confusion matrix on the test set using LSTM.

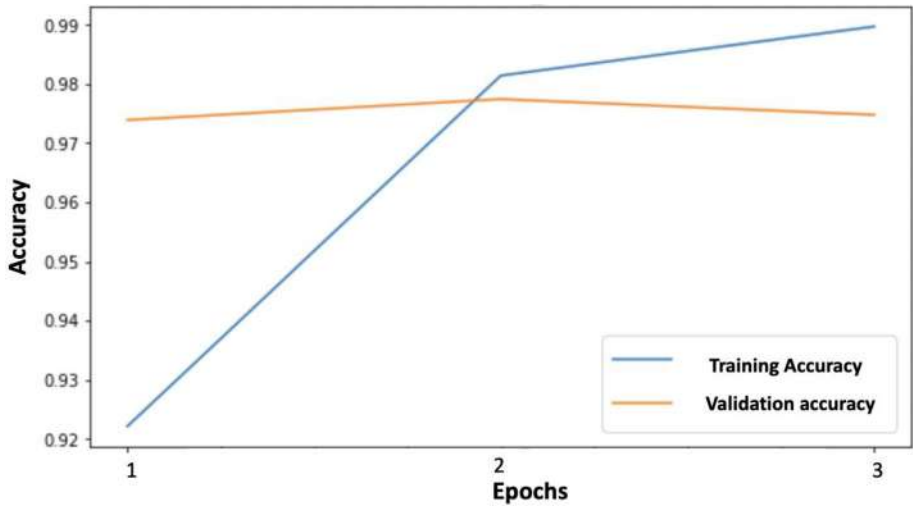

Fig. 8. Training and validation accuracies using BERT.

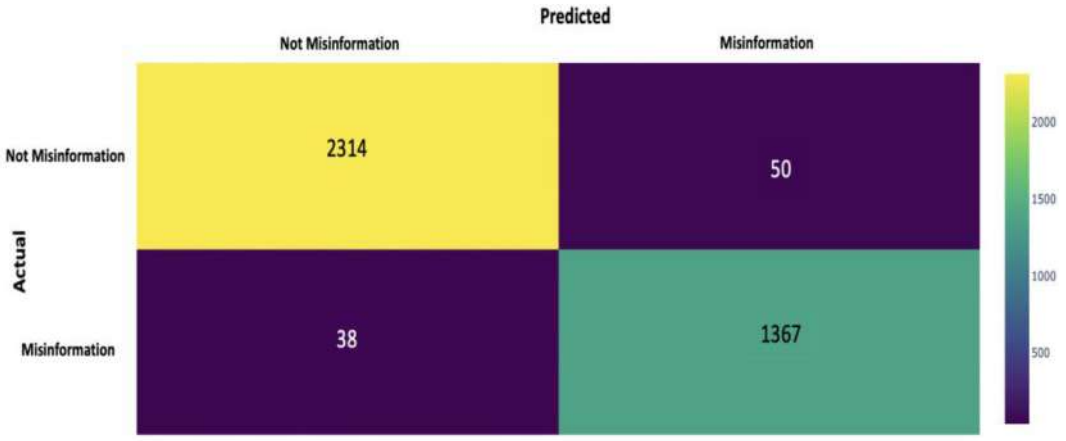

Fig. 9. Confusion matrix on the test set using BERT.

Finally, we used the pretrained BERT transformer model for classification. It was trained for three iterations with a 20% validation set taken from a subset of the training set. The training and validation accuracy curve is plotted in Fig. 8. No overfitting is apparent in this approach as well.

The maximum training accuracy using BERT was 99%, and the accuracy on the test set was 98%. The precision, recall, and F1-score on the test were 0.97, 0.98, and 0.98, respectively. The performance using BERT was superior compared with the previous two models. Fig. 9 displays the confusion matrix on the test set using BERT. Compared with the previous two models, BERT provides the lowest error rate (43%) on misclassifying the misinformation tweets, but it has a higher error rate in misclassifying the non-misinformation tweets.

Discussion

In the previous section, the effectiveness of all the models in vaccine misinformation detection was discussed. Consistent with the literature, superior performance was obtained using the deep learning models compared with XGBoost for a relatively larger training set. BERT is recommended for this application because it was able to predict most of the misinformation.

Table 2 presents a performance comparison between the existing works in COVID-19 misinformation classification and the proposed work. The results reported in this study are consistent with those reported in the previous literature. The focus of this work was specifically on classifying vaccine-related misinformation, unlike the existing works which focused on general COVID-19 misinformation. However, by making the dataset used in the proposed work publicly available, we encourage the research community to experiment with other models and approaches.

There are several implications of the proposed application that are not limited to the following: 1) the dataset and models presented in this work can be used by social media sites effectively to limit the spread of misinformation, 2) it would also facilitate the detection of social bots spreading vaccine misinformation, 3) the dataset can also be thoroughly analyzed to identify patterns of misinformation and their spread over the time, and 4) this study will raise awareness regarding the misinformation about vaccines in social media and also will trigger further research in this area. A limitation of this study is that statistical analysis was not presented. As the focus of this study was on detecting misinformation, an in-depth analysis of the vaccine misinformation tweets was not performed.

Table 2
Performance comparison with related COVID-19 misinformation detection works.

Source	Classification	F1-score
12	COVID-19 misinformation	0.58
14	COVID-19 news reliability detection	0.83 and 0.67
15	COVID-19 misinformation	0.92
16	COVID-19 misinformation	0.985
17	Arabic COVID-19 misinformation	0.74
19	Chinese COVID-19 misinformation	0.94
ANTi-Vax (Ours)	**COVID-19 vaccine misinformation**	**0.98**

As future work, it would be interesting to experiment the combination of general COVID-19 misinformation with vaccine misinformation. Moreover, a further performance enhancement is possible by using extracted tweet–level features including the number of capital letters, links, and emojis. Similarly, account-level features such as follower count, tweet count, retweets can potentially provide useful information to the models. Furthermore, sentiment analysis in the English language on COVID-19 vaccines can be performed using the large COVID-19 vaccine dataset. This would reveal the public perception of vaccines and how they evolved over the months. Also, the focus of this study was on English tweets, but researchers are encouraged to extend this study to multilingual tweets related to COVID-19 vaccines. The use of hashtags can provide insights into the general behavior of social media users,[44] and this could be utilized for future research. Finally, it is also worth investigating vaccine-related misinformation on social media platforms other than Twitter as well as blog posts.

Author statements

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Ethical approval

None sought.

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Competing interests

None declared.

Availability of data and materials

Both the COVID-19 vaccine tweets dataset and the annotated misinformation dataset are available publicly for researchers. Complying with Twitter's Terms of service, the dataset has been anonymized and contains only the tweet IDs. The dataset can be accessed using the following link: https://github.com/Sakib Shahriar95/ANTiVax.

References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020;**20**(5):533–4.
2. McKibbin W, Fernando R. The global macroeconomic impacts of COVID-19: seven scenarios. *Asian Econ Pap* 2021 May 15;**20**(2):1–30.
3. Aristovnik A, Keržič D, Ravšelj D, Tomaževič N, Umek L. Impacts of the COVID-19 pandemic on life of higher education students: a global perspective. *Sustainability* 2020;**12**(20).
4. Usher K, Durkin J, Bhullar N. The COVID-19 pandemic and mental health impacts. *Int J Ment Health Nurs* 2020 Jun;**29**(3):315–8. 2020/04/10.
5. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med* 2020 Dec 31;**383**(27):2603–15.
6. Roberts M. *Covid-19: pfizer/BioNTech vaccine judged safe for use in UK* [Internet]. BBC News; 2020 Dec 2 [cited 2021 Jul 26]; Available from: https://www.bbc.com/news/health-55145696.
7. Sallam M. COVID-19 vaccine hesitancy worldwide: a concise systematic review of vaccine acceptance rates. *Vaccines* 2021;**9**(2).
8. Lockyer B, Islam S, Rahman A, Dickerson J, Pickett K, Sheldon T, et al. *Understanding COVID-19 misinformation and vaccine hesitancy in context: findings from a qualitative study involving citizens in Bradford* [Internet]. UK: Health Expect; 2021 May 4. https://doi.org/10.1111/hex.13240 [cited 2021 Jul 25];n/a(n/a). Available from:.
9. Wang P, Angarita R, Renna I. Is this the era of misinformation yet: combining social bots and fake news to deceive the masses. In: *Companion proceedings of the the web conference 2018 [Internet]. Republic and canton of Geneva, CHE*. International World Wide Web Conferences Steering Committee; 2018. p. 1557–61. https://doi.org/10.1145/3184558.3191610 (WWW '18). Available from:.
10. Trabelsi Z, Hayawi K, Al Braiki A, Mathew SS. *Network attacks and defenses: a hands-on approach*. CRC Press; 2012.
11. Lalmuanawma S, Hussain J, Chhakchhuak L. Applications of machine learning and artificial intelligence for Covid-19 (SARS-CoV-2) pandemic: a review. *Chaos, Solit Fractals* 2020;**139**:110059.
12. Cui L, Lee D. *Coaid: covid-19 healthcare misinformation dataset*. ArXiv Prepr; 2020. ArXiv200600885.
13. Memon SA, Carley KM. *Characterizing covid-19 misinformation communities using a novel twitter dataset*. ArXiv Prepr; 2020. ArXiv200800791.
14. Zhou X, Mulay A, Ferrara E, Zafarani R. ReCOVery: a multimodal repository for COVID-19 news credibility research. In: *Proceedings of the 29th ACM international conference on information & knowledge management [Internet]*. New York, NY, USA: Association for Computing Machinery; 2020. p. 3205. https://doi.org/10.1145/3340531.3412880. 12. Available from:.
15. Abdul-Mageed M, Elmadany A, Nagoudi EMB, Pabbi D, Verma K, Lin R. *Megacov: a billion-scale dataset of 100+ languages for covid-19*. ArXiv Prepr; 2020. ArXiv200506012.
16. Abdelminaam DS, Ismail FH, Taha M, Taha A, Houssein EH, Nabil A. CoAID-DEEP: an optimized intelligent framework for automated detecting COVID-19 misleading information on Twitter. *IEEE Access* 2021;**9**:27840–67.
17. Haouari F, Hasanain M, Suwaileh R, Elsayed T. *ArCOV19-rumors: Arabic COVID-19 twitter dataset for misinformation detection*. ArXiv Prepr; 2020. ArXiv201008768.
18. Elhadad MK, Li KF, Gebali F. COVID-19-FAKES: a Twitter (Arabic/English) dataset for detecting misleading information on COVID-19. In: Barolli L, Li KF, Miwa H, editors. *Advances in intelligent networking and collaborative systems*. Cham: Springer International Publishing; 2021. p. 256–68.
19. Yang C, Zhou X, Zafarani R. CHECKED: Chinese COVID-19 fake news dataset. *Soc Netw Anal Min* 2021 Jun 22;**11**(1):58.
20. Muric G, Wu Y, Ferrara E. *COVID-19 vaccine hesitancy on social media: building a public twitter dataset of anti-vaccine content, vaccine misinformation and conspiracies*. ArXiv Prepr ArXiv210505134; 2021.
21. Sharma K, Zhang Y, Liu Y. *COVID-19 vaccines: characterizing misinformation campaigns and vaccine hesitancy on twitter*. ArXiv Prepr; 2021. ArXiv210608423.
22. DeVerna MR, Pierri F, Truong BT, Bollenbacher J, Axelrod D, Loynes N, et al. *CoVaxxy: a collection of English-language Twitter posts about COVID-19 vaccines*. ArXiv Prepr; 2021. ArXiv210107694.
23. Malagoli LG, Stancioli J, Ferreira CHG, Vasconcelos M, Couto da Silva AP, Almeida JM. A look into COVID-19 vaccination debate on Twitter. In: *13th ACM web science conference 2021 [Internet]*. New York, NY, USA: Association for Computing Machinery; 2021. p. 225–33. https://doi.org/10.1145/3447535.3462498 (WebSci '21). Available from:.
24. Hu T, Wang S, Luo W, Zhang M, Huang X, Yan Y, et al. Revealing public opinion towards COVID-19 vaccines with Twitter Data in the United States: a spatiotemporal perspective. *J Med Internet Res* 2021;**23**(9):e30854. https://www.jmir.org/2021/9/e30854. https://doi.rog/10.2196/30854.
25. Devgan S. *100 social media statistics for 2021 [+Infographic] | statusbrew* [Internet]. Statusbrew blog; 2021 [cited 2021 Jul 28]. Available from: https://statusbrew.com/insights/social-media-statistics/.
26. [Internet] *Vaccine myths debunked*. PublicHealth.org; 2021 [cited 2021 Jul 28]. Available from: https://www.publichealth.org/public-awareness/understanding-vaccines/vaccine-myths-debunked/.
27. Cassata C. *Doctors debunk popular COVID-19 vaccine myths and conspiracy theories* [Internet]. Healthline; 2021 [cited 2021 Jul 28]. Available from: https://www.healthline.com/health-news/doctors-debunk-9-popular-covid-19-vaccine-myths-and-conspiracy-theories.
28. [Internet] *COVID-19 vaccine facts*. Centers for Disease Control and Prevention; 2021 [cited 2021 Jul 28]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/facts.html.
29. The COVID-19 vaccine: myths versus facts [Internet]. [cited 2021 Jul 28]. Available from: https://www.muhealth.org/our-stories/covid-19-vaccine-myths-vs-facts.
30. Loper E, Bird S. *Nltk: the natural language toolkit*. ArXiv Prepr; 2002. Cs0205028.
31. Porter MF, Boulton R, Macfarlane A. *The English (porter2) stemming algorithm*, vol. 18; 2002. p. 2011.
32. Goodfellow I, Bengio Y, Courville A. *Deep learning*. MIT press; 2016.
33. Chen T, Guestrin C. XGBoost: a scalable tree boosting system. In: *Proceedings of the 22nd ACM SIGKDD international conference on knowledge discovery and data mining [Internet]*. New York, NY, USA: Association for Computing Machinery; 2016. p. 785–94. https://doi.org/10.1145/2939672.2939785 (KDD '16). Available from:.
34. Ramos J, others. Using tf-idf to determine word relevance in document queries. In: *Proceedings of the first instructional conference on machine learning*. Citeseer; 2003. p. 29–48.
35. Hochreiter S, Schmidhuber J. Long short-term memory. *Neural Comput* 1997;**9**(8):1735–80.
36. Shahriar S, Tariq U. Classifying maqams of Qur'anic recitations using deep learning. *IEEE Access* 2021;**1**–**1**.
37. Pennington J, Socher R, Manning CD. Glove: global vectors for word representation. In: *Proceedings of the 2014 conference on empirical methods in natural language processing*. EMNLP; 2014. p. 1532–43.
38. Nair V, Hinton GE. Rectified linear units improve restricted Boltzmann machines. In: *Icml*; 2010.
39. Srivastava N, Hinton G, Krizhevsky A, Sutskever I, Salakhutdinov R. Dropout: a simple way to prevent neural networks from overfitting. *J Mach Learn Res* 2014;**15**(1):1929–58.
40. Kingma DP, Ba J. *Adam: a method for stochastic optimization*. ArXiv Prepr; 2014. ArXiv14126980.
41. Devlin J, Chang M-W, Lee K, Toutanova K. *Bert: pre-training of deep bidirectional transformers for language understanding*. ArXiv Prepr; 2018. ArXiv181004805.
42. Wolf T, Chaumond J, Debut L, Sanh V, Delangue C, Moi A, et al. Transformers: state-of-the-art natural language processing. In: *Proceedings of the 2020 conference on empirical methods in natural language processing: system demonstrations*; 2020. p. 38–45.
43. Shahriar S, Al-Ali AR, Osman AH, Dhou S, Nijim M. Machine learning approaches for EV charging behavior: a review. *IEEE Access* 2020;**8**:168980–93.
44. Alothali E, Hayawi K, Alashwal H. Characteristics of similar-context trending hashtags in Twitter: a case study. In: Ku W-S, Kanemasa Y, Serhani MA, Zhang L-J, editors. *Web services – ICWS 2020*. Cham: Springer International Publishing; 2020. p. 150–63.

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Review Paper

Asymptomatic infection and transmission of COVID-19 among clusters: systematic review and meta-analysis

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ABSTRACT

Objectives: Countries throughout the world are experiencing COVID-19 viral load in their populations, leading to potential transmission and infectivity of asymptomatic COVID-19 cases. The current systematic review and meta-analysis aims to investigate the role of asymptomatic infection and transmission reported in family clusters, adults, children and health care workers, globally.

Study design: Systematic review and meta-analysis.

Methods: An online literature search of PubMed, Google Scholar, medRixv and BioRixv was performed using standard Boolean operators and included studies published up to 17 August 2021. For the systematic review, case reports, short communications and retrospective studies were included to ensure sufficient asymptomatic COVID-19 transmission data were reported. For the quantitative synthesis (meta-analysis), participant data from a collection of cohort studies focusing on groups of familial clusters, adults, children and health care workers were included. Inconsistency among studies was assessed using I^2 statistics. The data synthesis was computed using the STATA 16.0 software.

Results: This study showed asymptomatic transmission among familial clusters, adults, children and health care workers of 15.72%, 29.48%, 24.09% and 0%, respectively. Overall, asymptomatic transmission was 24.51% (95% confidence interval [CI]: 14.38, 36.02) among all studied population groups, with a heterogeneity of $I^2 = 95.30\%$ ($P < 0.001$). No heterogeneity was seen in the population subgroups of children and health care workers. The risk of bias in all included studies was assessed using the Newcastle Ottawa Scale.

Conclusions: For minimising the spread of COVID-19 within the community, this study found that following the screening of asymptomatic cases and their close contacts for chest CT scan (for symptomatic patients), even after negative nucleic acid testing, it is essential to perform a rigorous epidemiological history, early isolation, social distancing and an increased quarantine period (a minimum of 14–28 days). This systematic review and meta-analysis supports the notion of asymptomatic COVID-19 infection and person-to-person transmission and suggests that this is dependent on the varying viral incubation period among individuals. Children, especially those of school age (i.e. <18 years), need to be monitored carefully and follow mitigation strategies (e.g. social distancing, hand hygiene, wearing face masks) to prevent asymptomatic community transmission of COVID-19.

Introduction

Symptomatic COVID-19 viral infection is a significant risk factor for transmission of the disease within the general public. The major signs of COVID-19 infection include fever, dyspnoea, a dry cough and diarrhoea; these symptoms are reported to last up to 14 days, with a median incubation period of 9–12 days. Aerosol transmissions occur through sneezing or coughing and are reported to be the primary route of person-to-person infection.[1] However, simulation studies have also observed asymptomatic COVID-19 person-to-person transmission.[2] Polymerase chain reaction (PCR)-based assays are recommended in managing asymptomatic transmission of the virus.[3] He et al. reported the first case of asymptomatic transmission of

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COVID-19 on 21 February 2020.[4] Asymptomatic infection was reported as 'hidden coronavirus infections' ('infections' or 'covert coronavirus infections').[5] The COVID-19 prevention and control protocol (6th edition) states that asymptomatic COVID-19 cases should remain in quarantine for 14 days and that they should have two negative nucleic acid tests before being discharged. Worldwide, interest in asymptomatic COVID-19 infections and their transmission potential had increased.[6] In China, around 86% of asymptomatic COVID-19 transmission was undocumented before travel restrictions were introduced.[6]

To date, asymptomatic COVID-19 cases have been reported among family clusters,[7–12] pregnant women,[13,14] adults,[15–24] children,[1,25,26] health care workers[27–29] and travellers.[30–34] Considering the potential transmission of asymptomatic COVID-19 within the community, this study aimed to collate data from the general population, as well as vulnerable groups from different backgrounds, and perform a meta-analysis. Previous studies have reported the proportion of COVID-19 infections attributable to asymptomatic transmission to be around 20%, with some variation depending on the population group. In this study, a meta-analysis was performed that considered different population groups.

Methods

Study design

A systematic review and meta-analysis were performed.

Data sources and search strategy

For the systematic review and meta- analysis PRISMA guidelines were followed.[35,36] The following Boolean operators were used to search the PubMed database, Google scholar, medRxiv and BioRixv: 'asymptomatic transmission', '((COVID-19) AND (Coronavirus)) AND (Asymptomatic transmission)', '((COVID-19) OR (Coronavirus)) AND (asymptomatic transmission)', '(SARS-CoV-2) AND (asymptomatic transmission)', '(2019-nCoV) AND (asymptomatic transmission)', '(Wuhan pneumonia) AND (asymptomatic transmission)', '(Wuhan flu) AND (asymptomatic transmission)', '(2019-nCoV acute respiratory disease) AND (asymptomatic transmission)' and '(2019-nCoV respiratory syndrome) AND (asymptomatic transmission)'. This study included published literature in English language up to 17 August 2021..

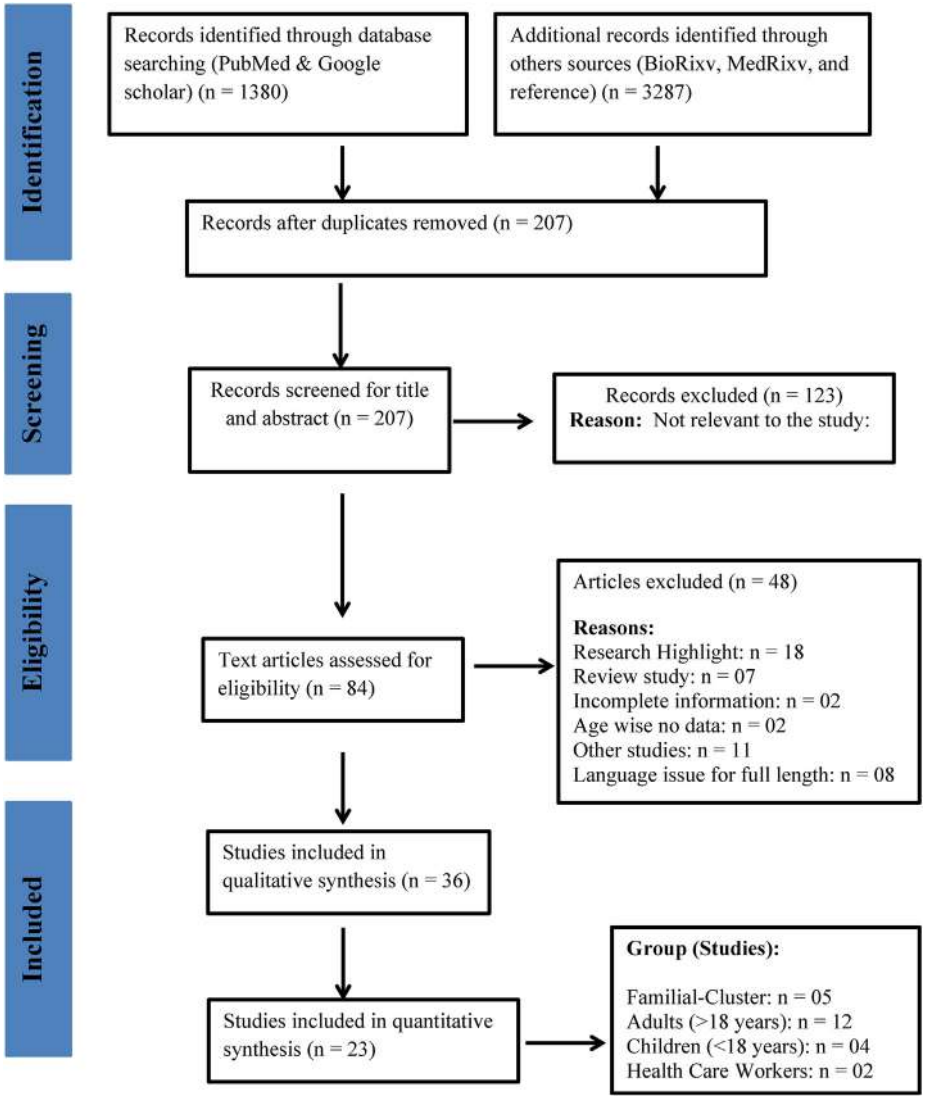

Fig. 1. PRISMA chart.

Table 1
Characteristics of the included studies.

Author	Country	Age, years [mean (±SD)/median (IRQ)]	Study Type	Type of test	Major findings
Family cluster					
Chan et al., 2020[8]	China	Family: 36-60 Child: 10	Cohort	RT-PCR	Supports person-to-person transmission between family
Chen et al., 2020[9]	China	8.5 ± 0.17	Case report	RT-PCR	The ability of COVID-19 transmission during the asymptomatic period even after negative viral testing
Lu et al., 2019[10]	China	8	Case report	RT-PCR	Supports rigorous investigation in the combination of various testing methods for asymptomatic COVID-19 cases
Qian et al., 2020[11]	China	6	Brief report	RT-PCR	Variation in clinical manifestation across individuals was observed
Ye et al., 2020[12]	China	38 ± 18.38	Cohort	RT-PCR	Possibility of COVID-19 transmission by the asymptomatic carrier during the incubation period
Bai et al., 2020[7]	China	20	Cohort	RT-PCR	Support asymptomatic transmission through a family contact
Xie et al., 2021[56]	China	>18	Cohort	RT-PCR	Handwashing, social distancing should be done
Zhang et al., 2021[57]	China	>18	Cohort	RT-PCR	Asymptomatic patients can transmit the disease and improve protective measures.
Adults					
Tian et al., 2020[21]	China	47.5	Cohort	RT-PCR	Early isolation and quarantine for close contacts to prevent asymptomatic transmission
Kim et al., 2020[17]	Korea	26 (22–47)	Research note	RT-PCR	Supports social distancing to prevent asymptomatic transmission
Kong et al., 2020[8]	China	37.7 (±19)	Cohort	RT-PCR	Suggest rigorous epidemiological history and chest CT scan as a practical tool to identify the asymptomatic COVID-19 cases in the community
Yin et al., 2020[22]	China	–	Cohort	RT-PCR	No difference in the transmission rate of COVID-19 between asymptomatic and symptomatic cases
Meng et al., 2020[55]	China	42.60 (±16.56)	Cohort	RT-PCR	Suggest chest CT scan as a vital tool to screen the asymptomatic COVID-19 cases in the community
Al Hosani et al., 2019[15]	UAE	37 (30–45)	Cohort	RT-PCR	No transmission among household contacts after the implication of strong isolation policies
He et al., 2020[16]	China	–	Cohort	RT-PCR	Significantly smaller transmissibility of asymptomatic cases than symptomatic
Qiu et al., 2020[20]	China	43 (8–84)	Cohort	RT-PCR	Suggested transmission occurred after 14 days quarantine periods
Zhou et al., 2020[24]	China	–	Short communication	RT-PCR	Recommended rigorous epidemiological history and nucleic acid testing
Park et al., 2020[19]	Korea	38 (20–0)	Report	RT-PCR	Supports contact tracing, testing and increasing quarantine to prevent asymptomatic COVID-19 transmission in the community
De laval et al., 2021[61]	France	40 (24–59)	Cohort	RT-PCR	The median incubation day was 4 (1–13) days.
Wong et al., 2020[34]	Brunei	–	Cohort	RT-PCR	Proposes differentiated testing strategies to account for different transmission risk
Huang et al., 2020[60]	China	–	Cohort	RT-PCR	To identify the presence of asymptomatic carriers as early as possible in the community. Infection occurs during the incubation period of asymptomatic cases.
Sugano et al., 2020[58]	Japan	–	Cohort	RT-PCR	Possibility of asymptomatic transmission and the period from exposure to illness ranged from 2 to 17 days.
Nsekye et al., 2021[62]	Rawanda	–	Cohort	RT-PCR	Contact tracing and testing should be done.
Children					
Hu et al., 2020[25]	China	<15	Cohort	RT-PCR	Suggest close contact tracing and nucleic acid testing to identify the asymptomatic COVID-19 tracing the community
Qiu et al., 2019[26]	China	8.3 (±3.5)	Cohort	RT-PCR	Possibility of asymptomatic COVID-19 transmission by close contacts
Tan et al., 2020[1]	China	–	Cohort	RT-PCR	Possibility of asymptomatic COVID-19 transmission by intrafamilial contact
Sun et al., 2020[59]	China	5.8	Cohort	RT-PCR	Both nasopharyngeal and anal swabs should be confirmed negative viral load before declaring full recovery to avoid oral-faecal transmission.
Health care Workers					
Kimball et al., 2020[27]	USA	–	Report	RT-PCR	Reported rapid transmission among health care worker
Schoierzeck et al., 2020[29]	Germany	48	Cohort	RT-PCR	Suggest nucleic acid testing for asymptomatic COVID-19 cases

Table 1 (*continued*)

Author	Country	Age, years [mean (±SD)/median (IRQ)]	Study Type	Type of test	Major findings
Lucar et al., 2020[28]	USA	>18	Cohort	RT-PCR	transmission reported because of prolonged surgery done on asymptomatic COVID-19 case
Traveller aged >18 years					
COVID-19 NERC, 2020[30]	Korea	>18	Cohort	RT-PCR	Supports asymptomatic transmission with minor symptoms
Mizumoto et al., 2020[32]	Japan	>18	Rapid communication	RT-PCR	Support social distancing to prevent the asymptomatic transmission
Wan et al., 2020[33]	China	>18	Short communication	RT-PCR	Possibility of asymptomatic transmission after 14 days quarantine from asymptomatic COVID-19 case
Wong et al., 2020[34]	Brunei	–	Rapid communication	RT-PCR	Support social distancing & nucleic acid testing of asymptomatic COVID-19 case
Le et al., 2020[54]	China	–	Abstract	–	Support asymptomatic COVID-19 viral transmissibility in the absence of signs and symptoms

Note: - Missing values (mean/median values were not reported).
IQR, interquartile range; RT-PCT, reverse transcription-polymerase chain reaction.

Inclusion and exclusion criteria

For the meta-analysis, the present study included cohort studies that reported asymptomatic person-to-person transmission among clusters. Studies that were published in the English language were included.

Data collection and study selection

Details of authors, sample size and numbers reported for the asymptomatic infection of COVID-19 were extracted and recorded independently. Data extraction was done separately by two independent reviewers, and disagreement was settled by a joint discussion. The data were carefully checked to minimise the risk of duplication.

Quality assessment

The Newcastle Ottawa scale (cohort studies) was used to evaluate the selected studies in the current systematic review and meta-analysis.[35,37]

Publication bias

Possible publication bias in this study was assessed for the included cohort studies.[38]

Statistical analyses and data synthesis

After extracting the results, studies were pooled and the effect of asymptomatic COVID-19 transmission was examined through the random effects method. For continuous outcomes, the standard error (SE) with 95% confidence intervals (CIs) were calculated. Heterogeneity between studies was assessed using the I^2 statistic (I^2 values indicating the existence of heterogeneity were assessed according to Higgins and colleagues).[35,39,40] Data for the meta-analysis were collated.[35,41] Data synthesis was conducted using the STATA 16.0 software.

Patient and public involvement

There was no direct patient or public involvement in this systematic review and meta-analysis.

Results

Literature search

The literature search and screening were performed according to the PRISMA chart (Fig. 1). Initially, 4667 published research articles were identified using the online database search. After removing 4460 duplicate publications, 207 research articles were shortlisted. After screening the title and abstracts, 123 articles were excluded and 84 full-text articles were assessed for eligibility. A further 48 studies were excluded because they were research highlight reports, review studies, had incomplete information, reported no age-specific data, were classified as 'other' non-relevant studies or had language issues. For the qualitative synthesis, 36 articles were selected and 23 studies were included in the meta-analysis. Studies were grouped into the following population subgroups: family clusters (n = 5), adults (n = 12), children (n = 4) and health care workers (n = 2).

Characteristics of the study participants

The main components of the included studies are summarised in Table 1. All published research articles were cohort (observational) study designs. Most of the studies are from China, Korea, the US, Japan and Germany. The current research includes articles published/available online up to 17 August 2021. The current systematic review reports data from 23 studies with a total of 1905 asymptomatic participants. The forest plots of asymptomatic positivity for COVID-19 among the study population (Fig. 2) and among different subgroups (Fig. 3) are shown.

Quality assessment

The Newcastle Ottawa Scale (for cohort studies) was used for qualitative evaluation of the studies included in the meta-analysis.[35,37] The risk of bias was assessed based on three domains (selection, comparability and outcome), as highlighted in Table 2.

Publication bias

The bubble plot (see Fig. 4) shows the study-specific effect size, where the size of each bubble is proportional to the precision of

each study. Asymptomatic participants' funnel plot (standard error) showed no obvious publication bias (Fig. 5).

Meta-analysis

The outcomes of the current meta-analysis (Table 3), and forest plots of asymptomatic positivity for COVID-19 among the study population (Fig. 2) and different subgroups (Fig. 3) are shown. A random-effects model was used for the different levels of reported asymptomatic COVID-19 transmission in the community. The current meta-analysis observed heterogeneity among familial clusters ($I^2 = 59.02\%$, $P = 0.04$, with a proportion of 15.72% [95% CI: 1.88, 36.10]) and adults aged ≥18 years ($I^2 = 97.47\%$, $P < 0.001$, with a proportion of 29.48% [95% CI: 15.56, 45.58]). This study did not observe any heterogeneity among children and health care workers, although the random effect model showed the proportion of asymptomatic transmission to be 24.09% (95% CI: 17.23, 31.62) and 0% (95% CI: 0.00, 3.17), respectively. We observed a significant difference ($P = 0.005$) of heterogeneity between groups ($I^2 = 95.30\%$).

Discussion

The current study summarised available literature reporting asymptomatic transmission of COVID-19 as retrospective studies and case reports from family clusters, adults, children, health care workers and travellers. The person-to-person asymptomatic transmission was observed among familial clusters in an asymptomatic COVID-19 child (aged 10 years old) who had an abnormal chest CT and in another asymptomatic child with mild chest CT manifestation; family members of these children showed signs of fever and respiratory issues and had a positive COVID-19 test result.[8,9] The current study suggests that thorough epidemiological investigations, in combination with multiple detection methods (e.g. reverse transcription PCR [RT-PCR], chest CT, rapid IgM-IgG and serum C-reactive protein [CRP] level), asymptomatic carriers in the community who are displaying different (or no) clinical manifestations can be identified.[10,11] Another study supports the possibility of asymptomatic transmission among familial clusters during the incubation period.[12] In addition, in a familial cluster of five COVID-19-positive patients, it was observed that they had contact with other asymptomatic family members who had returned from Wuhan, China, suggesting asymptomatic transmission.[7]

During any disease outbreak, the unborn babies of pregnant women are at high risk. It has been reported that pregnant women with asymptomatic COVID-19 infection have delivered babies who are negative for the COVID-19 nucleic acid test, suggesting no vertical transmission among neonates born to COVID-19-infected mothers.[14,42–49]

In Wuhan, a lower COVID-19 fatality rate and higher discharge rate were observed than in Beijing, China. It is essential to identify asymptomatic individuals and implement necessary control measures to prevent transmission.[21] In South Korea, 41 COVID-19 asymptomatic adults were identified (confirmed by RT-PCR) out of 213 individuals.[17] In another study among 100 asymptomatic cases, 60% developed delayed symptoms and none of the asymptomatic patients died, suggesting that asymptomatic transmission could take place during the incubation period.[18] Another study did not observe any difference in the symptomatic and asymptomatic COVID-19 transmission rates among patients.[22] In adults, CT imaging of asymptomatic COVID-19 individuals has advantages in highly suspicious cases with negative nucleic acid test results.[17] A serological investigation among 31 of 34 adult cases with

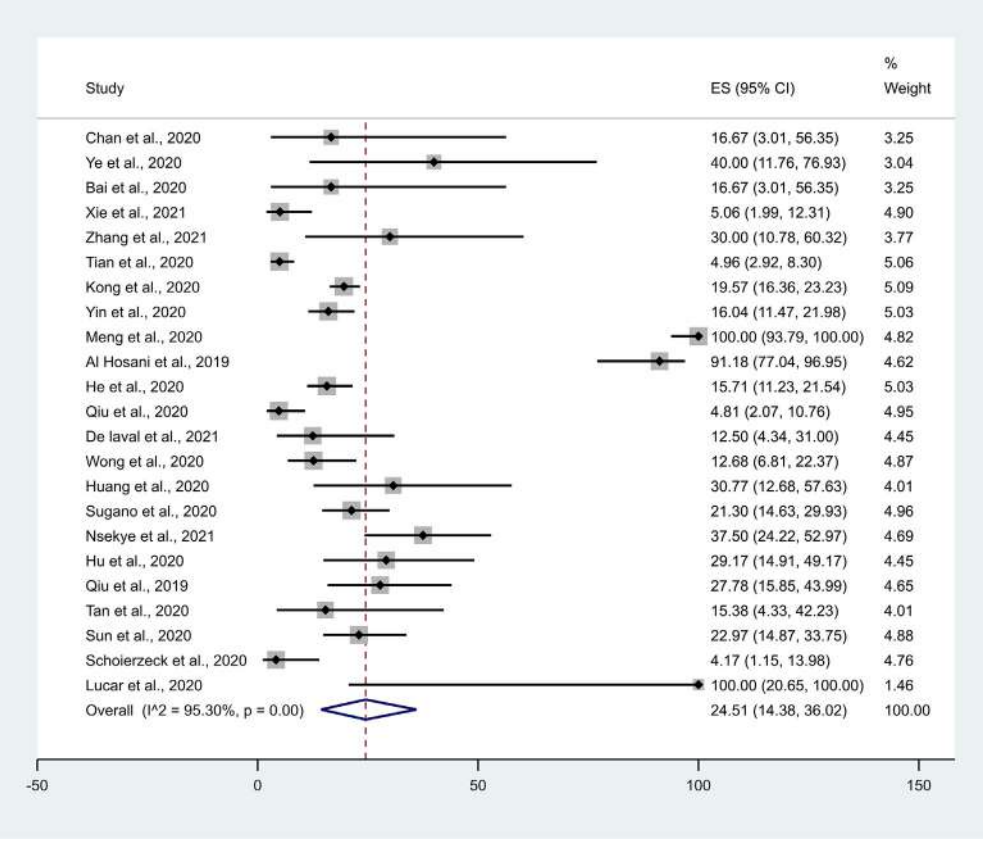

Fig. 2. Forest plot of asymptomatic positivity for COVID-19 among the study population. CI, confidence interval.

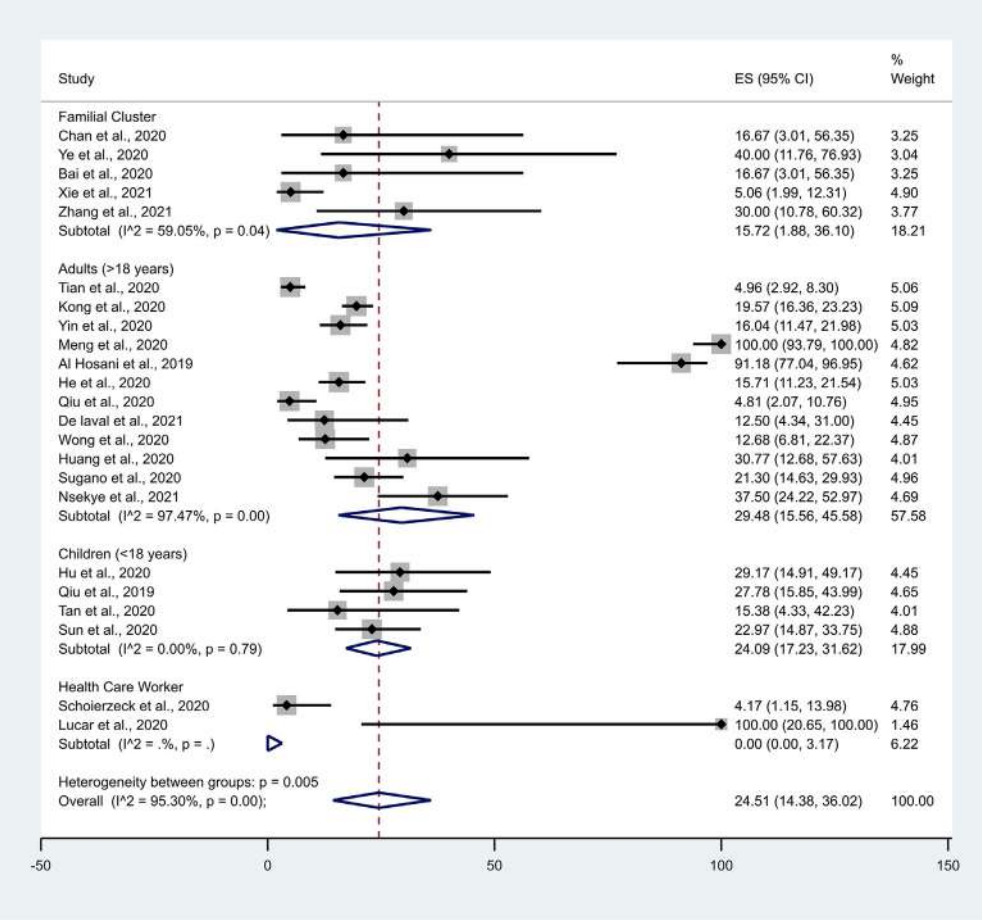

Fig. 3. Forest plot of asymptomatic positivity for COVID-19 among different population subgroups. CI, confidence interval.

asymptomatic COVID-19 infection did not require oxygen support during hospitalisation.[15] Theoretically, the quantified infection transmission rate shows the estimated risk ratio (RR) of infectivity of symptomatic against asymptomatic to be 3.9% (95% CI: 1.5, 11.8). In asymptomatic adults, the transmission was significantly smaller than in symptomatic cases.[16] No gender difference was observed for asymptomatic transmission.[20]

Further longitudinal surveillance using nucleic acid testing is warranted to identify and assess viral load among asymptomatic COVID-19 adults.[24] In one study, four asymptomatic cases were quarantined for 14 days; thus, these individuals were unable to transmit the infection due to proper isolation management.[19]

Asymptomatic COVID-19 transmission has been observed in children.[26] In one study, 24 asymptomatic cases were identified from close contacts of asymptomatic COVID-19 patients.[25] Another study supports multiple-site sampling of close contacts[1] among children. In a review, it was observed that adults with COVID-19 infection are more likely to show clinical symptoms and radiological manifestations than children, which is in line with previous reports for severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) coronaviruses.[50]

In a study investigating health care workers in a nursing facility, rapid transmission of COVID-19 was reported in 76 residents; 23 (30.3%) had positive test results, and 13 were asymptomatic on the day of testing, suggesting the possibility of asymptomatic transmission of COVID-19.[27] Establishing effective infection control strategies to prevent COVID-19 transmission among frontline health care workers and patients should be addressed urgently and as a priority. In another study, including 48 participants (healthcare worker), two asymptomatic cases become positive, suggesting appropriate testing strategies are essential to prevent outbreaks of COVID-19 within hospital settings.[29] In the United States, health care workers who were not wearing respirators were exposed to an asymptomatic COVID-19 patient without developing clinical illness.[28]

In Korea, COVID-19 was transmitted by 16 infected travellers from other countries; the disease was infectious at this stage, which resulted from close contact with asymptomatic carriers.[30] Most of the infections on board the Diamond Princess Cruise ship highlight the asymptomatic transmission of COVID-19 in confined settings. To further mitigate the transmissibility of COVID-19, it may be advised to minimise the number of individuals gathering in confined settings.[32] A 36-year-old traveller who returned from Wuhan tested positive for COVID-19 positive and health care workers who were in close contact with this patient also tested positive; however, the patient initially had no symptoms.[33] A high proportion of asymptomatic COVID-19 infection (12%) was reported among travellers returning to Brunei. Similarly, an asymptomatic COVID-19 patient showed viral transmissibility without showing any signs or symptoms after travelling in China.[31] In another study, it was suggested that testing facilities should be increased to help identify asymptomatic COVID-19 cases.[34]

Although this study recommends early isolation and social distancing for asymptomatic COVID-19 cases, it is important to recognise that this may lead to psychological and emotional distress (as reported in a qualitative study from the United

Table 2
Quality Assessment: Cohort study quality according to the Newcastle Ottawa scale.

Study	Selection******				Comparability**	Outcome*****			Total Quality Score
	1	2	3	4	5	6	7	8	
Family cluster									
Chan et al., 2020[8]	*	0	*	0	*	*	0	0	4
Ye et al., 2020[12]	*	0	*	0	0	*	0	0	3
Bai et al., 2020[7]	*	0	*	0	0	*	0	0	3
Xie et al., 2021[56]	*	0	*	0	0	*	0	0	3
Zhang et al., 2021[57]	*	0	*	0	0	*	0	0	3
Adults									
Tian et al., 2020[21]	*	0	*	0	0	*	0	0	3
Kong et al., 2020[8]	*	0	*	0	0	*	0	0	3
Yin et al., 2020[22]	*	0	*	0	0	*	0	0	3
Meng et al., 2020[55]	*	0	*	0	0	*	0	0	3
Al Hosani et al., 2019[15]	*	0	*	0	0	*	0	0	3
He et al., 2020[16]	*	0	*	0	0	*	0	0	3
Qiu et al., 2020[20]	*	0	*	0	0	*	0	0	3
De laval et al., 2021[61]	*	0	*	0	0	*	0	0	3
Wong et al., 2020[34]	*	0	*	0	*	*	0	0	4
Huang et al., 2020[60]	*	0	*	0	0	*	0	0	3
Sugano et al., 2020[58]	*	0	*	0	0	*	0	0	3
Nsekye et al., 2021[62]	*	0	*	0	0	*	0	0	3
Children									
Hu et al., 2020[25]	*	0	*	0	0	*	0	0	3
Qiu et al., 2019[26]	*	0	*	0	0	*	0	0	3
Tan et al., 2020[1]	*	0	*	0	0	*	0	0	3
Sun et al., 2020[59]	*	0	*	0	0	*	0	0	3
Health care Workers									
Schoierzeck et al., 2020[29]	*	0	*	0	0	*	0	0	3
Lucar et al., 2020[28]	*	0	*	0	0	*	0	0	3

Note: Selection; 1) Representativeness of the exposed cohort, 2) Selection of the non-exposed cohort, 3) Ascertain exposure, 4) Demonstration that outcome of interest was not present at the start of the study; **Comparability;** 5) Comparability of cohorts based on the design or analysis controlled for confounders; **Outcome:** 6) Assessment of outcome, 7) Was follow-up long enough for outcomes to occur, 8) Adequacy of follow-up of cohorts.
*Newcastle-Ottawa Scale contains 8 items within 3 domain and the total maximum score is 9. A study with score from 7-9, has high quality, 4-6, high risk, and 0-3 very high risk of bias.

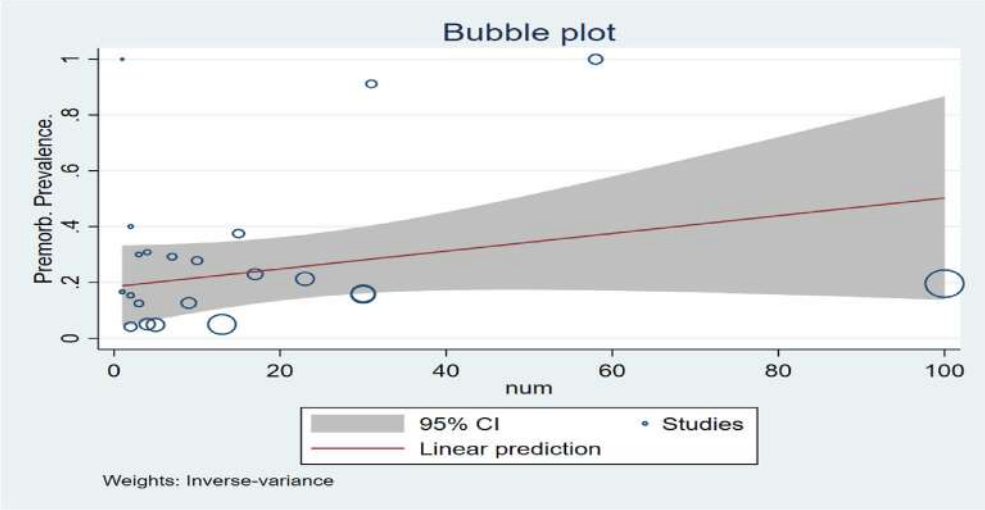

Fig. 4. Bubble Plot.

Kingdom).[51] Further studies are warranted based on the 'one health' approach to tackle asymptomatic transmission.[52] A study by Tao et al. suggested the inclusion of infection fatality rate (IFR) in surveillance data to minimise asymptomatic COVID-19 cases in the community.[53]

Limitations

There are some limitations in the current systematic review and meta-analysis. A mixed population, a continuous variable, variation in clinical conditions and use of different statistical methods may result in heterogeneity among studies included in the current meta-analysis. Furthermore, the current study only included reported cases of asymptomatic COVID-19 transmission.

Study importance

This is the first study to review the possibility of asymptomatic COVID-19 transmission among different population subgroups in the community. This study also identifies the potential role of

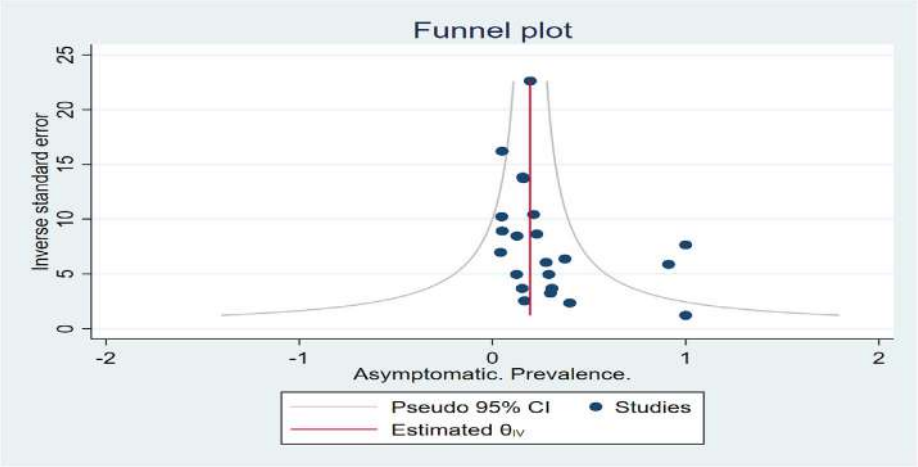

Fig. 5. Funnel Plot.

Table 3
The meta-analysis of asymptomatic transmission for COVID-19 among different population subgroups.

Risk factor (Asymptomatic) Group	Studies	Asymptomatic Population (n)	Total Sample Size (N)	Proportion (95% CI)	I^2, *P*-Value
Family Cluster	5	11	106	15.72 (1.88, 36.10)	59.02%, $P = 0.04$
Adults (≥18 years age)	12	321	1603	29.48 (15.56, 45.58)	97.47%, $P < 0.001$
Children (<18 years age)	4	36	147	24.09 (17.23, 31.62)	0.00%, $P = 0.79$
Health care Workers	2	3	49	0.00 (0.00, 3.17)	–
Combined (groups)	23	71	1905	24.51 (14.38, 36.02)	95.30%, $P < 0.001$

CI, confidence interval.

isolation, identification of close contacts, social distancing, and testing asymptomatic COVID-19 cases with chest CT scan and nucleic acid testing to minimise the spread of the virus in the community.

Conclusions

Currently, there is no evidence that COVID-19 can be transmitted in the asymptomatic stage; however, results suggest that asymptomatic infections are not limited to one population group (e.g. neonates, children, adults). In young people, it has been suggested that their strong immune status protects against COVID-19 severity. We hypothesise that asymptomatic carriers, either children or adults, should be vigilant as they are capable of transmitting COVID-19 during the incubation period without showing any signs or symptoms. As previous reports support the involvement of lung function in asymptomatic COVID-19 cases, we recommend chest CT scans among symptomatic cases, which is a convenient tool to monitor and track patients in their incubation period.

Author statements

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Competing interests

None declared.

Contributors

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References

1. Tan X, Huang J, Zhao F, Zhou Y, Li J-Q, Wang X-Y. Clinical features of children with SARS-CoV-2 infection: an analysis of 13 cases from Changsha, China. *Zhongguo Dang Dai Er Ke Za Zhi Chin J Contemp Pediatr* 2020;**22**(4):294–8.
2. Chen T-M, Rui J, Wang Q-P, Zhao Z-Y, Cui J-A, Yin L. A mathematical model for simulating the phase-based transmissibility of a novel coronavirus. *Infect Dis Poverty* 2020;**9**(1):24. https://doi.org/10.1186/s40249-020-00640-3.
3. Rahimi F, Talebi Bezmin Abadi A. Challenges of managing the asymptomatic carriers of SARS-CoV-2. *Trav Med Infect Dis* 2020:101677. https://doi.org/10.1016/j.tmaid.2020.101677. Published online April.
4. He G, Sun W, Fang P, et al. The clinical feature of silent infections of novel coronavirus infection (COVID-19) in Wenzhou. *J Med Virol* 2020. https://doi.org/10.1002/jmv.25861. Published online 10th April.
5. Wang Y, Kang H, Liu X, Tong Z. Asymptomatic cases with SARS-CoV-2 infection. *J Med Virol* 2020:25990. https://doi.org/10.1002/jmv.25990. Published online 22nd May jmv.

6. Park SW, Cornforth DM, Dushoff J, Weitz JS. The time scale of asymptomatic transmission affects estimates of epidemic potential in the COVID-19 outbreak. *Epidemics* 2020;**31**:100392. https://doi.org/10.1016/j.epidem.2020.100392.
7. Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. *J Am Med Assoc* 2020;**323**(14):1406. https://doi.org/10.1001/jama.2020.2565.
8. Chan JF-W, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020;**395**(10223):514–23. https://doi.org/10.1016/S0140-6736(20)30154-9.
9. Chen M, Fan P, Liu Z, et al. A SARS-CoV-2 familial cluster infection reveals asymptomatic transmission to children. *J Infect Public Health* 2020;**13**(6):883–6. https://doi.org/10.1016/j.jiph.2020.05.018.
10. Lu S, Lin J, Zhang Z, et al. Alert for non-respiratory symptoms of Coronavirus Disease 2019 (COVID-19) patients in epidemic period: a case report of familial cluster with three asymptomatic COVID-19 patients. *J Med Virol* 2020. https://doi.org/10.1002/jmv.25776. Published online 19th March.
11. Qian G, Yang N, Ma AHY, et al. COVID-19 transmission within a family cluster by presymptomatic carriers in China. *Clin Infect Dis* 2020:ciaa316. https://doi.org/10.1093/cid/ciaa316. Published online 23rd March.
12. Ye F, Xu S, Rong Z, et al. Delivery of infection from asymptomatic carriers of COVID-19 in a familial cluster. *Int J Infect Dis* 2020;**94**:133–8. https://doi.org/10.1016/j.ijid.2020.03.042.
13. Chang L, Yan Y, Wang L. Coronavirus disease 2019: coronaviruses and blood safety. *Transfus Med Rev* 2020;**34**(2):75–80. https://doi.org/10.1016/j.tmrv.2020.02.003.
14. Lu D, Sang L, Du S, Li T, Chang Y, Yang X. Asymptomatic COVID-19 infection in late pregnancy indicated no vertical transmission. *J Med Virol* 2020:25927. https://doi.org/10.1002/jmv.25927. Published online 30th April jmv.
15. Al Hosani FI, Kim L, Khudhair A, et al. Serologic follow-up of Middle East respiratory syndrome coronavirus cases and contacts—Abu Dhabi, United Arab Emirates. *Clin Infect Dis* 2019;**68**(3):409–18. https://doi.org/10.1093/cid/ciy503.
16. He D, Zhao S, Lin Q, et al. The relative transmissibility of asymptomatic COVID-19 infections among close contacts. *Int J Infect Dis* 2020;**94**:145–7. https://doi.org/10.1016/j.ijid.2020.04.034.
17. Kim G -u, Kim M-J, Ra SH, et al. Clinical characteristics of asymptomatic and symptomatic patients with mild COVID-19. *Clin Microbiol Infect* 2020. https://doi.org/10.1016/j.cmi.2020.04.040. Published online May S1198743X20302688.
18. Kong W, Wang Y, Hu J, Chughtai A, Pu H. Comparison of clinical and epidemiological characteristics of asymptomatic and symptomatic SARS-CoV-2 infection: a multi-center study in Sichuan Province, China. *Trav Med Infect Dis* 2020:101754. https://doi.org/10.1016/j.tmaid.2020.101754. Published online May.
19. Park SY, Kim Y-M, Yi S, et al. Coronavirus disease outbreak in call center, South Korea. *Emerg Infect Dis* 2020;**26**(8). https://doi.org/10.3201/eid2608.201274.
20. Qiu C, Deng Z, Xiao Q, et al. Transmission and clinical characteristics of coronavirus disease 2019 in 104 outside-Wuhan patients, China. *J Med Virol* 2020:25975. https://doi.org/10.1002/jmv.25975. :. Published online May 5 jmv.
21. Tian S, Hu N, Lou J, et al. Characteristics of COVID-19 infection in beijing. *J Infect* 2020;**80**(4):401–6. https://doi.org/10.1016/j.jinf.2020.02.018.
22. Yin G, Jin H. Comparison of transmissibility of coronavirus between symptomatic and asymptomatic patients: reanalysis of the ningbo COVID-19 data. *JMIR Public Health Surveill* 2020;**6**(2):e19464. https://doi.org/10.2196/19464.
23. Yuen K-S, Ye Z-W, Fung S-Y, Chan C-P, Jin D-Y. SARS-CoV-2 and COVID-19: the most important research questions. *Cell Biosci* 2020;**10**(1):40. https://doi.org/10.1186/s13578-020-00404-4.
24. Zhou R, Li F, Chen F, et al. Viral dynamics in asymptomatic patients with COVID-19. *Int J Infect Dis* 2020;**96**:288–90. https://doi.org/10.1016/j.ijid.2020.05.030.
25. Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci* 2020;**63**(5):706–11. https://doi.org/10.1007/s11427-020-1661-4.
26. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis* 2020;**20**(6):689–96. https://doi.org/10.1016/S1473-3099(20)30198-5.
27. Kimball A, Hatfield KM, Arons M, et al. Asymptomatic and presymptomatic SARS-CoV-2 infections in residents of a long-term care skilled nursing facility — king county, Washington, march 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**(13):377–81. https://doi.org/10.15585/mmwr.mm6913e1.
28. Lucar J, Navalkele B, Becker BP, Reed CD, Parham J. Healthcare personnel exposure to a patient with asymptomatic SARS-CoV2 infection during a prolonged surgical intervention. *Am J Infect Control* 2020. https://doi.org/10.1016/j.ajic.2020.05.036. Published online June S0196655320303527.
29. Schwierzeck V, König JC, Kühn J, et al. First reported nosocomial outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a pediatric dialysis unit. *Clin Infect Dis* 2020:ciaa491. https://doi.org/10.1093/cid/ciaa491. Published online 27th April.
30. COVID-19 National Emergency Response Center. Epidemiology and case management team, Korea centers for disease control and prevention. Early epidemiological and clinical characteristics of 28 cases of coronavirus disease in South Korea. *Osong Public Health Res Perspect* 2020;**11**(1):8–14. https://doi.org/10.24171/j.phrp.2020.11.1.03.
31. Hu X, Gao J, Luo X, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vertical transmission in neonates born to mothers with coronavirus disease 2019 (COVID-19) pneumonia. *Obstet Gynecol* 2020. https://doi.org/10.1097/AOG.0000000000003926. Publish Ahead of Print.
32. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill* 2020;(10):25. https://doi.org/10.2807/1560-7917.ES.2020.25.10.2000180.
33. Wan R, Mao Z-Q, He L-Y, Hu Y-C, Wei-Chen. Evidence from two cases of asymptomatic infection with SARS-CoV-2: are 14 days of isolation sufficient? *Int J Infect Dis* 2020;**95**:174–5. https://doi.org/10.1016/j.ijid.2020.03.041.
34. Wong J, Abdul Aziz ABZ, Chaw L, et al. High proportion of asymptomatic and presymptomatic COVID-19 infections in air passengers to Brunei. *J Trav Med* 2020:taaa066. https://doi.org/10.1093/jtm/taaa066. Published online 5th May.
35. Malik VS, Ravindra K, Attri SV, Bhadada SK, Singh M. Higher body mass index is an important risk factor in COVID-19 patients: a systematic review. *SSRN Electron J* 2020. https://doi.org/10.2139/ssrn.3605087. Published online.
36. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097.
37. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med* 2000;**342**(10):681–9. https://doi.org/10.1056/NEJM200003093421002.
38. Lau J, Ioannidis JPA, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. *BMJ* 2006;**333**(7568):597–600. https://doi.org/10.1136/bmj.333.7568.597.
39. Krüger K, Mooren F-C, Pilat C. The immunomodulatory effects of physical activity. *Curr Pharmaceut Des* 2016;**22**(24):3730–48. https://doi.org/10.2174/1381612822666160322145107.
40. Lasselin J, Alvarez-Salas E, Grigoleit J-S. Well-being and immune response: a multi-system perspective. *Curr Opin Pharmacol* 2016;**29**:34–41. https://doi.org/10.1016/j.coph.2016.05.003.
41. Pearson-Stuttard J, Blundell S, Harris T, Cook DG, Critchley J. Diabetes and infection: assessing the association with glycaemic control in population-based studies. *Lancet Diabetes Endocrinol* 2016;**4**(2):148–58. https://doi.org/10.1016/S2213-8587(15)00379-4.
42. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020;**395**(10226):809–15. https://doi.org/10.1016/S0140-6736(20)30360-3.
43. Chen S, Huang B, Luo DJ, et al. [Pregnancy with new coronavirus infection: clinical characteristics and placental pathological analysis of three cases]. *Zhonghua Bing Li Xue Za Zhi* 2020;**49**(5):418–23. https://doi.org/10.3760/cma.j.cn112151-20200225-00138.
44. Chen Y, Peng H, Wang L, et al. Infants born to mothers with a new coronavirus (COVID-19). *Front Pediatr* 2020;**8**:104. https://doi.org/10.3389/fped.2020.00104.
45. Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol* 2020;**222**(6):521–31. https://doi.org/10.1016/j.ajog.2020.03.021.
46. Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. *J Infect* 2020. https://doi.org/10.1016/j.jinf.2020.02.028. Published online March S0163445320301092.
47. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med* 2020;**26**(4):502–5. https://doi.org/10.1038/s41591-020-0817-4.
48. Zhang L, Jiang Y, Wei M, et al. [Analysis of the pregnancy outcomes in pregnant women with COVID-19 in Hubei Province]. *Zhonghua Fu Chan Ke Za Zhi* 2020;**55**(3):166–71. https://doi.org/10.3760/cma.j.cn112141-20200218-00111.
49. Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr* 2020;**9**(1):51–60. https://doi.org/10.21037/tp.2020.02.06.
50. Zimmermann P, Curtis N. COVID-19 in children, pregnancy and neonates: a review of epidemiologic and clinical features. *Pediatr Infect Dis J* 2020;**39**(6):469–77. https://doi.org/10.1097/INF.0000000000002700.
51. Williams SN, Armitage CJ, Tampe T, Dienes K. Public perceptions and experiences of social distancing and social isolation during the COVID-19 pandemic: a UK-based focus group study. *BMJ Open* 2020;**10**(7):e039334. https://doi.org/10.1136/bmjopen-2020-039334.
52. Tao J, Zhang X, Zhang X, et al. The time serial distribution and influencing factors of asymptomatic COVID-19 cases in Hong Kong. *One Health* 2020;**10**:100166. https://doi.org/10.1016/j.onehlt.2020.100166.
53. Tao J, Zhang X, Musa SS, Yang L, He D. High infection fatality rate among elderly and risk factors associated with infection fatality rate and asymptomatic infections of COVID-19 cases in Hong Kong. *Front Med* 2021;**8**:678347. https://doi.org/10.3389/fmed.2021.678347.
54. Le T, Takemura T, Moi ML, Nabeshima T, Nguyen L, Hoang V, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Shedding by Travelers, Vietnam, 2020. *Emerg Infect Dis* 2020;**26**(7):1624–6. https://doi.org/10.3201/eid2607.200591.
55. Meng H, Xiong R, He R, Lin W, Hao B, Zhang L, et al. CT imaging and clinical course of asymptomatic cases with COVID-19 pneumonia at admission in

Wuhan, China. *J Infect* 2020;**81**(1):e33–9. https://doi.org/10.1016/j.jinf.2020.04.004.
56. Xie W, Chen Z, Wang Q, Song M, Cao Y, Wang L, et al. Infection and disease spectrum in individuals with household exposure to SARS-CoV-2: A family cluster cohort study. *J Med Virol* 2021;**93**(5):3033–46. https://doi.org/10.1002/jmv.26847.
57. Zhang H, Song S, Chen Z, Bai M, He Z, Fu T, et al. A Cluster Transmission of Coronavirus Disease 2019 and the Prevention and Control Measures in the Early Stage of the Epidemic in Xi'an, China, 2020. *Int Med J Experi Clin Res* 2021;**27**:e929701. https://doi.org/10.12659/MSM.929701.
58. Sugano N, Ando W, Fukushima W. Cluster of Severe Acute Respiratory Syndrome Coronavirus 2 Infections Linked to Music Clubs in Osaka, Japan. *J Infect Dis* 2020;**222**(10):1635–40. https://doi.org/10.1093/infdis/jiaa542.
59. Sun D, Li H, Luv XX, Xiao H, Ren J, Zhang FR, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pedia: WJP* 2020;**16**(3):251–9. https://doi.org/10.1007/s12519-020-00354-4.
60. Huang K, Zhang J, Wu W, Huang D, He C, Yang Y, et al. A retrospective analysis of the epidemiology, clinical manifestations, and imaging characteristics of familial cluster-onset COVID-19. *Ann Trans Med* 2020;**8**(12):747. https://doi.org/10.21037/atm-20-3759.
61. de Laval F, Grosset-Janin A, Delon F, Allonneau A, Tong C, Letois F, et al. Lessons learned from the investigation of a COVID-19 cluster in Creil, France: effectiveness of targeting symptomatic cases and conducting contact tracing around them. *BMC Infect Dis* 2021;**21**(1):457. https://doi.org/10.1186/s12879-021-06166-9.
62. Nsekuye O, Rwagasore E, Muhimpundu MA, El-Khatib Z, Ntabanganyimana D, Kamayirese EN, et al. Investigation of Four Clusters of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Rwanda, 2020. *Int J Environ Res Public Health* 2021;**18**(13):7018. https://doi.org/10.3390/ijerph18137018.

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Original Research

Characteristics and patterns of health and social service use by families with babies and toddlers in Germany

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ABSTRACT

Objectives: In the field of family health, cross-sectoral collaboration is promoted to reach vulnerable groups and overcome the prevention dilemma. To understand the extent to which these measures counteract the effects of social inequality with respect to health and social service uptake, we aim to identify socio-economic, health-related and psychosocial characteristics and patterns that are associated with the (non-)use of services.

Study design: This was a German representative cross-sectional study of 6860 mothers with a child younger than 48 months who answered the written questionnaire during child developmental examinations at paediatric practices in 2015.

Methods: Associations were measured using logistic regression, and characteristics of user patterns were analysed using latent class analysis.

Results: Mothers using universal services were less likely to report psychosocial stress and had more likely more socio-economic resources than mothers who did not use these services. The selective services *pregnancy counselling* (18.2%) were predominantly used by mothers who considered abortion during pregnancy (Odds Ratio [OR] = 3.9), mothers who received social welfare benefits (OR = 2.4), single parents (OR = 1.6) and mothers without social support (OR = 1.5). Four patterns of service use were identified: *multi-service users* (5.6%), *low-service users* (22.5%), *medical service users* (30.5%) and *medical and social service users* (41.6%). Families with less socio-economic resources were found in both the *low-service group* and the *multi-service group*; *multi-users* were more likely to have children with adverse perinatal characteristics and parenting stress.

Conclusion: We discuss whether *low-service users* are hard to reach, whereas *multi-users* are difficult to supply. Overall, there is a need to strengthen early psychosocial support.

Introduction

Early childhood is a sensitive phase of life, which puts high demands on parents and is salient for children's future development. In several countries, preventive services for families with small children have been established to support them and respond to their various needs. However, existing literature suggests that families in need may nevertheless be difficult to reach because of their lower acceptance of and demand for such public services.[1,2] The resulting prevention dilemma is not only an underuse of prevention services for families in need but also an overuse of services for families with more socio-economic resources.[3] In discussing this phenomenon, particular attention has been paid to the role of financial resources. Unsurprisingly, access to preventive services is limited if these services are costly and income is scarce.[4,5]

The present article aims to shed light on characteristics and patterns of health and social service use among families with small children. Our study uses nationally representative data from Germany, where health services and social services are provided free of charge, thus allowing an analysis of the role of socio-economic and psychosocial characteristics rather than issues of financial accessibility.

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The prevention dilemma

Linked to financial resources, education is not only a core characteristic of socio-economic status but also a key predictor of service use. For example, high parental education is associated with a higher probability of regular attendance at paediatric child development examinations[6] and more frequent use of early intervention services.[7] Low education and its associated risk factors, in combination with barriers to health and social service access, may lead to health problems and illness, which, in turn, contribute to an increased need for medical care consumption.[8] The results of this study in Sweden with 9000 children at the 8-month check-up indicate that social inequality and its determinants pass through generations and lead to disadvantages for children of socio-economically deprived parents.

Patterns of service use

Few studies have examined the combined use of different services and the characteristics of the populations who utilise or underutilise these services (except:[9,10]). A study with 869 children aged 5 years provided four groups with high-service and low-service use and two groups with moderate-service use. The *low-service group* consisted of the most socially and economically disadvantaged families.[9] The *multi-users* were families of children with behavioural health issues, who could mitigate negative outcomes related to poorer health and cognitive functioning in later years.[9] Another study including 531 low-income families with children at age 2 also identified four user groups of prevention services.[10] Both *multi- and low-service users* had healthcare-related issues but differed in their financial, housing and employment status, their need for family planning, their child's physical health, as well as their experiences with mental health problems or substance abuse.[10] In both studies, high parental education and impaired child health were found to predict higher levels of service use.[9,10] Social support[10] and maternal well-being[9] were associated with different patterns indicating that psychosocial characteristics are important determinants for utilisation of health and social services.

Conditions and provisions in Germany

Germany provides a suitable context for understanding the psychosocial characteristics that impede or encourage the use of prevention services because the families themselves have almost no direct cost barriers to their access to health and social services. Despite Germany's social insurance system, where most services are covered by the health and social insurance entities, there is still a social gap in service uptake services and health status.

However, one major barrier to the utilisation of the social welfare system is that the use of some services (e.g. child and youth welfare services) is sometimes perceived as stigmatising.[2] In contrast, services provided within the context of the healthcare system highly valued as paediatricians and family doctors are perceived as persons of trust. As almost all families with small children attend the regular paediatric child development examinations (up to 99%[11]), doctors may serve as important collaborators in identifying and referring families in need to targeted prevention programmes.[2] To overcome the prevention dilemma, cross-sectoral collaboration has been increasingly promoted to reach vulnerable groups.[12]

In Germany, the national programme on *Early Childhood Intervention* (ECI) supporting early preventive services for families from pregnancy through the first three years of a child's life was established in 2006.[2] So far, we knew little about the characteristics of the families using preventive services and the different user groups of service constellations. Most importantly, we did not know whether these services reach families with psychosocial stress and the extent to which the prevention dilemma is reflected in the patterns of service use.

The aim of our study is therefore (1) to analyse the use of universal, selective, and indicated prevention services and its associations with socio-economic, maternal and child health, and psychosocial characteristics; (2) to identify patterns of service use; and (3) to examine differences between those patterns with regards to socio-economic, maternal and child health, and psychosocial characteristics.

Methods

Data collection

The *KiD 0-3* main study was conducted in 2015 as a nationally representative, cross-sectional study of mothers and fathers. The families were invited to complete questionnaires during child development examinations (so-called U3 to U7a screening) at community-based paediatric practices. It was embedded in a study series which was conducted as part of the long-term policy programme *Federal Initiative for Early Childhood Intervention* from 2012 to 2017 (see https://www.fruehehilfen.de), described elsewhere.[13–15] A total of 271 paediatric practices participated (15% of the gross sample $n = 1859$ randomly drawn from a nearly complete address file of all paediatric practices). A total of 8063 parents (response rate 75%) completed the questionnaire independently and anonymously in accordance with the Declaration of Helsinki.[16] The present analyses are based on the subsample of mothers with a child up to 48 months of age ($n = 6860$).

Data measurement

The questionnaire contained questions on the family's socio-economic, health and psychosocial characteristics and questions about their knowledge and use of regular prevention services. The included characteristics were selected based on a literature search of systematic reviews on risk factors for child maltreatment and developmental deficiencies.[17–19] As far as possible, indicators were based on established psychometric instruments (see Appendix A). Based on the health behaviour model,[20] we included socio-economic characteristics of the families, maternal pregnancy-related and child health characteristics, child regulatory problems, and maternal psychosocial characteristics in the analyses of this study.

The knowledge and use of universal, selective and indicated prevention services (see Table 1) was measured by dichotomous questions (yes/no).

Statistical analyses

After descriptive analyses for each prevention service (see Appendix B), logistic regression models were used to examine the associations between the most frequently used services and the socio-economic, maternal and child health and psychosocial characteristics. We used a complex survey weighting as product of design weighting for the German federal states and a post-stratification weighting adjusting for individual characteristics (maternal age, nationality, education, vocation and household composition) of the German Micro Census 2011.[21] For regression models, listwise deletion was used. Child's regulatory problems were not included in the model for pregnancy counselling, as this

Table 1
Description of prevention services in Germany in *KiD 0-3*.

Universal prevention
Prenatal classes
A nationwide universal medical prevention service for expecting mothers (and partners) at 28-30 weeks of pregnancy, with the aim of informing parents, preparing families for birth and assuaging fears or worries. Prenatal classes are paid by the statutory health insurance (with a maximum duration of 14 h) and conducted out by a licensed midwife or physiotherapist.
Midwifery assistance from birth up to week 8
A nationwide universal, mainly medical, preventive service for mothers (and partners) beginning at the weeks 9th to 12th of pregnancy (time point of the first antenatal examination) up to the 8th week after birth, with the aim of providing information and support for questions concerning pregnancy and birth, preventive examinations such as weight control or monitoring of the child's heartbeat, preparation for birth, exercise after the birth, and support in case of breastfeeding difficulties as well as help with pregnancy problems and during birth. During the first 10 days after the birth, the mother is entitled to a daily visit and thereafter to further counselling. The statutory health insurance pays for this service, but the families must organise contact with the midwives themselves.
Medical aid for mothers (e.g. postnatal exercises)
A nationwide universal medical prevention service for mothers in the 6th–8th week after birth with the aim of health promotion and prevention of health problems. The statutory health insurance covers the costs of, for example, postnatal exercises gymnastics and similar services (over a maximum duration of 10 h), carried out by a licensed midwife or provider.
Parent–child groups (e.g. breastfeeding group, toddler group and baby swimming)
A nationwide frequently used early service consisting of toddler groups, play-groups, music groups or parent–child gymnastics for children aged 1–3 years. The concept serves to give parents space for the exchange of experience and information as well as for social contact. At the same time, the children can experience a variety of play situations and social contacts with other children and adults, which are important for comprehensive development. The main providers are family centres, which are headed by pedagogues, but adult education centres, mother's centres and similar institutions also offer the courses.
Services in family centres or city district centres (e.g. parents café)
A nationwide universal early educational prevention that offers family support and counselling, whereby the family centres should form the nodes in a network of education, parenting and care in the natural environment of the families. In this way, family centres can create a place of social exchange between parents in a family-friendly atmosphere. The services in the family centres or city district centres are often nationalised or co-financed by churches and non-profit organisations.
Parenting programmes (e.g. Triple P – Positive Parenting Programme)
These nationwide programmes are designed as universal or selective prevention, depending on the course concept. Their aim is to strengthen parenting competencies, teach supportive parenting styles and thus to prevent developmental disadvantages for children. The courses are often organised by child welfare services, for example, in family centres or child guidance centres. Parents are also referred to parenting programmes by Kindergarten teachers in the day care centres, who often recognise early on whether children and parents need support and assistance. The costs vary, often there is a discount for low-income families.
Selective prevention
Pregnancy counselling
A selective prevention service for women and couples, often from pregnancy to the first 3 years, for counselling and support in questions on pregnancy, pregnancy conflicts, unwanted pregnancy, the situation of single parents and other legal and medical issues. The state-approved pregnancy counselling centres with pedagogically trained professionals provide a nationwide range of services and can financially support large families with many children, single parents in financial hardship and pregnant women in distress. The financial assistance scheme is covered through a stable funding arrangement (Federal Foundation), granted by the Federal Government.
Child guidance centres
A nationwide selective prevention service for providing counselling on, for example, general parenting issues, problems and conflicts between family members, separation, divorce and development issues. Counselling is provided by psychologists and social workers, often in a multidisciplinary team. It is offered by independent and municipal agencies and is free of charge for families, as it is a service provided by child and youth welfare services.
Specialised counselling (e.g. crying/feeding/sleeping patterns)
A nationwide selective prevention service for counselling and support (e.g. counselling sessions instructions on how to deal with the child and calming strategies, therapeutically guided group offers) by specialised professionals (e.g. medical doctors, psychologists, midwives and social workers) with a focus on families with children aged 0-3 years with early regulatory disorders. The first point of contact is often the paediatrician who makes the diagnosis, and therefore, the costs are covered by the health insurance company.
Home-visiting programmes
A selective prevention service offered by local networks of early childhood intervention (ECI), a cooperation between health service and child welfare system. It is characterised by the home-visiting work of specialised professionals (family midwives and family nurses) and should therefore have a low-threshold access. Regular home visits are intended to provide comprehensive support (accompanied visits to the doctor, answering questions about the child and coping with everyday tasks) for families with psychosocial stress with children aged between 0 and 3 years. It is provided nationwide but with local adaptions. The costs are covered by the local authorities.
Indicated prevention
Early intervention for special needs (e.g. disabilities)
A nationwide rather indicated prevention service for families with children with developmental delays and (threatening) disability. The aim is to mitigate or eliminate possible consequences through early intervention. The educational and therapeutic measures can extend to school enrolment (depending on the federal state or institution). They are carried out by different professional groups, such as doctors, psychologists, curative pedagogues, physiotherapists, speech therapists and occupational therapists. The aim is to help children (and their parents) to deal with the (possible) impairment of their child, development promotion and to advise parents on legal and financial conditions. The first point of contact is often the paediatrician who prescribes the treatment, so that the costs are covered by health insurance companies. In addition, the services can also be financed by the social welfare institutions of the child and youth welfare service.

service use happened before child's birth. The latent class analysis was conducted to identify different classes of service users. The decision for the best number of latent classes was based on a comparison of different information criteria, including but not limited to Bayesian information criterion (BIC). The overall precision of classification was assessed by the relative entropy (E_K), ranging between 0 and 1. To assess the class-specific classification certainty, we used the modal class assignment proportion (mcaP) to compare for model specification errors as large distance to the model-estimated marginal class proportion (πk). Details can be found in the supplementary material (see Appendix C-E). We extended the model by including maternal education and age of child as predictors of the classes. The best fitting model was applied to another national sample of 2105 families with children 0–6 for validation (data obtainable on request). Finally, we checked the associations (see Appendix F) and calculated logistic regression between the conditional latent classes derived from the model and the health and socio-economic characteristics.[22] Data analyses were carried out using Stata (version 15.1) by StataCorp.[23]

Results

In accordance with the first study aim, Table 2 presents the descriptive overview of knowledge and use of the different health and social services, classified in universal, selective and indicated prevention. The use of *prenatal classes* (61.2%), *midwifery assistance* (86.9%), *medical aid for mothers* (57.9%) and, in part, *pregnancy counselling* (18.2%) are covered by the statutory health insurance. The nearly nationwide (2015: available in 87.9% of communities[24]) longer-lasting *home-visiting programme* is offered to families in difficult circumstances as psychosocial support service.[2] In our study, 29.5% of families reported that they had been offered the service (not presented), and 13.1% of families reported that they had used it. *Early intervention*, a nationwide indicated service for families with a child at risk for a disability, was used by only 5.2% of the families.

Based on the rough classification of universal, selective and indicated services, we chose the services with the most frequent uptake within each of these groups and examined associations between service use and the respondent's characteristics. Table 3 shows the findings of these logistic regression analyses. The universally available service, *midwifery assistance,* was more likely to be used by non-migrant mothers and mothers who did not receive social welfare benefits. These mothers were more likely to have high levels of educational attainment and were less likely to report psychosocial stress than mothers who did not use the service. Selective *pregnancy counselling* was used by more disadvantaged families. These respondents often were recipients of social welfare, experienced pregnancy-related health issues, particularly thoughts of abortion and first child and reported a lack of social support. Families with adverse perinatal characteristics such as disability, preterm birth, or low birth weight were more likely to use *home-visiting programmes* and indicated *early intervention*. The use of *early intervention* is also associated with child's feeding regulatory problems.

To address the second study aim, we identified patterns of service use using latent class analysis (Table 4). The results of the latent class analysis indicated four groups. We improved the model by including education and age of child as covariates and obtained a stable four-class solution based on the BIC and other information criteria. The relative entropy (0.59) is somewhat weak (see Appendix C). We referred to the discovered patterns as *low-service users* (22.5%), *multi-service users* (5.6%), *medical service users* (30.5%) and *medical and social services users* (41.6%). Fifty-eight percent of the *low-service group* (class 1) had used *midwifery assistance* and none of the other services. The *multi-service users* (class 2) used a broad and cross-sectoral range of diverse services. The *users of medical service only* (class 3) were characterised by the uptake of *prenatal classes* (71.9%), *midwifery assistance* (97.1%) and *medical aid for mothers* (69.5%). The services used by the *medical and social services users* (class 4) were characterised by both medical and social services, predominantly *midwifery assistance* (99.5%) and *parent–child groups* (98.1%).

With regard to study aim 3, the results of the logistic regression models are presented in Table 5. We compared each of the classes from the latent class analysis to the *medical service users* (class 3) to analyse the associations between the derived classes and relevant characteristics. Mothers with low levels of educational attainment and mothers who received social welfare benefits were overrepresented in the two extreme groups: in the *low-service* or *multi-service user groups*. Unplanned pregnancy and maternal considerations of abortion during pregnancy were more likely to be reported in both groups. In particular, families with child-related health problems and parenting stress were more likely to be *multi-users*. The group of *medical and social service users* consisted of well-educated, socially well-situated mothers predominantly without pregnancy- or health-related problems, who were often seeking those services for their first child. They were also less likely to have a child with sleeping problems and were less likely to report a lack of social support for questions about their child.

Table 2
Use of prevention services of the health care and social system since child birth.[a]

	Use	
	%	*N*
Universal prevention		
Midwifery assistance	86.94	6452
Prenatal classes	61.23	6493
Medical aid for mothers (e.g. postnatal exercises)	57.88	6449
Parent–child group	54.80	6443
Family (district) centres	13.84	6458
Selective prevention		
Pregnancy counselling	18.21	6418
Home-visiting programmes	13.08	6333
Parenting programmes	7.59	6432
Specialised counselling (e.g. crying patterns)	6.25	6452
Child guidance centres	4.78	6435
Indicated prevention		
Early intervention for special needs (e.g. disabilities)	5.19	6411

[a] Design and poststratification weighting procedure as described in the Methods.

Discussion

Our study aimed to analyse the use of universal, selective and indicated prevention services to identify patterns of service use and to explore the relationship between patterns of service use and socio-economic, maternal and child health–related and psychosocial characteristics. Generally, universal services were used by the majority of families, whereas selective services reached different target groups, and the indicated *early intervention* was more likely to be used by families with a child experiencing adverse perinatal characteristics and feeding problems. This suggests that the system is working generally as it should be. Detecting patterns of service utilisation provided additional information on families who are potentially under- or over-using health and social services.

Service use of disadvantaged families

One of our key questions addressed the access of social disadvantaged families to preventive services. In this study, users of the universal medical service of *midwifery assistance* were less psychosocially stressed. Universal services are wide reaching, but still, families with low levels of educational attainment, recipients of social welfare benefits or migration backgrounds are underserved or have barriers to service utilisation. Selective services addressed diverse target groups with higher levels of psychosocial stress or health issues. Only *pregnancy counselling* reached mothers with psychosocial stress, that is, feelings of no social support. One explanation might be that families in *pregnancy counselling* often get help for financial support. In contrast, *home-visiting programmes* reached families with a migration background, young mothers and adverse perinatal characteristics more likely. These families are possibly easy to identify and therefore may be more likely to be offered support. In contrast, mothers with signs of depression or anxiety symptoms, parenting stress and low social support are hard to identify and there is still an underprovision.[25]

Table 3
Use of midwifery assistance, pregnancy counselling, home-visiting programme and early intervention in logistic regression models[a,b]

	Midwifery assistance	Pregnancy counselling	Home-visiting programme	Early intervention
	OR/95% CI	*OR/95% CI*	*OR/95% CI*	*OR/95% CI*
Socio-economic characteristics				
Migration background	0.40***	1.1	1.33*	0.57**
	0.31, 0.52	0.89, 1.35	1.06, 1.67	0.38, 0.85
Social welfare receipt	0.62**	2.40***	1.03	1.18
	0.46, 0.84	1.82, 3.16	0.78, 1.36	0.70, 1.99
Single parent household	1.15	1.57*	1.18	1.19
	0.79, 1.66	1.08, 2.27	0.82, 1.69	0.70, 2.00
Education (Ref: High)				
Low	0.31***	1.23	1.39	1.22
	0.21, 0.45	0.87, 1.73	0.94, 2.04	0.65, 2.30
Medium	0.65**	1.29*	1.2	1.24
	0.49, 0.85	1.06, 1.57	0.98, 1.45	0.90, 1.71
Age of mother in years				
≤24	1.14	1.60**	1.71**	0.26**
	0.78, 1.66	1.20, 2.14	1.24, 2.36	0.12, 0.59
≥35	1.13	0.63***	1.08	1.18
	0.85, 1.51	0.51, 0.78	0.86, 1.35	0.84, 1.65
Age of child in months (metric)	1	1	1	1.01*
	0.99, 1.01	0.99, 1.01	0.99, 1.01	1.00, 1.03
Pregnancy- and health-related characteristics				
Pregnancy intention (Ref: Probably intended)				
Unplanned pregnancy	0.51***	1.60***	0.73*	1.37
	0.39, 0.66	1.26, 2.03	0.54, 0.99	0.91, 2.06
Unplanned pregnancy and abortion thoughts	0.68	3.87***	0.95	1.27
	0.42, 1.11	2.67, 5.60	0.56, 1.63	0.64, 2.53
Smoking/alcohol during pregnancy	0.47***	0.70*	1.03	1.23
	0.36, 0.62	0.51, 0.95	0.74, 1.45	0.74, 2.06
Regular pregnancy check-ups	2.48**	1.18	0.71	0.98
	1.27, 4.85	0.59, 2.37	0.39, 1.29	0.34, 2.81
First child	1.85***	1.22*	1.13	0.71*
	1.47, 2.34	1.02, 1.46	0.93, 1.36	0.51, 0.97
Adverse perinatal characteristics	0.83	0.96	1.64***	4.25***
	0.59, 1.15	0.74, 1.25	1.26, 2.14	3.14, 5.76
Child's current regulatory problems				
Feeding problems	0.98		1.22	2.83**
	0.39, 2.48		0.55, 2.69	1.42, 5.62
Sleeping problems	1.06		1.21	0.73
	0.76, 1.49		0.91, 1.62	0.42, 1.28
Crying problems	0.74		1.13	2.18
	0.40, 1.36		0.57, 2.21	0.96, 4.95
Maternal current psychosocial characteristics				
No social support	0.82	1.45**	1.16	1.15
	0.64, 1.06	1.14, 1.84	0.89, 1.52	0.79, 1.65
Signs of depression or anxiety symptoms	1	1.18	1.12	1.39
	0.74, 1.36	0.92, 1.51	0.83, 1.51	0.91, 2.10
Parenting stress	1.33	1.01	0.9	1.42
	0.97, 1.81	0.79, 1.29	0.67, 1.21	0.99, 2.03
N	5008	4983	4938	4997
F	17.51***	18.42***	3.6***	8.44***
R^2 (McKelvey for weighted data)	0.193	0.145	0.035	0.163

OR: odds ratio; 95% CI: 95% confidence interval; Ref: reference category.
[a] Design and poststratification weighting procedure as described in the Methods.
[b] $P < .1$; *$P < .05$; **$P < .01$; ***$P < .001$.

Patterns of service use

Our four-class solution contributes to a broader perspective of service use and, in part, is consistent with the findings of earlier studies.[9,10] Consistent with these previous studies, we identified four patterns of user groups, and high education and poor child health predicted higher service use. Also consistent, the *low-service users* mainly consisted of socio-economically disadvantaged families.[9] *Low-service users* in this study were a small group. It is possible that these families are hard to reach because of low acceptance of support and/or health literacy. It might be a group that is still underserved by health and social services. This finding suggests that socio-economic characteristics remain structural core mechanisms of the prevention dilemma.

In contrast, the *multi-users users* might be families with serious child health problems. Therefore, they could more easily be detected by medical doctors and other professionals to be encouraged to take the help they need. As the *multi-users* are more likely to be socio-economically disadvantaged and have more likely parenting stress, this group may not be overserved, but the intense support corresponds with their multiple needs. The challenges the *multi-users* face may also include finding the best fitting service targeting their specific needs. Also Leventhal et al.[9] identified a specialised group of *health service users*, which was dominated by

Table 4
Service users according to the four-class solution from latent class analysis and including education and age of child as covariates.[a]

	Class 1: low-service users (%)	Class 2: multi-service users (%)	Class 3: medical service users (%)	Class 4: medical and social service users (%)
Class proportion	22.45	5.55	30.45	41.55
Prenatal class	12.69	51.50	71.93	92.11
Midwifery assistance	57.91	85.07	97.09	99.49
Medical aid for mothers (e.g. postnatal exercises)	4.86	43.59	69.46	92.77
Parent–child group	12.77	62.13	45.67	98.15
Family district centre	0.30	18.62	1.57	17.72
Parenting programme	2.37	35.65	3.37	29.73
Pregnancy counselling	19.56	51.21	15.36	11.34
Child guidance centre	1.98	33.56	0.91	3.78
Specialised counselling (e.g. crying patterns)	0.98	18.84	3.07	10.97
Home-visiting programme	9.78	33.35	11.94	11.56
Early intervention for special needs (e.g. disabilities)	3.35	23.80	1.98	5.33

[a] Design and post-stratification weighting procedure as described in the Methods, $n = 6564$.

health characteristics such as low birthweight.[9] However, our results differ from other study results where *multi-users* were characterised by good maternal health, a given health insurance status[9] and non-immigrant status.[10] One explanation for the differences might result from the German healthcare system, in which basic insurance provides many social and health services for the majority of the population free of additional costs. Moreover, *multi-users* in *KiD 0-3* might have benefitted from Germany's ECI programme that promotes systematic collaboration between health and child or youth welfare sectors and has a 'pilotage service,' including identification of families in need, counselling and referral to appropriate support services.[2]

The users of *medical and social services* have better social situations than the other user groups. Similarly, Leventhal et al.[9] showed that the *medical and social services users* are less socioeconomically burdened and, in a follow-up examination, evidenced superior cognitive, behavioural and health outcomes. This user group might be described – in terms of the prevention dilemma – as a population group, which has the educational and economic resources to get the service they may need.

Study limitations and strengths

As the study is a cross-sectional study, no causal conclusions can be drawn. However, it is a national representative study with a huge sample size. Furthermore, data are based on parental self-reported responses that may be subject to social desirability, but we get in-depth information on a broad range of psychosocial characteristics that could not be measured economically in another way. From a methodological point of view, the regression model

Table 5
Logistic regression models of service users.[a,b]

		Class 1: low-service users		Class 2: multi-service users		Class 4: medical and social services users	
		OR	95% CI	OR	95% CI	OR	95% CI
Socio-economic characteristics							
Migration background		1.86***	1.50, 2.30	1.18	0.86, 1.61	0.54***	0.45, 0.66
Social welfare receipt		1.69***	1.27, 2.24	2.09***	1.43, 3.03	0.57***	0.42, 0.76
Single parent household		1.45*	1.03, 2.05	1.91**	1.18, 3.09	0.88	0.59, 1.32
Education (Ref: High)	Low	12.45***	8.59, 18.04	8.97***	5.29, 15.20	0.09***	0.03, 0.22
	Medium	1.90***	1.53, 2.36	2.03***	1.36, 3.02	0.68***	0.57, 0.80
Age of mother in years	≤24	1.52*	1.08, 2.12	1.2	0.75, 1.91	0.37***	0.25, 0.56
(Ref: 25–34)	≥35	0.92	0.74, 1.15	0.98	0.65, 1.47	0.98	0.83, 1.17
Age of child in months		1.02***	1.01, 1.03	1.05***	1.04, 1.06	1.04***	1.03, 1.05
Pregnancy- and health-related characteristics							
Pregnancy intention	Unplanned pregnancy	1.68***	1.32, 2.15	1.3	0.87, 1.96	0.79*	0.63, 0.99
(Ref: Probably intended)	Unplanned pregnancy and abortion thoughts	1.3	0.78, 2.15	2.10**	1.24, 3.57	0.67	0.43, 1.03
Smoking/alcohol during pregnancy		1.78***	1.31, 2.41	1.33	0.85, 2.09	0.48***	0.32, 0.71
Regular check-ups		0.42*	0.21, 0.86	0.38*	0.16, 0.93	1.4	0.72, 2.70
First child		0.60***	0.49, 0.74	0.70*	0.51, 0.96	1.40***	1.20, 1.64
Adverse perinatal characteristics		1.1	0.83, 1.46	1.74**	1.14, 2.64	0.68**	0.53, 0.86
Child's current regulatory problems							
Feeding problems		1.12	0.43, 2.90	1.15	0.41, 3.23	1.14	0.64, 2.02
Sleeping problems		1.12	0.82, 1.53	1.06	0.67, 1.68	0.79*	0.63, 1.00
Crying problems		1.17	0.58, 2.36	1.22	0.50, 3.01	1.11	0.62, 1.97
Maternal current psychosocial characteristics							
No social support		1.2	0.95, 1.51	1.1	0.79, 1.55	0.81*	0.66, 0.99
Signs of depression or anxiety symptoms		1.06	0.81, 1.38	1.01	0.67, 1.51	1	0.81, 1.23
Parenting stress		0.84	0.65, 1.09	1.49*	1.02, 2.18	0.95	0.74, 1.22
R^2		0.362		0.293		0.168	

OR: odds ratio; 95% CI: 95% confidence interval; ref: reference category.
[a] Design and poststratification weighting procedure as described in the Methods $N = 5111$. $F = 17.61$. Reference category class 3: medical service users.
[b] $P < .1$; *$P < .05$; **$P < .01$; ***$P < .001$.

based on a latent class analysis must be seen as explorative because of the group assignments based on probabilities. However, they can provide insight for further research questions and extended finite mixture models.

Conclusion

The *KiD 0-3* study was the first one that measured the use of single services of universal, selective and indicated prevention programmes in early childhood in Germany. By assessing a broad range of socio-economic, health-related and psychosocial characteristics, we were able to describe families using prevention services and identify different patterns of service use. In the developing field of family-focused health prevention, *KiD 0-3* provided data that help us to understand how families use different services and which families are currently easier to reach for health and social services. Universal services are used by less burdened families, and selective and indicated services seem to basically reach their target groups. However, migration background and low educational attainment remain barriers to the use of prevention services. Further research is needed to understand the barriers in service uptake. The results also suggest that it is important to develop tailor-made support services locally with low threshold (e.g. home-visiting programmes by well-regarded professionals).[2,26] In our German example, there is not much evidence for an overprovision of services, as the *multi-service user group* is primarily comprised of families with health and psychosocial difficulties trying to access the help they need. The analyses of the combination of service use revealed patterns of underserved families, and further research is necessary to understand the needs of these families and to find possibilities to reach them.

Author statements

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Ethical approval

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Competing interests

None declared.

Consents to participate and publication

Participants answered the questionnaire anonymously and gave informed consent in line with the 1964 Helsinki Declaration and its later amendments.

Author's contribution

S.M.U. contributed to conceptualisation, methodology, software, validation, formal analysis, data curation, writing the original draft visualisation. S.W. contributed to reviewing and editing the article and supervision. I.R. contributed to investigation and reviewing and editing the article. C.L. contributed to conceptualisation, investigation, resources, reviewing and editing the article and project administration.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.11.018.

References

1. Neumann A, Renner I. Barrieren für die Inanspruchnahme Früher Hilfen: Die Rolle der elterlichen Steuerungskompetenz. [Obstacles for the use of early childhood prevention services: The role of expected ability to control sources]. *Bundesgesundheitsblatt, Gesundheitsforsvchung, Gesundheitsschutz*. 2016;**59**(10):1281–91. https://doi:10.1007/s00103-016-2424-6.
2. Renner I, Saint V, Neumann A, Ukhova D, Horstmann S, Boettinger U, et al. Improving psychosocial services for vulnerable families with young children: strengthening links between health and social services in Germany. *BMJ* 2018;**363**:k4786. https://doi:10.17623/BZGA:224-E-Bbook-2018.
3. Franzkowiak P. Prävention und Krankheitsprävention. In: *Leitbegriffe der Gesundheitsförderung und Prävention: glossar zu Konzepten, Strategien und Methoden*; 2018. https://doi:10.17623/BZGA:224-i091-2.0. [Accessed 5 June 2021].
4. AAP Council on community pediatricians. Poverty and child health in the United States. *Pediatr* 2016;**137**:e20160339. https://doi:10.1542/peds.2016-0339.
5. Rosenbach ML. The impact of Medicaid on physician use by low-income children. *Am J Publ Health* 1989;**79**:1220–6. https://doi:10.2105/ajph.79.9.1220.
6. Prickett KC, Augustine JM. Maternal education and investments in children's health. *J Marriage Fam* 2016;**78**:7–25. https://doi:10.1111/jomf.12253.
7. McManus BM, Carle AC, Rapport MJ. Classifying infants and toddlers with developmental vulnerability: who is most likely to receive early intervention? *Child Care Health Dev* 2014;**40**:205–14. https://doi:10.1111/cch.12013.
8. Mangrio E, Hansen K, Lindström M, Köhler M, Rosvall M. Maternal educational level, parental preventive behavior, risk behavior, social support and medical care consumption in 8-month-old children in Malmö, Sweden. *BMC Publ Health* 2011;**11**:891. https://doi:10.1186/1471-2458-11-891.
9. Leventhal T, Brooks-Gunn J, McCormick C, McCarton CM. Patterns of service use in preschool children: correlates, consequences, and the role of early intervention. *Child Dev* 2000;**71**:802–19.
10. Spielberger J, Lyons SJ. Supporting low-income families with young children: patterns and correlates of service use. *Child Youth Serv Rev* 2009;**31**:864–72. https://doi:10.1016/j.childyouth.2009.03.009.
11. Schmidtke C, Kuntz B, Starker A, Lampert T. Utilization of early detection examinations by children in Germany. Results of the cross-sectional KiGGS Wave 2 study. *J Health Monit* 2018;**3**:62–70. https://doi.org/10.17886/RKI-GBE-2018-100.
12. Renner I, Scharmanski S, van Staa J, Neumann A, Paul M. Gesundheit und Frühe Hilfen: Die intersektorale Kooperation im Blick der Forschung. [The health sector and early childhood intervention: intersectoral collaboration in research]. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz*. 2018;**61**(10):1225–35. https://doi:10.1007/s00103-018-2805-0.
13. Liel C, Ulrich SM, Lorenz S, Eickhorst A, Fluke J, Walper S. Risk factors for child abuse, neglect and exposure to intimate partner violence in early childhood: Findings in a representative cross-sectional sample in Germany. *Child Abuse Negl* 2020;**106**:104487. https://doi.org/10.1016/j.chiabu.2020.104487.
14. Eickhorst A, Brand C, Lang K, Liel C, Neumann A, Schreier A, et al. Die Prävalenzstudie „Kinder in Deutschland – KiD 0-3“ zur Erfassung von psychosozialen Belastungen und Frühen Hilfen in Familien mit 0-3-jährigen

Kindern: Studiendesign und Analysepotential. *Soz Passagen* 2015;**7**(2):381–7. https://doi.org/10.1007/s12592-015-0212-z.
15. Lorenz S, Ulrich SM, Sann A, Liel C. Self-reported psychosocial stress in parents with small children. Results from the Kinder in Deutschland-KiD-0-3 study: In Press. *Dtsch Arztebl Int* 2020;**117**:709–16. https://doi:10.3238/arztebl.2020.0.
16. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;**310**:2191–4. https://doi:10.1001/jama.2013.281053.
17. Stith SM, Green NM, Smith DB, Ward DB. Marital satisfaction and marital discord as risk markers for intimate partner violence: a meta-analytic review. *J Fam Violence* 2008;**23**:149–60. https://doi:10.1007/s10896-007-9137-4.
18. Parrish JW, Young MB, Perham-Hester KA, Gessner BD. Identifying risk factors for child maltreatment in Alaska: a population-based approach. *Am J Prev Med* 2011;**40**:666–73. https://doi:10.1016/j.amepre.2011.02.022.
19. Sidebotham P, Heron J. Child maltreatment in the "children of the nineties": a cohort study of risk factors. *Child Abuse Negl* 2006;**30**:497–522. https://doi:10.1016/j.chiabu.2005.11.005.
20. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? *J Health Soc Behav* 1995;**36**:1–10.
21. Federal Statistical Office of Germany (Statistisches Bundesamt). *German microcensus*. Own calculations; 2011.
22. Masyn KE. Latent class Analysis and finite mixture modeling. In: Little TD, editor. *The Oxford handbook of quantitative methods*. New York: Oxford University Press; 2013. p. 551–611.
23. StataCorp. *Stata statistical software: release*, vol. 15. College Station, TX: StataCorp LLC; 2017.
24. Küster EU, Pabst C, Sann A. *Einsatz von Gesundheitsfachkräften in den Frühen Hilfen. Faktenblatt 7 zu den Kommunalbefragungen zum Auf- und Ausbau der Frühen Hilfen*. Köln: NZFH; 2017.
25. Renner I, Hoffmann T, Paul M. Frühe Hilfen für Kinder psychisch kranker Eltern – Forschungsergebnisse des Nationalen Zentrums Frühe Hilfen. [Early childhood intervention for children of parents with mental health issues - results of the research program of the national center for early prevention]. *Prax Kinderpsychol Kinderpsychiatr* 2020;**69**(5):416–25. https://doi:10.13109/prkk.2020.69.5.416.
26. Benz M, Sidor A. Early intervention in Germany and in the USA: a comparison of supporting health services. An overview article. *Ment Health Prev* 2013;**1**:44–50.

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Original Research

Chronic exposure to nitrate in drinking water and the risk of bladder cancer: a meta-analysis of epidemiological evidence

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ABSTRACT

Objective: This study aimed to assess the association between chronic exposure to nitrate in drinking water and the risk of bladder cancer.
Study design: Meta-analysis.
Methods: After a systematic retrieval of eligible epidemiological studies, pooled odds ratios (ORs) with 95% confidence intervals (CIs) of bladder cancer for people in the highest vs the lowest categories of nitrate exposure were calculated using the fixed- or random-effects model. We conducted two separate meta-analyses, one considering nitrate exposure as nitrate concentration in drinking water and the other one as daily nitrate intake from drinking water.
Results: A total of five studies (three case–control and two cohort studies) were included. The pooled OR (95% CI) of bladder cancer for the highest vs the lowest category of nitrate concentration in drinking water was 0.98 (0.60, 1.57), and daily nitrate intake from drinking water was 1.00 (0.69, 1.45). Both meta-analyses showed high heterogeneity across studies (I^2 = 80.8% and 65.0%, respectively). Removing studies with the high risk of bias increased the risk and reduced the heterogeneity: [(nitrate concentration in drinking water: 1.36 (1.03, 1.79), I^2 = 0.0%) and (daily nitrate intake from drinking water: 1.14 (0.90, 1.46), I^2 = 8.4%)].
Conclusion: The current epidemiological evidence failed to establish a conclusive relationship between chronic exposure to nitrate in drinking water and the risk of bladder cancer. While no association and high heterogeneity across studies were detected in the two meta-analyses, removing studies with the high risk of bias increased the risk and dissolved the heterogeneity.

Introduction

Nitrate is a natural component of drinking water; however, the increasing use of nitrogen fertilizers has led to a concomitant increase in nitrate concentration in drinking water.[1,2] Ingested nitrate is absorbed from the upper small intestine and rapidly distributed to human tissue. Up to 25% of the ingested nitrate is transported to the salivary glands, where it gets concentrated, actively secreted into saliva, partly reduced to nitrite by the oral microflora, and swallowed to re-enter the stomach. Under certain physiological and pathological conditions, the nitrosation process undergoes in the stomach to form powerful nitrosating agents such as *N*-nitroso compounds that are linked to the development of numerous cancers.[3–7] Thus, the International Agency for Research on Cancer classified nitrate intake under the conditions of nitrosation as a '*probable human carcinogen*'.[8]

Although nitrate from drinking water contributes to a small share of total nitrate ingestion compared with green leafy vegetables and processed meat,[9] this share was shown to be associated with increased risk of colorectal cancer,[10] renal cancer,[11] ovarian cancer,[12] and thyroid cancer[13] resulting in huge direct and indirect costs attributed to medication and lost productivity.[14]

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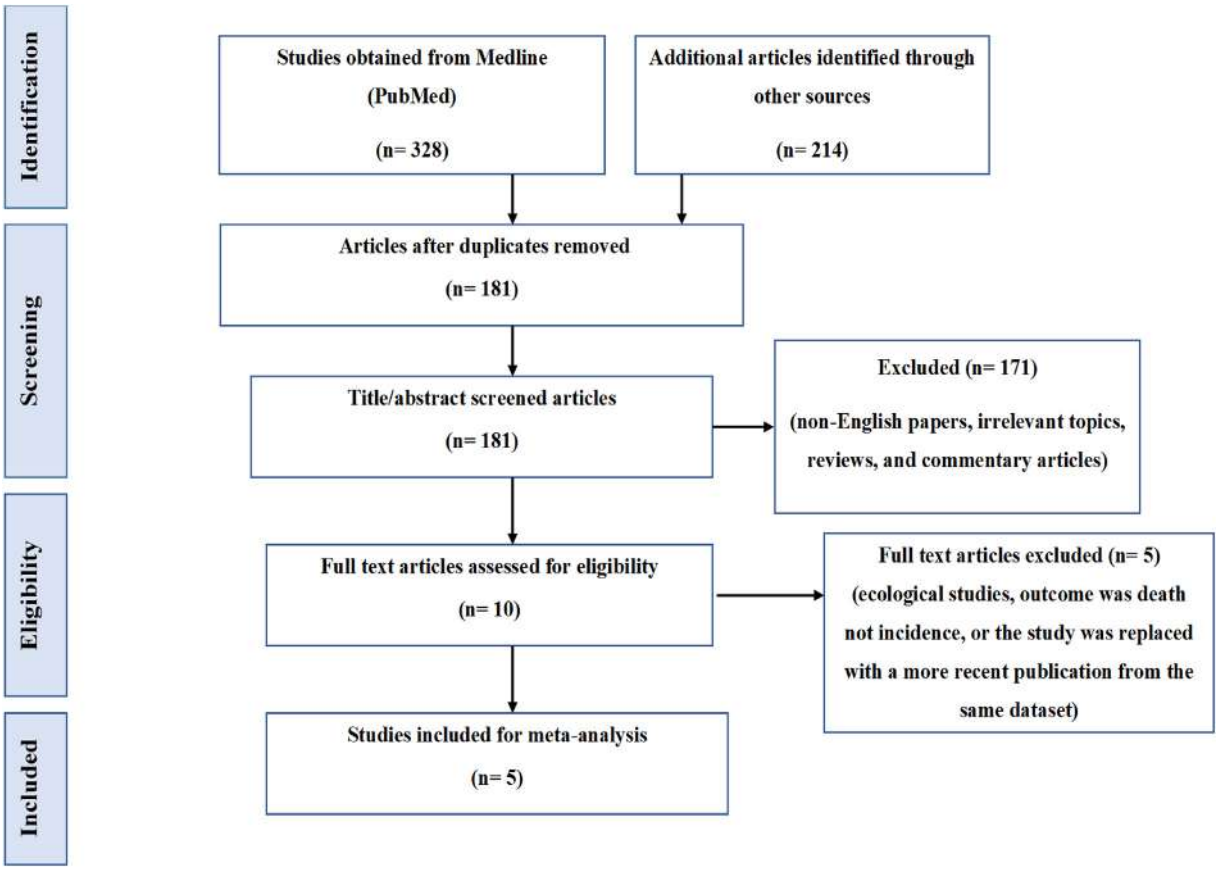

Fig. 1. Flow chart of the study selection process.

A few epidemiological studies investigated the possible association between chronic exposure to nitrate in drinking water and bladder cancer risk;[15–20] one of the most prevalent cancers worldwide with several preventable environmental and occupational risk factors,[21] and reached inconsistent conclusions. To date, one meta-analysis has addressed this relationship,[22] yet it pooled the risk of bladder cancer incidence with bladder cancer deaths, nitrate concentration in drinking water with daily nitrate intake from drinking water, and ecological studies with epidemiological studies. Besides, three more recent studies have been published since then to explore the same association.[18–20] We, therefore, conducted an updated meta-analysis to investigate the association between chronic exposure to nitrate in drinking water in the form of nitrate concentration in drinking water or daily nitrate intake from drinking water with the risk of bladder cancer based on available epidemiological evidence.

Methods

Literature search

This meta-analysis was reported according to the checklist of PRISMA.[23] We searched MEDLINE (PubMed), Google Scholar, and Cochrane Library for potential studies published in English before 30/5/2021 using the following terms: (Nitrate OR Water OR Drinking water) AND (Bladder cancer). Then, we conducted a manual search of the reference lists of retrieved articles to obtain additional studies.

Study selection

Studies were selected for analysis if they met the following criteria: (1) the exposure was nitrate concentration in drinking water (mg/L as *NO3–N*) or intake of nitrate from drinking water (mg/day as *NO3–N*), (2) the outcome was bladder cancer, (3) the study was an epidemiological study, and (4) the risk of bladder cancer among people exposed to nitrate from drinking water was calculated. No limitations were set regarding the year of publication, but no efforts were made to retrieve unpublished data.

After reviewing the full manuscripts of all studies detected by the primary search, the extracted studies were carefully reviewed to reach a shortlist of studies to be included in the current meta-analysis. Relevant information was extracted from the shortlist studies: last name of the first author, year of publication, country, study design, population characteristics, and odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for the highest vs lowest category of nitrate concentration in drinking water or daily nitrate intake from drinking water.

Eventually, we retrieved 181 studies before excluding 176 studies for irrelevance, being review articles or ecological studies, assessing bladder cancer deaths, or being replaced with a more recent publication using the same data but with a longer follow-up period, leaving a shortlist of five studies for this meta-analysis (Fig. 1).

Table 1
Characteristics of the included studies.

Study ID	Country	Design	Population	Characteristics	Nitrate concentration (mg/L) categories (Highest vs Lowest)	Daily water nitrate intake (mg) categories (Highest vs Lowest)	Covariates
Ward (2003)[16]	USA	Case-control	808 newly diagnosed cases vs 1259 controls from drivers and Medicare records	Men and women, aged 40–85 years, drinking from public supplies	Men: ≥3.09 (116 cases) vs < 0.6 (171 cases) Women: ≥2.48 (47 cases) vs < 0.67 (57 cases)	–	1,5
Zeegers (2006)[17]	Netherlands	Cohort	889 cases vs subcohort of 4441	Men and women, aged 55–69 years, drinking from 364 pumping stations and followed up for 9.3 years	–	≥1.75 (193 cases) vs ≤0.20 (167 cases)	1,2,5,6
Espejo-Herrera (2015)[18]	Spain	Case-control	531 cases vs 556 controls	Hospitalized men and women, aged >18 years, drinking from public supplies	≥2.25 (171 cases) vs ≤1.13 (250 cases)	>1.82 (184 cases) vs ≤0.91 (245 cases)	1,2,3,4,5,6
Jones (2016)[19]	USA	Cohort	258 cases out of 34,708 subjects from drivers' records	Women, aged 55–69 years, drinking from public supplies, and followed up for 25 years	>2.97 (39 cases) vs < 0.47 (29 cases)	–	1,5
Barry (2020)[20]	USA	Case-control	1037 newly diagnosed cases vs 1225 controls from drivers and Medicare records	Men and women, aged 30–79 years, drinking from public supplies and private wells	>2.07 (66 cases) vs ≤ 0.21 (259 cases)	>4.59 (59 cases) vs ≤ 0.30 (214 cases)	1,2,3,4,5

Covariates: 1: Age, 2: Sex, 3: Area, 4: Occupation, 5: Smoking, 6: Other sources of nitrates.

Statistical analysis

The fixed- or random-effects model was used to compute the pooled ORs[24] while the I^2 was calculated to test the statistical heterogeneity across studies.[25] Two forest plots showing the ORs and 95% CIs of the selected studies were presented: one for nitrate concentration in drinking water and the other one for daily nitrate intake from drinking water. Sensitivity analysis was conducted to assess the influence of individual studies on the values of OR and I^2 by leaving out studies one by one and combining the remaining studies in separate analyses. Publication bias was assessed using the regression test for funnel plot asymmetry. The quality of studies and their risk of bias were determined using the Newcastle–Ottawa Scale based on selection, comparability, and exposure/outcome. All analyses were conducted using R-3.2.0 statistical package (Metafor: A Meta-Analysis Package for R).[26]

Results

We included five epidemiological studies: three were case–control studies[16,18,20] and two were cohort studies.[17,19] The studies were conducted in the USA, the Netherlands, and Spain and were published between 2002 and 2020. Four studies calculated nitrate concentration in drinking water[16,18–20] and three studies calculated daily nitrate intake from drinking water.[17,18,20] Except for one hospital-based study,[18] all studies were population-based.[16,17,19,20] Only one study was restricted to women[19] while the remaining studies included both sexes,[16,17,18,20] however, one study[16] computed sex-specific ORs instead of the overall risk (Table 1).

Individually, no studies showed statistically significant positive associations between nitrate concentration in drinking water or daily nitrate intake from drinking water and the risk of bladder cancer. Combining the ORs of the included studies revealed no association [(nitrate concentration in drinking water: pooled OR = 0.98, 95% CI: 0.60, 1.57) and (daily nitrate intake from drinking water: pooled OR = 1.00, 95% CI: 0.69, 1.45)] (Figs. 2 and 3). Significant levels of heterogeneity across studies were noticed in both meta-analyses [(nitrate concentration in drinking water: I^2 = 80.81%, *P*-value for heterogeneity< 0.001) and (daily nitrate intake from drinking water: I^2 = 65.04%, *P*-value for heterogeneity = 0.057)] (Table 1).

No significant changes in the risk estimates or the heterogeneity across studies were observed after restricting the analysis to the studies conducted in the USA [(nitrate concentration in drinking water: pooled OR = 0.96, 95% CI: 0.53, 1.47; I^2 = 85.41%, *P*-value for heterogeneity<0.001) and (daily nitrate intake from drinking water: OR = 1.4, 95% CI: 0.89, 2.2)] or restricting the analysis to the studies with case–control design [(nitrate concentration in drinking water: pooled OR = 0.88, 95% CI: 0.51, 1.51; I^2 = 81.32%, *P*-value for heterogeneity = 0.001) and (daily nitrate intake from drinking water: pooled OR = 0.95, 95% CI: 0.45, 2.02; I^2 = 81.76%, *P*-value for heterogeneity = 0.019)] (Table 2).

However, sensitivity analyses showed that removing Ward et al. study[16] led to a statistically significant increase in the risk of bladder cancer among people exposed to the highest nitrate concentration in drinking water (pooled OR = 1.36, 95% CI: 1.03, 1.79) and the heterogeneity across studies was dissolved (I^2 = 0.00%, *P*-value for heterogeneity = 0.547). Alike, removing Espejo-Herrera et al. study[18] led to a noticeable increase, however statistically insignificant, in the risk of bladder cancer among people with the highest average daily nitrate intake from drinking water (pooled OR = 1.14, 95% CI: 0.90, 1.46) and a simultaneous decrease in the heterogeneity across studies was also observed (I^2 = 8.35%, *P*-value for heterogeneity = 0.296) (Table 3).

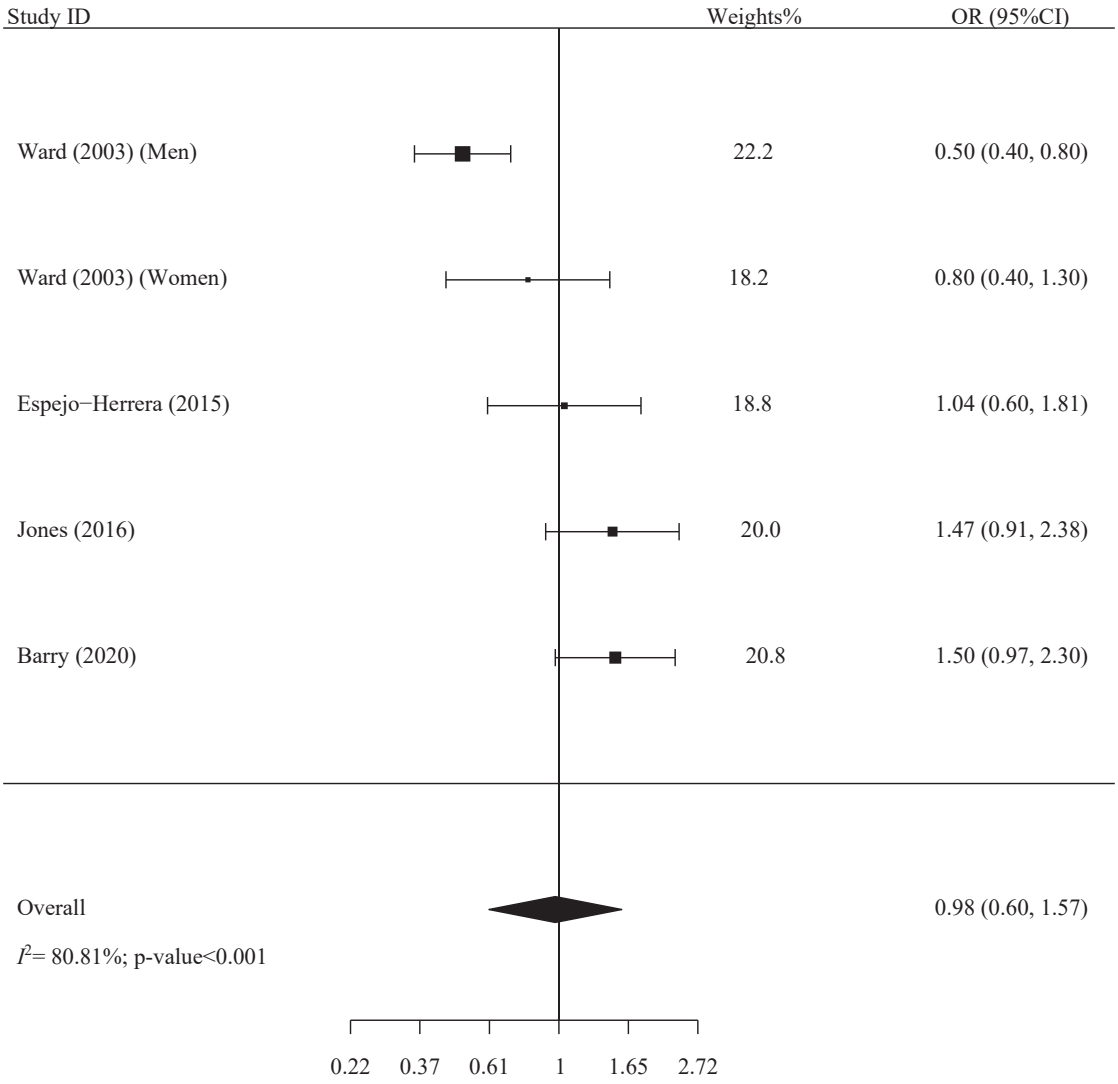

Fig. 2. Forest plot of the association between nitrate concentration in drinking water and the risk of bladder cancer.

According to the Newcastle–Ottawa Scale, three studies were of good quality and had a minimal risk of bias[17,19,20] while the studies by Ward et al. study[16] and Espejo-Herrera et al. study[18] showed a high risk of bias (Supplementary Table 1). No significant evidence of publication bias was reported [Nitrate concentration in drinking water (Z = 0.580, *P*-value for publication bias = 0.562) and daily nitrate intake from drinking water (Z = −0.179, *P*-value for publication bias = 0.858)].

Discussion

This meta-analysis showed no association between nitrate concentration in drinking water or daily nitrate intake from drinking water and risk of bladder cancer; however, removing studies with the high risk of bias increased that risk indicating difficulty in reaching a conclusive finding based on the available epidemiological evidence.

We could also notice a high level of heterogeneity across studies that was not unexpected given the variations in study designs and subjects' sociodemographic characteristics. However, stratifying the analyses by country or study design did not dissolve the heterogeneity suggesting that other factors might have contributed to this heterogeneity. One of these factors could be the differences in the cut-off values of nitrate concentration or daily nitrate intake for the highest and lowest categories. For example, the cut-off values for the highest category of nitrate concentration in drinking water ranged between 2.07 and 3.09 mg/L while the cut-off values for the lowest category ranged between 0.21 and 1.13 mg/L. Alike, the cut-off values for the highest and lowest categories of daily nitrate intake from drinking water ranged between 1.75 and 4.59 mg and 0.20–0.91 mg, respectively.

Notably, removing Ward et al.[16] and Espejo-Herrera et al.[18] studies in the sensitivity analyses led to significant drops in the heterogeneity across studies. On the one hand, Ward et al. study[16] had several limitations that were summarized in the following points: (1) a large number of subjects was excluded for different reasons, which could have affected the study representativeness, (2) the measurements of nitrate levels included the recent decades only, (3) the ORs were not adjusted for many potential confounding variables such as other sources of nitrate intake and occupation, and (4) only sex-specific risk values were shown, thus, combining both risk values in one meta-analysis, given the high heterogeneity across studies, could have overestimated the study weight. On the other hand, Espejo-Herrera et al. study[15] showed the following shortcomings: (1) the study had a hospital-based design; therefore, patients who were recruited to serve as control might have shared

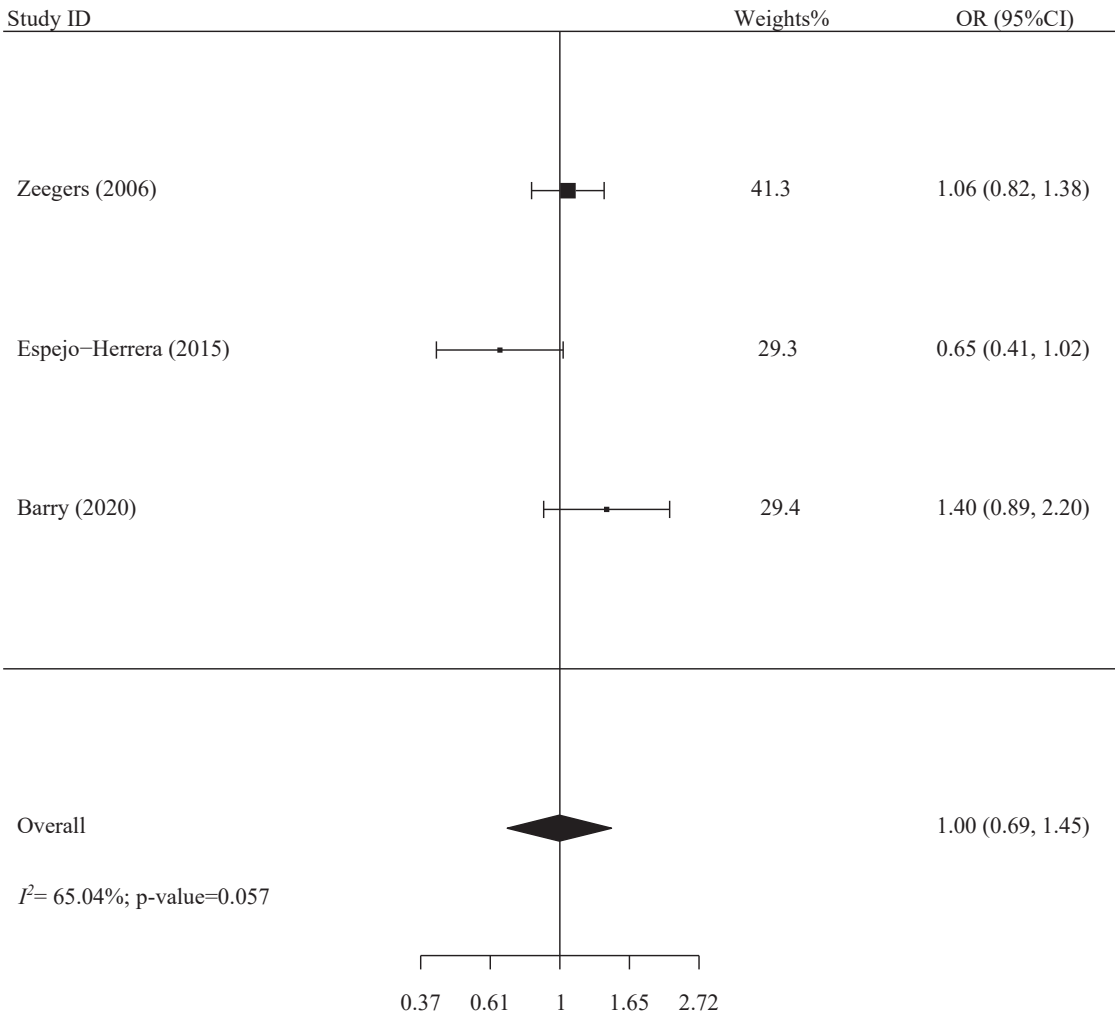

Fig. 3. Forest plot of the association between daily nitrate intake from drinking water and the risk of bladder cancer.

other potential risk factors with patients with bladder cancer, and both cases and controls mostly have carried dissimilar socio-demographic characteristics and medical histories to those of the general population, (2) the limited number of nitrate measurements, (3) nitrate measurements covered mostly recent years, (4) the study encompassed a high possibility of nondifferential misclassification bias.

Although this meta-analysis indicated that chronic exposure to nitrate in drinking water was not likely to be associated with the increased risk of bladder cancer, we cannot entirely exclude the possibility of a positive undetected association for three main reasons. First, removing Ward et al.[16] and Espejo-Herrera et al.[18] studies that showed a high risk of bias led to significant increases in the risk of bladder cancer among people exposed to the highest levels of nitrate in drinking water. Second, all included studies were conducted in developed countries where nitrate concentrations in drinking water were so far below the regulatory levels (10 mg/L). Nitrate concentrations in drinking water in some developing countries reached high levels;[8] therefore, it could be speculated that if we had reports from developing countries, we might have reached a positive association. This speculation is supported by the finding of Jones et al.[19] who detected that people exposed to nitrate concentration in drinking water > five mg/L (more than half the regulatory levels) for ≥ four years were at a higher risk to develop

Table 2
Subgroup analyses by country and study design.

Characteristics		OR (95% CI)	I^2% (*P*-value for heterogeneity)
Nitrate concentration in drinking water			
Country	USA	0.96 (0.53, 1.47)	85.41 (<0.001)
	Europe	1.04 (0.60, 1.81)	–
Study design	Case-control	0.88 (0.51, 1.51)	81.32 (0.001)
	Cohort	1.47 (0.91, 2.38)	–
Daily nitrate intake from drinking water			
Country	USA	1.40 (0.89, 2.20)	–
	Europe	0.86 (0.54, 1.46)	70.02 (0.068)
Study design	Case-control	0.95 (0.45, 2.02)	81.76 (0.019)
	Cohort	1.06 (0.82, 1.38)	–

Table 3
Sensitivity analyses by removing studies one by one and combining the remainders.

Study removed	OR (95% CI)	I^2% (*P*-value for heterogeneity)
Nitrate concentration in drinking water		
Ward (2003)[16]	1.36 (1.03, 1.79)	0.00 (0.547)
Espejo-Herrera (2015)[18]	0.96 (0.53, 1.74)	85.41 (<0.001)
Jones (2016)[19]	0.88 (0.51, 1.51)	81.32 (0.001)
Barry (2020)[20]	0.87 (0.52, 1.46)	78.65 (0.003)
Daily nitrate intake from drinking water		
Zeegers (2006)[17]	0.95 (0.45, 2.02)	81.76 (0.019)
Espejo-Herrera (2015)[18]	1.14 (0.90, 1.46)	8.35 (0.296)
Barry (2020)[20]	0.86 (0.54, 1.38)	70.02 (0.068)

bladder cancer compared with those who never experienced such high levels: OR (95% CI) = 1.61 (1.05, 2.47) and each year of exposure was associated with a six% increase in bladder cancer risk. Third, when Barry et al.[20] incorporated, in addition to public sources, measurements from private wells that usually have a relatively higher nitrate concentration than public sources,[27] they revealed a positive association between nitrate concentration in drinking water and risk of bladder cancer with substantial dose-response relationship (*P*-value for trend = 0.01).

It should be noted that this meta-analysis included two limitations that should be addressed. First, while water quality and nitrate contamination differ across continents,[8] the available evidence came from the United States and other European countries; therefore, extrapolating our results to developing countries should be done cautiously. Second, performing a linear dose–response meta-analysis was not available because linear regression was scarcely conducted in the included studies.

The current epidemiological evidence failed to reach a conclusive relationship between chronic exposure to nitrate in drinking water and the increased risk of bladder cancer. While no association and high heterogeneity across studies were detected in the two meta-analyses, removing studies with the high risk of bias increased the risk and reduced the heterogeneity. Given the limitations of the included studies, more prospective studies using representative samples are needed. Future studies in developing countries, where people are likely to be subjected to higher levels of nitrate in drinking water, are warranted.

Author statements

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Ethical approval

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Competing interests

The authors declare that they have no conflict of interest.

Author contributions

A.A. designed the study, collected the data, analyzed the data, and wrote the manuscript. E.E. and A.E. collected the data, conducted the technique review, and edited the manuscript. A.A. is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.11.019.

References

1. Davidson E, David M, Galloway J, Goodale C, Haeuber R, Harrison J. Excess nitrogen in the U.S. environment: trends, risks, and solutions. *Issues Ecol* 2012;**15**:1–17.
2. Pennino M, Compton J, Leibowitz S. Trends in drinking water nitrate violations across the United States. *Environ Sci Technol* 2017;**51**:13450–60.
3. D'Ischia M, Napolitano A, Manini P, Panzella L. Secondary targets of nitrite-derived reactive nitrogen species: nitrosation/nitration pathways, antioxidant defense mechanisms and toxicological implications. *Chem Res Toxicol* 2011;**24**:2071–92.
4. van Breda SG, Mathijs K, Sági-Kiss V, Kuhnle GG, van der Veer B, Jones RR, et al. Impact of high drinking water nitrate levels on the endogenous formation of apparent N-nitroso compounds in combination with meat intake in healthy volunteers. *Environ Health* 2019;**18**:87.
5. Loh Y, Jakszyn P, Luben R, Mulligan A, Mitrou P, Khaw K. N-nitroso compounds and cancer incidence: the European prospective investigation into cancer and nutrition (EPIC)-Norfolk study. *Am J Clin Nutr* 2011;**93**:1053–61.
6. Zhu Y, Wang PP, Zhao J, Green R, Sun Z, Roebothan B, et al. Dietary N-nitroso compounds and risk of colorectal cancer: a case-control study in Newfoundland and Labrador and Ontario, Canada. *Br J Nutr* 2014;**111**:1109–17.
7. Xu L, Qu YH, Chu XD, Wang R, Nelson HH, Gao YT, et al. Urinary levels of N-nitroso compounds in relation to risk of gastric cancer: findings from the shanghai cohort study. *PLoS One* 2015;**10**:e0117326.
8. International Agency for Research on Cancer (IARC). Ingested nitrate and nitrite and cyanobacterial peptide toxins. *IARC Monogr Eval Carcinog Risks Hum* 2010;**94**:9–464.
9. Inoue-Choi M, Virk-Baker MK, Aschebrook-Kilfoy B, Cross AJ, Subar AF, Thompson FE, et al. Development and calibration of a dietary nitrate and nitrite database in the NIH-AARP Diet and Health Study. *Publ Health Nutr* 2016;**19**:1934–43.
10. Schullehner J, Hansen B, Thygesen M, Pedersen C, Sigsgaard T. Nitrate in drinking water and colorectal cancer risk: a nationwide population-based cohort study. *Int J Cancer* 2018;**1**:73–9.
11. Jones RR, Weyer PJ, DellaValle CT, Robien K, Cantor KP, Krasner S, et al. Ingested nitrate, disinfection by-products, and kidney cancer risk in older women. *Epidemiology* 2017;**28**:703–11.
12. Inoue-Choi M, Jones RR, Anderson KE, Cantor KP, Cerhan JR, Krasner S, et al. Nitrate and nitrite ingestion and risk of ovarian cancer among postmenopausal women in Iowa. *Int J Cancer* 2015;**137**:173–82.
13. Ward M, Kilfoy B, Weyer P, Anderson K, Folsom A, Cerhan J. Nitrate intake and the risk of thyroid cancer and thyroid disease. *Epidemiology* 2010;**21**:389–95.
14. Temkin A, Evans S, Manidis T, Campbell C, Naidenko O. Exposure-based assessment and economic valuation of adverse birth outcomes and cancer risk due to nitrate in United States drinking water. *Environ Res* 2019;**176**:108442.
15. Weyer PJ, Cerhan JR, Kross BC, Hallberg GR, Kantamneni J, Breuer G, et al. Municipal drinking water nitrate level and cancer risk in older women: the Iowa Women's Health Study. *Epidemiology* 2001;**12**:327–38.

16. Ward M, Cantor K, Riley D, Merkle S, Lynch C. Nitrate in public water supplies and risk of bladder cancer. *Epidemiology* 2003;**14**:183–90.
17. Zeegers M, Selen R, Kleinjans J, Goldbohm R, van den Brandt P. Nitrate intake does not influence bladder cancer risk: The Netherlands cohort study. *Environ Health Perspect* 2006;**114**:1527–31.
18. Espejo-Herrera N, Cantor KP, Malats N, Silverman DT, Tardón A, García-Closas R, et al. Nitrate in drinking water and bladder cancer risk in Spain. *Environ Res* 2015;**137**:299–307.
19. Jones RR, Weyer PJ, DellaValle CT, Inoue-Choi M, Anderson KE, Cantor KP, et al. Nitrate from drinking water and diet and bladder cancer among postmenopausal women in Iowa. *Environ Health Perspect* 2016;**124**:1751–8.
20. Barry KH, Jones RR, Cantor KP, Beane Freeman LE, Wheeler DC, Baris D, et al. Ingested nitrate and nitrite and bladder cancer in northern New England. *Epidemiology* 2020;**31**:136–44.
21. Sanli O, Dobruch J, Knowles MA, Burger M, Alemozaffar M, Nielsen ME, et al. Bladder cancer. *Nat Rev Dis Prim* 2017;**3**:17022.
22. Wang W, Fan Y, Xiong G, Wu J. Nitrate in drinking water and bladder cancer: a meta-analysis. *J Huazhong Univ Sci Technolog Med Sci* 2012;**32**:912–8.
23. Moher D, Liberati A, Tetzlaff J, Altman D, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:2535.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials* 1986;**7**:177–88.
25. Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60.
26. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Software* 2010;**36**:1–48.
27. Burow K, Nolan B, Rupert M, Dubrovsky N. Nitrate in groundwater of the United States, 1991-2003. *Environ Sci Technol* 2010;**44**:4988–97.

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Short Communication

Does smoking have an impact on the immunological response to COVID-19 vaccines? Evidence from the VASCO study and need for further studies

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ABSTRACT

Objectives: The aim of this study was to investigate the possible impact of smoking on the humoral response to the BNT162b2 mRNA COVID-19 vaccine (also known as the BioNTech-Pfizer COVID-19 vaccine).
Study design: A longitudinal sero-epidemiological study was conducted in sample of Italian healthcare workers (HCWs).
Methods: HCWs who were administered two doses of the BNT162b2 mRNA vaccine, 21 days apart, between December 2020 and January 2021, were invited to undergo multiple serology tests to identify SARS-CoV-2 S-RBD-specific immunoglobulin G (IgG) antibodies. Participants also responded to questions about their smoking status (i.e. current smokers vs non-smokers) in a survey.
Results: Sixty days after the completion of the vaccination cycle, serological analyses showed a difference in vaccine-induced IgG titre between current smokers and non-smokers, with median antibody titres of 211.80 AU/mL (interquartile range [IQR] 149.80–465.50) and 487.50 AU/mL (IQR 308.45–791.65) [*P*-value = 0.002], respectively. This significant difference in vaccine-induced IgG titres between current smokers and non-smokers remained after adjusting for age, sex, and previous infection with SARS-CoV-2.
Conclusions: This study observed that vaccine-induced antibody titres decrease faster among current smokers than non-smokers. Further research to investigate the impact of smoking on the immunological response to COVID-19 and non-COVID-19 vaccines is required.

Introduction

Monitoring the level and time trend of the humoral response to COVID-19 vaccines represents an essential tool in the study of immunological response and enables a greater understanding of the protection offered by the vaccination during the SARS-CoV-2 pandemic.[1] This study presents a subanalysis of the VASCO project ('Monitoraggio della risposta al Vaccino Anti-SARS-CoV-2/COVID-19 negli operatori sanitari del Pineta Grande Hospital'), an ongoing longitudinal study that investigates the effectiveness, immunogenicity, and safety of the BNT162b2 mRNA COVID-19 vaccine (also known as the BioNTech-Pfizer COVID-19 vaccine) in a sample of healthcare workers (HCWs).[1,2] The study includes an analysis of the dynamics of antibody response to BNT162b2 mRNA COVID-19 vaccine at monthly intervals over a period of 6 months. A decrease in vaccine-induced anti-S-RBD immunoglobulin G (IgG)

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antibodies was seen at the second month (i.e. Sixty days) after the completion of the vaccination cycle.[1]

Methods

Complete cohort characteristics and study methods have been described in previous articles.[1,2] In brief, HCWs who were administered two doses of the BNT162b2 mRNA vaccine, 21 days apart, between December 2020 and January 2021, underwent multiple quantitative serology tests to identify SARS-CoV-2 S-RBD-specific IgG. Participant HCWs also responded to questions about their smoking status (i.e. current smokers vs non-smokers). This study focused on the differences in SARS-CoV-2 S-RBD IgG dynamics according to smoking status. Antibody level was assessed using the Snibe–Maglumi® SARS-CoV-2 S-RBD IgG chemiluminescent immunoassay, with a reactivity cutoff of 1.0 AU/mL.[1] A Mann–Whitney U test was used to assess differences of median IgG levels between current smokers and non-smokers. A multivariate linear regression model was built to investigate the association between IgG level and smoking status, adjusting for possible covariates, namely, age, sex, and previous infection with SARS-CoV-2.

Results

Overall, 162 HCWs participated in this study; the majority were women (58.0%), with a mean age of 42.5 years (±11.9 standard deviation). In total, 28 participants had a history of previous SARS-CoV-2 infection. Sixty days after the completion of the vaccination cycle, serological analyses of 63 participants (19 current smokers and 44 non-smokers; 30.2% vs 69.8%) showed a difference in vaccine-induced IgG titre, with median antibody titres of 211.80 AU/mL (interquartile range [IQR] 149.80–465.50) and 487.50 AU/mL (IQR 308.45–791.65) [*P*-value = 0.002], respectively. This significant difference in vaccine-induced IgG titres between current smokers and non-smokers remained after adjusting for age (mean: 41.4 ± 11.8 years), sex (female: 65.1%), and previous SARS-CoV-2 infection (in 11.1% HCWs). The results from the multivariate regression models showed that the β coefficient is equal to −335.62 (95% confidence interval: −557.41 to −113.83; $P = 0.004$) for current smokers (Fig. 1). Differences in IgG titres between current smokers and non-smokers were not significant one month after the completion of the vaccination cycle; in addition, the differences were no longer significant at the serological analyses after the second month.

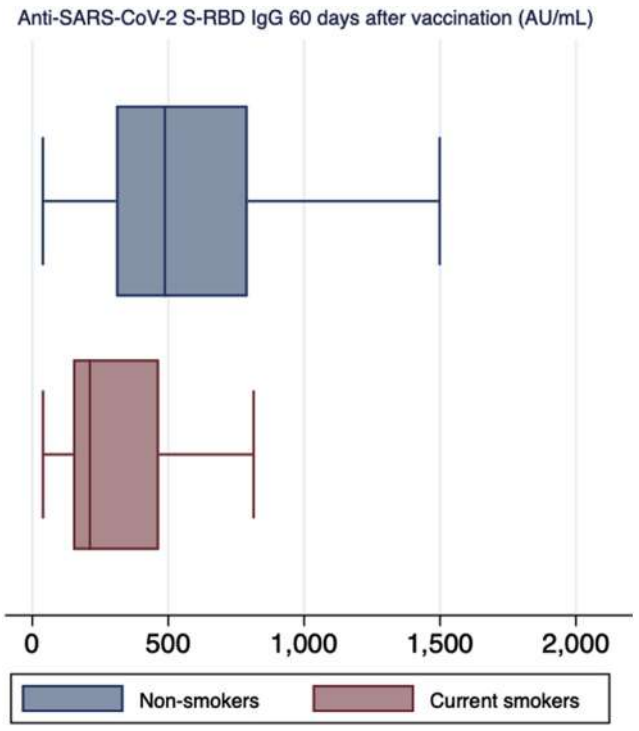

Fig. 1. Difference in vaccine-elicited SARS-CoV-2 S-RBD IgG between current smokers and non-smokers 60 days after vaccination with BNT162b2 COVID-19 vaccine.

Conclusions

This study showed that smoking may result in the rapid decrease in vaccine-induced IgG antibody levels. Emerging evidence has described lower antibody levels in response to COVID-19 mRNA vaccine in smokers, irrespectively of duration of smoking or number of cigarettes per day.[3] However, the pathophysiological basis for the impact of smoking on the dynamics of vaccine-elicited anti-SARS-CoV-2 antibodies have not yet been suggested. Previous literature observed that smoking may impact the immune response after vaccinations other than anti-COVID-19, such as hepatitis B and influenza vaccines, with a more rapid decrease in postvaccination antibodies in smokers.[4] Exposure to cigarette smoking impairs the immune system and thus the ability to form memory cells that are critical to the maintenance of the protective immune response induced by vaccines.[4,5] It is important to note that human IgG subclasses and specific antibodies generally have a half-life of approximately 3–4 weeks, depending on IgG isotype and attributes. Cigarette smoking is associated with increased monocyte-macrophage counts, which may influence the clearance of circulating antibodies.[5]

The present analysis shows that antibody titres decrease faster among current smokers than non-smokers. The mechanisms by which tobacco smoke decreases the immunological responses to COVID-19 vaccines deserve further research.

To date, the IgG threshold below which the risk of breakthrough infections is not yet known;[1] therefore, it is important to determine possible factors that may impair or decrease vaccine immunological response.[1] In this context, the findings from this study could be used to promote smoking cessation with the additional benefit of improving vaccine effectiveness. The results of the present study may also be used as a reference for further research on the impact of smoking on vaccine response.

It is worth noting that this study relies on observational data and used a specific and sensitive antibody test, which precisely correlates with vaccine-elicited humoral response. However, when interpreting the results, the small sample size must be taken into consideration, and the involvement of any undetected confounders of the vaccine-induced humoral response cannot be completely excluded.

Author statements

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Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki. The VASCO project was approved by the

Institutional Review Board - Comitato Etico Campania Nord, with referral number CECN/1614/2021. All participants provided written informed consent before enrollment into the study.

Funding

This research received no external funding.

Competing interests

R.P. is a full tenured professor of Internal Medicine at the University of Catania (Italy) and Medical Director of the Institute for Internal Medicine and Clinical Immunology at the same University. In relation to his recent work in the area of respiratory diseases, clinical immunology, and tobacco control, R.P. has received lecture fees and research funding from Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, MSD, Boehringer Ingelheim, Novartis, Duska Therapeutics, and Forest Laboratories. Lecture fees from a number of European EC industry and trade associations (including FIVAPE in France and FIESEL in Italy) were directly donated to vaper advocacy no-profit organizations. R.P. has also received grants from European Commission initiatives (U-BIOPRED and AIRPROM) and from the Integral Rheumatology & Immunology Specialists Network (IRIS) initiative. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, CV Therapeutics, Boehringer Ingelheim, Novartis, Duska Therapeutics, ECITA (Electronic Cigarette Industry Trade Association, in the UK), Arbi Group Srl. and Health Diplomats. R.P. has served on the Medical and Scientific Advisory Board of Cordex Pharma, Inc., CV Therapeutics, Duska Therapeutics Inc, Pfizer and PharmaCielo. R.P. is also founder of the Center for Tobacco Prevention and Treatment at the University of Catania and of the Center of Excellence for the acceleration of Harm Reduction at the same University, which has received support from Foundation for a Smoke-Free World to conduct eight independent investigator-initiated research projects on harm reduction. R.P. is also currently involved in the following pro bono activities: scientific advisor for LIAF, Lega Italiana Antifumo (Italian acronym for Italian Anti-Smoking League), the Consumer Advocates for Smoke-free Alternatives, and the International Network of Nicotine Consumers Organizations; Chair of the European Technical Committee for standardization on 'Requirements and test methods for emissions of electronic cigarettes' (CEN/TC 437; WG4). All other authors declare no conflicts of interest.

Authors' contributions

P.F. and D.P. conceived and designed the VASCO study. P.F. and R.P had the idea for this Short Communication. P.F. led the statistical analyses and wrote the first draft of the article. All authors contributed to data collection and acquisition, database development, discussion and interpretation of the results, and writing the article. All authors have read and approved the final article.

References

1. Ponticelli D, Antonazzo IC, Caci G, Vitale A, Della Ragione G, Romani ML, et al. Dynamics of antibody response to BNT162b2 mRNA COVID-19 vaccine after 6 months. *J Trav Med* 2021. https://doi.org/10.1093/jtm/taab173.
2. Ponticelli D, Madotto F, Conti S, Antonazzo IC, Vitale A, Della Ragione G, et al. Response to BNT162b2 mRNA COVID-19 vaccine among healthcare workers in Italy: a 3-month follow-up. *Intern Emerg Med* 2021. https://doi.org/10.1007/s11739-021-02857-y.
3. Nomura Y, Sawahata M, Nakamura Y, Kurihara M, Koike R, Katsube O, et al. Age and smoking predict antibody titres at 3 Months after the second dose of the BNT162b2 COVID-19 vaccine. *Vaccines* 2021;**9**(9):1042. https://doi.org/10.3390/vaccines9091042.
4. Qiu F, Liang C-L, Liu H, Zeng Y, Hou S, Huang S, et al. Impacts of cigarette smoking on immune responsiveness: up and down or upside down? *Oncotarget* 2017;**8**(1):268–84.
5. Pedersen KM, Çolak Y, Ellervik C, Hasselbalch HC, Bojesen SE, Nordestgaard BG. Smoking and increased white and red blood cells. *Arterioscler Thromb Vasc Biol* 2019;**39**(5):965–77. https://doi.org/10.1161/ATVBAHA.118.312338.

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Original Research

Economic burden of public health care and hospitalisation associated with COVID-19 in China

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ABSTRACT

Objectives: This study aimed to evaluate the socio-economic burden imposed on the Chinese healthcare system during the coronavirus disease 2019 (COVID-19) pandemic.
Study design: A cross-sectional study was used to investigate how COVID-19 impacted health and medical costs in China. Data were derived from a subdivision of the Centers for Disease control and Prevention of China.
Methods: We prospectively collected information from the Centers for Disease Control and Prevention and the designated hospitals to determine the cost of public health care and hospitalisation due to COVID-19. We estimated the resource use and direct medical costs associated with public health.
Results: The average costs, per case, for specimen collection and nucleic acid testing (NAT [specifically, polymerase chain reaction {PCR}]) in low-risk populations were $29.49 and $53.44, respectively; however, the average cost of NAT in high-risk populations was $297.94 per capita. The average costs per 1000 population for epidemiological surveys, disinfectant, health education and centralised isolation were $49.54, $247.01, $90.22 and $543.72, respectively. A single hospitalisation for COVID-19 in China cost a median of $2158.06 ($1961.13-$2325.65) in direct medical costs incurred only during hospitalisation, whereas the total costs associated with hospitalisation of patients with COVID-19 were estimated to have reached nearly $373.20 million in China as of 20, May, 2020. The cost of public health care associated with COVID-19 as of 20, May, 2020 ($6.83 billion) was 18.31 times that of hospitalisation.
Conclusions: This study highlights the magnitude of resources needed to treat patients with COVID-19 and control the COVID-19 pandemic. Public health measures implemented by the Chinese government have been valuable in reducing the infection rate and may be cost-effective ways to control emerging infectious diseases.

Introduction

During the coronavirus disease 2019 (COVID-19) pandemic, there has been a substantial impact on global health care and medical systems. By 9, June, 2020, a total of 7,085,894 cases had been confirmed worldwide and 405,168 deaths had been reported. The case fatality rate of COVID-19 (5.70%) is gradually approaching that of severe acute respiratory syndrome (SARS; 9.6%).[1,2] As of 20, May, 2020, there were 82,967 confirmed cases, 740,967 close contacts and 4634 deaths in China.[3] Faced with an enormous number of cases within a short period of time, the government, healthcare professionals and healthcare systems voiced concern that demand would exceed the existing capacity, and they requested the urgent provision of additional resources and financial support. An effective method of mitigating the impact of the pandemic on the healthcare system is to reduce the percentage of the population who become infected by implementing preventive measures mediated by public health officials.[4,5] Therefore, the government, healthcare system and medical insurance system had

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[e] Xizhou An and Lun Xiao have the same contribution.

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to provide sufficient public health resources and hospital accommodation to quickly curb the spread of COVID-19.

The COVID-19 pandemic was brought under control in China within a relatively short period of time; therefore, it is useful to evaluate the costs of public health measures and hospitalisation due to COVID-19 in China. Such information is critical for efficiently developing strategies to mitigate the impacts of potential outbreaks of new infectious diseases in the future.

In China, the healthcare system is composed of two sections: (i) medical institutions (e.g. hospitals, primary medical and health centres, such as township hospitals or community health centres); and (ii) public health organisations, such as the Centers of Disease Control and Prevention (CDC) and Centres of Health Supervision (these medical organisations are stratified into five levels: state, province, city, county/district and town).[6] After the outbreak of the COVID-19 pandemic, the Chinese government released pandemic control policies called a 'unanimous nationwide system' to form a joint defence and control programme with multiple departments.[7] All hospitals and primary medical centres were administrated by Health Commissions (HCs) and CDCs at each level.[7] The HCs and CDCs at each level planned the supplies and human resources for the hospitals and primary medical centres in their areas.[8]

However, limited studies have reported the costs of emerging infectious diseases. Bartsch et al.[9] used a mathematical model to quantify the cost of Ebola virus disease (EVD) from the perspectives of providers and society in Guinea, Liberia and Sierra Leone. In addition, two studies[10,11] developed computational models to forecast the potential economic burden and the cost-effectiveness of measures addressing Zika in the US. Bartsch et al.[12] also developed a computational model to estimate the potential resource use and direct medical costs of COVID-19 in the US under various conditions. Previous cost studies primarily used a proxy disease to obtain estimates of the clinical costs of an emerging infectious disease and used a mathematical model to forecast the medical costs associated with the target infectious disease; these studies have lacked a clear scientific source of the estimated costs.[13] A few studies have estimated healthcare utilisation and cost using structured interview methods, but a review of the literature reveals that, to date, there are no studies determining the costs of both public health and hospitalisation associated with COVID-19.

In this study, we investigate the actual expenses associated with public healthcare resources and hospitalisation from COVID-19. From these figures, we estimate the healthcare costs of COVID-19 control in China during the initial outbreak period of the pandemic. This study estimates the potential financial cost to control the outbreak of an infectious disease, without health insurance support, in an emergency situation. Results from this study will help governments worldwide in the management of infectious disease outbreaks.

Methods

Study design

A cross-sectional study was used to investigate how COVID-19 impacted health and medical costs in China. Data were derived from a subdivision of the CDC of China.

Data sources for the COVID-19 epidemic in China

This study used COVID-19 data from the official website of the National Health Commission of the People's Republic of China from 20, January, 2020, to 20, May, 2020. The epidemiological data included the daily numbers of total confirmed cases, suspected cases, close contacts, people under medical observation, inpatient cases, severe cases, deaths and discharged cases.

Definition of medical costs

Medical expenses associated with COVID-19 are composed of the costs of public health care and treatment during hospitalisation (see supplementary figure S2). Public healthcare costs included nucleic acid testing (NAT [specifically, polymerase chain reaction {PCR}]) (including NAT for both people and the environment), epidemiological surveys, centralised quarantine (see supplementary figure S2), disinfection and health education. The costs associated with public health care had two dimensions, namely, financing resources (e.g. protective equipment, medical materials, medical equipment and ambulances) and human resources (i.e. medical staff participating in the prevention of COVID-19). The hospitalisation costs include the direct cost of acute hospitalisation according to the discharge settlement amount.

Data collection

To accurately estimate the costs of pandemic control, including both public health care and hospitalisation, three criteria were taken into consideration when selecting the study district, as follows: first, there must be sufficient residents and COVID-19 cases in this district; second, the chosen district should contain both urban and rural areas so that urban-rural differences could be eliminated; and finally, the district must have hospitals with sufficient funds to cover total medication costs for patients with COVID-19 and isolation expenses for residents.

The Jiulongpo District was selected as the study area. In total, 1.2 million people permanently resided in Jiulongpo District and there were >20 reported cases of COVID-19. Jiulongpo District is located to the west of the Chongqing metropolitan region, with both semirural and semiurban areas, including nine urban streets and four rural towns. Furthermore, in this district, there are sufficient hospitals, including every grade of hospital in China, which formed a loop, so that the centralised isolation and treatment of patients with COVID-19 could be carried out locally to make the cost data transparent. Therefore, in Chongqing, the Jiulongpo District met all the three selection criteria and thus provides a suitable study area resulting in good representation for the costs associated with COVID-19 in China.

Data on medical costs related to the treatment of COVID-19 were collected using a micro-cost survey approach. The total public healthcare costs in Jiulongpo District were collected. The urban area in Jiulongpo District is very prosperous, and it could represent the typical costs of COVID-19 in the urban areas of Chongqing or other metropolitan cities. In addition, the four rural towns in Jiulongpo District can represent rural areas of Chongqing. The survey was administered to one CDC, seven secondary or tertiary medical institutions, 15 community health centres and 10 township hospitals or temporary medical institutions in Jiulongpo District, which includes all subdistricts and towns (in the countryside), with 1.2 million permanent residents.

Medical cost data were collected by conducting a series of key information interviews at the CDC and designated medical institutions. The questionnaire survey of local survey data was collected from the CDC and hospitals and health insurance system. All relevant medical centres at all levels in Jiulongpo District were investigated, and the CDC of Jiulongpo District provided support for all the surveys. The detailed method of quantitative cost collection is provided in Supplementary Method 1.

Method of cost calculation

The average exchange rate of RMB to US$ equivalent during the period of the survey was 1 RMB = 0.1402 US$. The detailed method of cost calculation is provided in Supplementary Method 2.

Statistical analyses

The Wilcoxon test was used to compare the differences in various hospitalisation expenses, payment methods (e.g. paid by medical insurance, medical insurance subsidies for official staff, medical insurance claims for large expenses, social assistance, the hospital and the patient) and duration of hospitalisation in different subgroups. The 95% confidence interval (CI) of the median or mean cost was calculated by the bootstrap method with 1000 iterations. In addition, a generalised linear regression model (GLM) was used to estimate the factors impacting the hospitalisation costs, which were log-transformed to ensure a normal distribution.

Data analyses for this study were conducted using SAS, version 9.4, software (Copyright © 2016 SAS Institute Inc. Cary, NC, USA). A significant difference was defined by an α level of 0.05 with a two-sided test.

Results

The cost of public health care

The per sample cost of obtaining samples for NAT at the CDC, secondary or tertiary hospitals, community healthcare centres and township hospitals or temporary institutions were \$8.81, \$42.10, \$23.94 and \$23.76, respectively, with corresponding labour costs of 0.13 days, 0.52 days, 0.33 days and 0.40 days, respectively (Table 1). Moreover, single-use personal protective equipment (PPE) cost approximately \$50.95 (see Supplementary Table S1). The average per sample cost of NAT among different medical institutes was \$29.49, and the human resources used were the equivalent of 0.38 days. There were significantly different detection times and costs for NAT between low-risk (those who did not closely contact with confirmed cases) and high-risk (close contacts) populations (Supplementary Table S2). The costs of NAT and diagnostic examinations for the first time and the last time tests for people before diagnosed as suspected cases was \$154.41 per capita, including \$124.92 for test material cost and \$29.49 of NAT cost. And NATs of people after diagnosed as suspected cases for the first time and for the last time NATs was \$77.86. Moreover, the costs of NATs for predischarge and postdischarge of confirmed cases were \$119.64 and \$147.54, respectively (in Supplementary Table S3).

The CDC completed 156 epidemiological surveys (on-site investigations or telephone follow-ups), including 3629 individuals in high-risk populations, and the direct costs (labour costs, PPE and ambulance costs) were calculated (Table 2). The average epidemiological costs for people in centralised isolation, home isolation and jail were \$4.57, \$10.59 and \$2.36 per case, respectively. Moreover, the average epidemiological costs of antibody-positive individuals, close contacts of people with confirmed cases, people with confirmed cases, people who retested positive after recovery and individuals with suspected cases were \$10.52, \$14.78, \$389.84, \$214.42, \$136.70 and \$243.50 per case, respectively. The average epidemiological cost associated with the inspection of hospital fever clinics by the CDC was \$214.42 per incident. The total

Table 1
The cost of obtaining sample specimens for NAT in different medical institutes.

Items	Number of samples	Labour resource of medical staff, days	Price, \$	Cost per sample, \$	Human resource, days/per sample
In CDC					
Labour to obtain specimen	4267	214	42.06	2.11	0.05
Community policeman	4267	81	28.04	0.53	0.019
Labour to deliver specimen	4267	252	28.04	1.66	0.059
Ambulance	4267	252	16.82	0.99	–
PPE	4267	295	50.95	3.52	–
Total average cost*	–	–	–	**8.81**	**0.128**
In secondary or tertiary hospitals					
Labour to obtain specimen	9547	3760	42.06	16.56	0.394
Community policeman	9547	1164	28.04	3.42	0.122
Labour to deliver specimen	9547	1164	16.82	2.05	–
Ambulance	9547	3760	50.95	20.07	–
Total average cost*	–	–	–	**42.1**	**0.516**
Community healthcare centre					
Labour to obtain specimen	4850	939	42.06	8.14	0.194
Labour to deliver specimen	4850	642	28.04	3.71	0.132
Ambulance	4850	642	16.82	2.23	–
PPE	4850	939	50.95	9.86	–
Total average cost*	–	–	–	**23.94**	**0.326**
Township hospitals or temporary participating institutions					
Labour to obtain specimen	192	23	42.06	5.04	0.12
Labour to deliver specimen	192	54	28.04	7.89	0.281
Ambulance	192	54	16.82	4.73	–
PPE	192	23	50.95	6.1	–
Total average cost*	–	–	–	**23.76**	**0.401**
Total average cost in all medical institutes					
Labour to obtain specimen	18,856	4936	42.06	11.01	0.262
Community policeman	18,856	81	28.04	0.12	0.004
Labour to deliver specimen	18,856	2112	28.04	3.14	0.112
Ambulance	18,856	2112	16.82	1.88	–
PPE	18,856	4936	50.95	13.34	–
Total average cost*	–	–	–	**29.49**	**0.378**

CDC: Centers for Disease Control and Prevention; PPE: personal protective equipment; NAT: nucleic acid testing.
*The cost per sample in bold, was calculated by adding the cost of subgroups, such as 8.81=2.11+0.53+1.66+0.99+3.52. The human resource (days per sample) in bold, was calculated by adding the human resource of subgroups, such as 0.128=0.05+0.019+0.059.
Note: The typical exchange rate of RMB to US\$ equivalent in the period of this survey is 1 RMB = 0.1402 US\$.

Table 2
The cost of epidemiological surveys for COVID-19.

Type of cases	Survey administrations	Cases	Survey cost of CDC				Total labour, days	Total labour cost, $	Total cost, $[a]	Cost per case or per administration, $
			Survey labour, days	Data analysis labour, days	PPE cost, $	Survey cost, $				
Centralised quarantine locations[b]	15	697	19	0	1885.1	2663.2	27	1016.5	3187.6	4.57
Home quarantine	2	66	4	0	407.56	575.8	6	224.32	699.18	10.59
Jail[c]	14	1816	28	0	2445.5	3581.1	40	1472.1	4287.7	2.36
Antibody-positive individuals	1	18	3	2	–	189.27	5	189.27	189.27	10.52
Close contacts of cases	81	872	280	1	764.23	12,583	287	11,959	12,892	14.78
Patients with confirmed cases	10	19	62	100	458.59	7272.3	165	6897.8	7406.9	389.84
Fever clinics[d]	5	15	6	3	560.38	917.89	12	427.61	1072.1	214.42[e]
Patients who retested as positive after recovery	2	2	3	4	–	273.39	7	273.39	273.39	136.7
Individuals with suspected cases	26	124	323	391	152.82	30,163	714	30,024	30,193	243.5

CDC: Centers for Disease Control and Prevention; PPE: personal protective equipment.
Note: The typical exchange rate of RMB to US$ equivalent in the period of this survey is 1 RMB = 0.1402 US$.
[a] Including the PPE, total labor and ambulance costs.
[b] Three missing data points represented by the median (33).
[c] Prison staff and criminals in custody.
[d] The CDC supervised and inspected the fever clinics of hospitals four times. The number of cases was not recorded, and average cost per time was used.
[e] Cost per time.

epidemiological costs were $60,201.18, and the average epidemiological cost per 1000 population was $49.54.

The financial costs of disinfection, PPE, health education and centralised isolation were calculated (Table 3). The total cost of disinfectant was $300,141.84 in Jiulongpo District, and the average cost of disinfectant per 1000 population was $247.01, including disinfectant materials at $238.71 and a disinfectant labour cost of $8.30. The cost of PPE was $1,568,651.95 from 20, January, 2020 to 30, April, 2020, and the average cost of PPE per 1000 population was $1290.97. The total human resource costs and publicity material costs associated with COVID-19 health education were $59,865.40 and $49,758.31, respectively; the average health education costs for human resources and publicity materials were $49.27 and $40.95 per 1000 population, respectively. The average cost of health education per 1000 population was $90.22. The costs of centralised isolation for people from abroad, close contacts and discharged patients were $647.72, $647.72 and $1295.45 per case, respectively, and the average cost of centralised isolation per 1000 population was $543.72 in Jiulongpo District.

The cost of hospitalisation

The median hospitalisation costs associated with COVID-19 were analysed based on the hospitalisation costs of 220 inpatients with COVID-19 (Table 4 and Supplementary Table S4). A single SARS-CoV-2 infection cost a median of $2158.06 (95% CI = $1991.93–$2321.28) in direct medical costs, that is, only including the costs that were accrued during the course of hospitalisation. The median cost of hospitalisation in the negative-pressure isolation ward (NPIW) was higher than that in the general isolation ward ($3439.00 [95% CI = $2942.59-$4573.96] vs $1902.26 [95% CI = $1745.77-$2146.22]; $P < 0.001$). Hospitalisation with non-invasive ventilation cost a median of $9278.05 (95% CI = $6990.72-$11,151.19), which was higher than the cost of hospitalisation without ventilation ($2017.16 [95% CI = $1837.62-$2224.99]; $P < 0.001$). The median cost of hospitalisation in the intensive care unit (ICU) was significantly higher than that in general isolation wards ($11,114.88 [95% CI = $9278.05-$31,283.93] vs $2114.65 [95% CI = $1880.72-$2254.52]; $P < 0.001$). In addition, the median cost of hospitalisation for severe and critical COVID-19 was markedly higher than that for mild and moderate COVID-19 ($3439.00 [95% CI = $3055.95-$4573.96] vs $1898.59 [95% CI = $1731.59-$2130.93]; $P < 0.001$). Patients with two or more hospitalisations for COVID-19 had a higher hospitalisation cost than those with a single hospitalisation ($3437.72 [95% CI = $2432.65-$5828.88] vs $2120.00 [95% CI = $1898.59-$2257.09]; $P = 0.002$). Also, the median cost of hospitalisation for patients from abroad was $4567.89 (95% CI = $2992.07-$5072.00), which was higher than for local patients ($2132.99 [95% CI = $1938.52-$2298.65]; $P = 0.01$).

The total direct hospitalisation medical expenses consist of drug fees ($364.16 [95% CI = $330.21-$390.17]), medical examination fees ($200.21 [95% CI = $200.21-$266.94]), clinical laboratory fees ($513.24 [95% CI = $481.57-$543.49]), consultation fees ($52.58 [95% CI = $47.67-$57.48]), treatment fees ($182.45 [95% CI = $152.64-$232.66]), nursing fees ($62.25 [95% CI = $57.20-$68.98]), bed fees ($205.04 [95% CI = $177.70-$226.16]), medical supply fees ($409.52 [95% CI = $357.55-$460.71]), other hospitalisation fees ($27.60 [95% CI = $25.41-$31.51]), median of basic medical fees ($0.14 [95% CI = $0.08-$0.22]), median of Chinese patent medicine fees ($28.49 [95% CI = $12.25-$49.36]), median of surgery fees ($2.61 [95% CI = $0-$8.15]) and median of Chinese herbal medicine fees ($6.77 [95% CI = $3.56-$10.07]) (Table 4).

The median and mean hospitalisation costs are compared in Table 4. Treatments in the NPIW with non-invasive ventilation or

Table 3
Costs of disinfection, PPE, health education and centralised quarantine.

Items	Price/suit, $	Number	Total price, $
Cost of disinfectant			
Effervescent tablets for disinfection	5.61	4,760	26,694.08
Medical 84 disinfectant	15.84	16,624	263,367.38
Total cost of disinfectant materials*	-	-	***290,061.46***
Human resource for disinfecting	-	215	6,028.6
Ambulance	16.83	-	757.36
Ultra-low-volume sprayer	140.2	6	757.08
Fuel atomizer	490.7	5	841.2
Total cost of disinfectant*	-	-	***300,141.8***
Average cost of disinfectant materials, per 1000	-	-	238.71
Average cost of disinfectant labor, per 1000	-	-	8.3
Average cost of disinfecting, per 1000*	-	-	***247.01***
Cost of PPE			
Surgical mask	1.26	64,574	81,479.47
N95 mask	6.73	7,770	52,288.99
3M mask	4.21	5,162	21,711.37
Protective suit	67.3	6,988	470,264.45
Medical gown	15.14	44,257	670,121.79
Gloves	0.7	233,707	163,828.61
Shoe cover	0.07	28,190	1,976.12
Medical hat	0.07	42,402	2,972.38
Face shield	28.04	3,424	96,008.96
Medical goggles	6.31	1,268	7,999.81
Total cost of PPE, $*	-	-	***1,568,652***
Cost of PPE, per 1000, $*	-	-	***1,290.97***
Health education			
Human resources, person time (days)	28.04	2,135	59,865.4
Average human resources, per 1000	-	-	49.27
Publicity materials			
Making informational film	42.06	480	20,188.8
Printing publicity materials	0.13	222,010	29,569.51
Materials, per 1000	-	-	40.95
Average cost of health education, per 1000*	-	-	***90.22***
Centralized isolation			
People from abroad	647.72	550	356,248.2
Close contacts	647.72	430	278,521.32
Discharge patients	1295.45	20	25,908.96
Average cost of centralized isolation, per 1000*	-	-	***543.72***

PPE: personal protective equipment.
Note: The typical exchange rate of RMB to US$ equivalent in the period of this survey is 1 RMB =0.1402 US$
* Total cost in italic bold represented the sum of each items of cost in the corresponding category.
# The average cost per 1000 in italic bold represented the total price of all items in the corresponding category for every 1000 samples.

in the ICU were associated with relatively higher hospitalisation costs (all $P < 0.05$). Severe and critical COVID-19 was associated with higher hospitalisation costs than mild and moderate COVID-19 ($P < 0.001$). Moreover, patients with two or more hospitalisations and patients from abroad had higher hospitalisation fees than their counterparts (all $P < 0.05$).

In addition, multivariable GLM analyses revealed that the factors impacting hospitalisation cost were age (45–59 years vs < 18 years; $P = 0.027$), duration of hospitalisation ($P < 0.001$), hospitalisation in the NPIW ($P < 0.001$), the use of non-invasive ventilation ($P < 0.001$), admission to the ICU ($P < 0.001$), the classification of COVID-19 as severe and critical ($P < 0.001$) and the number of hospitalisations ($P = 0.001$) (Table 5).

Compensation methods for hospitalisation cost

The methods of paying for hospitalisation include basic medical insurance, medical insurance claims for large expenses, other assistance and out-of-pocket payments. The results (Table 4 and Supplementary Table S4) revealed that the mean hospitalisation costs for COVID-19 were mainly paid by medical insurance ($2531.85 [95% CI = $1953.46-$3310.91]) and by the patients ($1134.45 [95% CI = $610.75-$2084.81]). Compared with their counterparts, the compensation paid by medical insurance was higher for patients who were hospitalised in the NPIW ($5046.69 [95% CI = $3033.67-$7605.15] vs $1610.27 [95% CI = $1480.19-$1750.64]; $P = 0.003$), received non-invasive ventilation ($10,789.11 [95% CI = $6362.94-$16,478.35] vs $1751.32 [95% CI = $1480.90-$2218.23]; $P < 0.001$) and were hospitalised in the ICU ($16,940.65 [95% CI = $8334.59-$26,511.06] vs $1773.50 [95% CI = $1578.50-$1988.21]; $P < 0.001$). In addition, patients with severe and critical COVID-19 and those with two or more hospitalisations received more compensation from medical insurance than their counterparts (all $P < 0.001$). The government paid the medical expenses that should have been paid by patients with COVID-19 in China.

Furthermore, the results show that the expense percentages paid by basic medical insurance and medical insurance claims for large expenses were 51.92% and 16.48%, respectively, and that the expense percentages paid by medical insurance, the government and other forms of compensation were 68.40%, 30.65% and 0.95%, respectively (Supplementary Table S5). The government paid approximately $94.12 million for the hospitalisation of patients with confirmed COVID-19 in China until 20, May, 2020. Medical insurance covered 60.08–84.49% of the hospitalisation costs for COVID-19.

Table 4
The cost of hospitalisation for COVID-19, median (95% CI).[a]

Variables	Total	Negative-pressure isolation ward			Noninvasive ventilation		
		No	Yes	*P*	No	Yes	*P*
Sample size, n	220	161	59		201	19	
Duration of hospitalization, days	18 (17.00-20.00)	17 (16.00-19.00)	20 (17.00-25.00)	0.053	18 (16.00-19.00)	27 (20.00-35.00)	0.001
Drug fee, $	364.16 (330.21-390.17)	353.63 (329.04-381.36)	416.63 (294.02-496.55)	0.446	338.3 (315.43-372.78)	1522.11 (1145.39-2466.65)	<0.001
Medical examination fee, $	200.21 (200.21-266.94)	200.21 (200.21-215.35)	241.85 (200.21-333.68)	0.205	200.21 (200.21-209.74)	467.15 (400.41-492.94)	<0.001
Clinical laboratory fee, $	513.24 (481.57-543.49)	472.05 (442.72-493.19)	890.59 (639.94-1140.39)	<0.001	492.31 (469.25-531.43)	2430.44 (1496.00-3235.54)	<0.001
Consultation fee, $	52.58 (47.67-57.48)	50.47 (46.27-54.68)	58.88 (49.07-71.50)	0.044	51.87 (46.27-54.68)	79.91 (60.29-100.94)	<0.001
Treatment fee, $	182.45 (152.64-232.66)	152.27 (119.55-185.62)	292.2 (213.97-500.54)	<0.001	158.65 (134.98-188.61)	1757.9 (1383.51-2119.68)	<0.001
Nursing fee, $	62.25 (57.20-68.98)	60.57 (55.52-65.61)	67.97 (57.20-85.80)	0.088	61.24 (55.52-65.61)	92.53 (72.34-122.82)	<0.001
Bed fee, $	205.04 (177.70-226.16)	159.83 (150.36-181.56)	514.53 (385.55-685.23)	<0.001	186.82 (168.24-216.96)	817.02 (577.27-1280.38)	<0.001
Medical supply fee, $	409.52 (357.55-460.71)	375.15 (331.69-443.16)	531.91 (388.99-775.53)	0.018	372.13 (333.94-426.39)	1404.57 (1008.86-1529.84)	<0.001
Basic medical fee, $	0.14 (0.08-0.22)	0.12 (0.08-0.14)	0.13 (0.10-0.23)	0.042	0.14 (0.08-0.20)	0.21 (0.14-0.32)	0.007
Chinese patent medicine fee, $	28.49 (12.25-49.36)	12.76 (9.77-17.48)	60.72 (40.28-166.78)	<0.001	19.14 (11.29-40.32)	82.46 (48.39-557.21)	<0.001
Surgery fee, $	2.61 (0.00-8.15)	2.61 (0.00-2.61)	2.61 (0.00-18.20)	0.115	2.61 (0.00-2.61)	5.75 (0.00-18.20)	<0.001
Chinese herbal medicine fee, $	6.77 (3.56-10.07)	4.13 (3.31-8.58)	9.79 (4.20-14.07)	<0.001	6.77 (3.44-10.07)	7.36 (4.04-11.70)	0.175
Other hospitalization fees, $	27.60 (25.41-31.51)	25.94 (23.83-29.30)	38.56 (27.44-46.76)	<0.001	26.95 (24.54-29.30)	44.3 (38.56-55.73)	<0.001
Total medical expenses, $	2158.06 (1961.13-2325.65)	1902.26 (1745.77-2146.22)	3439 (2942.59-4573.96)	<0.001	2017.16 (1837.62-2224.99)	9278.05 (6990.72-11151.19)	<0.001
Compensation methods							
Paid by medical insurance, $	1467.21 (1367.85-1700.27)	1415.33 (1294.50-1529.39)	2176.95 (1471.08-2864.34)	0.003	1415.33 (1301.30-1525.23)	5717.11 (4795.72-6058.62)	<0.001
Paid by medical insurance claims for large expenses, $	0 (0.00-0.00)	0 (0.00-0.00)	0 (0.00-0.00)	<0.001	0 (0.00-0.00)	2023.71 (0.00-3706.92)	<0.001
Total general medical insurance, $	1467.21 (1369.82-1700.27)	1415.33 (1294.50-1529.39)	2176.95 (1471.08-2924.36)	0.003	1415.33 (1301.30-1525.23)	8053.25 (5320.54-10804.81)	<0.001
Paid by the patient, $[b]	406.35 (317.92-491.63)	381.81 (292.35-476.83)	554.89 (318.88-902.85)	0.061	404.88 (298.80-490.05)	902.85 (318.50-1688.98)	0.017
Other assistance, $	0 (0.00-0.00)	0 (0.00-0.00)	0 (0.00-0.10)	0.012	0 (0.00-0.00)	0.21 (0.00-65.05)	<0.001

CI, confidence interval.
Note: The typical exchange rate of RMB to US$ equivalent in the period of this survey is 1 RMB= 0.1402 US$.
[a] The 95% confidence interval of the median was based on 1000 bootstrap iterations (seed: 30459584).
[b] The fee that would ordinarily have been paid by the patients was covered by the government subsidies.

Table 5
The factors influencing total medical expenses ($n = 218$).

Variables	Univariate GLM			Multivariate GLM[a]		
	β	SE	*P*-Value	β	SE	*P*-Value
Sex, female vs male	0.016	0.083	0.848	0.003	0.03	0.926
Age, ref. <18 years						
18–44	0.345	0.189	0.068	0.081	0.069	0.243
45–59	0.517	0.19	0.007	0.154	0.07	0.027
≥60	0.639	0.198	0.001	0.132	0.073	0.072
Duration of hospitalisation, days	0.054	0.003	<0.001	0.045	0.002	<0.001
Negative-pressure isolation ward, yes vs no	0.614	0.084	<0.001	0.226	0.039	<0.001
Non-invasive ventilation, yes vs no	1.434	0.114	<0.001	0.756	0.078	<0.001
ICU, yes vs no	1.635	0.176	<0.001	0.459	0.102	<0.001
Severe and critical COVID-19, yes vs no	0.631	0.083	<0.001	–	–	
Frequency of hospitalisation, ≥2 vs. 1	0.43	0.206	0.037	0.243	0.076	0.001
Imported from abroad, yes vs no	0.555	0.25	0.026	0.013	0.098	0.894

Note: The typical exchange rate of RMB to US$ equivalent in the period of this survey is 1 RMB = 0.1402 US$.
GLM: generalized linear regression model (dependent variable was logarithm of total medical expenses); ICU: intensive care unit; SE: standard error.
[a] The variable of severe and critical COVID-19 was excluded because it had collinearity with hospitalization in the negative-pressure isolation ward.

The estimated cost of COVID-19 in China

The cost of public health care associated with COVID-19 included the cost of centralised quarantine, NAT, epidemiological surveys, disinfectant and PPE (see Supplementary Table S6). The costs of centralised quarantine for high-risk individuals from abroad, close contacts and postdischarge patients were $1.11 million, $479.93 million and $101.37 million, respectively, totalling $582.41 million. The cost of centralised isolation was $761.24 million, based on the cost of centralised quarantine per 1000 population in Chongqing. This may reflect the true cost because some regions did not report the number of people in the high-risk population at the beginning of the pandemic. The cost of NAT was assessed for the high-risk population and for other populations. The costs of NAT for the high-risk population, including individuals from abroad, close contacts, individuals with suspected cases and individuals with confirmed cases were $0.13 million, $89.09 million, $21.18 million and $53.40 million, respectively. In addition, the costs of NAT for the low-risk population of people from Wuhan, from abroad, from Hubei outside of Wuhan, from Guangdong and from other regions were $599.22 million, $18.12 million, $159.24 million, $362.89 million and $1833.99 million, respectively. Based on the total population of 1.4005 billion in mainland China at the end of 2019, the costs of epidemiological surveys, disinfectant, PPE and health education were $69.36 million, $345.83 million, $1807.42 million and $126.31 million, respectively. Finally, the total cost of public health care as a result of COVID-19 was $6.83 billion.

As of 20, May, 2020, the total number of COVID-19 cases in China was 82,967, which included 1709 cases from abroad and 81,258 local cases; the estimated number of severe cases was 17,147, and there were 4634 deaths and 78,249 recoveries. According to the average hospitalisation cost of $3792.69 of all cases, the total direct cost of hospitalisation in China was $314.668 million. According to the source of cases, the hospitalisation cost was $314.43 million, and individuals from abroad and local individuals were $7.20 million and $307.23 million, respectively (see Supplementary Table S6). Moreover, 17,147 patients with severe COVID-19 cost $140.10 million, which was almost equal to the cost for 65,820 patients with mild and moderate COVID-19 ($144.04 million). In addition, the hospitalisation cost for 98,430 patients with suspected cases was $58.53 million, and the total hospitalisation cost for patients with confirmed and suspected cases was $373.20 million. The estimated total direct costs of public health care and hospitalisation were approximately $7.2 billion, and the components related to COVID-19 are shown in Supplementary Figure S3.

Discussion

This study found that the total direct medical costs for public health care as a result of COVID-19 were $6.83 billion, which is substantially higher than the hospitalisation cost of $0.37 billion (these sums only consider the increased direct costs during the pandemic period and not the costs due to lost productivity or the indirect costs of the efforts to control COVID-19). Our study estimates the public healthcare costs from six aspects, namely, the costs due to centralised quarantine, NAT, epidemiological surveys, disinfectants, PPE and health education. The estimation in our analysis revealed that the cost of NAT was enormous and that NAT has imposed a tremendous economic burden on the healthcare system. In addition, we also estimated the hospitalisation costs, and the results showed that the average cost of hospitalisation for severe COVID-19 was four times that of hospitalisation for non-severe COVID-19 ($9278.05 vs $2017.16).

Estimating the cost of public health interventions for COVID-19 will provide a reference for determining the financial budget of government policy-making departments. Public health measures play critical roles in preventing the spread of emerging novel infectious diseases, such as COVID-19.[14–16] Such diseases require the government and the healthcare system to provide financial support and effective public health care. In addition to outpatient and inpatient treatment expenses, public health services should be paid for by the government. However, there are limited studies estimating the cost of public health care,[17] and to date, no study has calculated the public healthcare cost due to COVID-19. This is the first study to document the public healthcare cost associated with COVID-19 (i.e. not including the cost of the traditional monitoring of the incidence of communicable diseases and performance of routine investigations).

The public health costs in our study were associated with efforts to control the COVID-19 outbreak and epidemiological investigations. Of the public health measures taken, NAT, when both sampling and testing costs were considered, imposed the largest burden.[17–19] Our study found that the costs of obtaining samples in secondary or tertiary hospitals were five times and two times, respectively, more than the costs of obtaining samples at the CDC, community healthcare centres and township hospitals owing to the higher costs of labour and PPE; this agrees with the findings of a previous study.[17] The average cost of NAT (such as PCR) and diagnostic testing in the high-risk population reached $297.94 per capita, which was six times that in the low-risk population owing to the fact that the number of tests per capita was far larger in the

high-risk population.[20,21] The huge cost of NAT should be considered when deciding which population groups need to be tested and which medical institutes should perform priority NAT.

In addition to pathogen detection, epidemiological field investigations in high-risk populations are important to control COVID-19[22] because they can reduce the spread of the pandemic. The main cost incurred by epidemiological investigation is that associated with labour.[17] This study found that the average epidemiological survey costs were approximately $389.84 for confirmed cases and $243.50 for suspected cases, which is 20–30 times higher than costs for other populations. Moreover, our study revealed that epidemiological survey costs accounted for approximately 1.02% of the total increased medical costs associated with COVID-19; this may be significantly lower than the actual cost, as our study only included the subsidy for labour involved in the control of COVID-19 and did not include the general salaries of medical employees.

Another critical measure for preventing the spread of SARS-CoV-2 in China is to require the use of disinfectant[23] and PPE.[24] Based on the current estimation, the cost of the additional disinfectant accounted for more than 5% ($0.35 billion) of the public healthcare costs associated with COVID-19, primarily driven by the cost of the disinfectant solutions and the materials themselves. The cost of disinfection reported in our study is lower than the actual cost because the labour cost associated with the disinfection of hospital waste was not calculated. Wang et al.[23] found that the disinfection of hospital waste and wastewater is very important for controlling the COVID-19 pandemic.

In addition to NAT, the cost of PPE accounted for 26.46% of the public healthcare costs in our study, in part due to the shortages in medical masks, gowns and protective suits at the beginning of the pandemic. There are debates about whether wearing masks is effective and who needs to wear masks;[13,25,26] one study suggested wearing PPE in certain circumstances,[25] and one study from Wuhan found that the use of PPE can protect healthcare professionals from COVID-19.[27]

Moreover, the centralised quarantine of high-risk populations is another effective way to reduce transmission,[28] minimising the spread of COVID-19 among family members and the community.[29] In this study, we found that the cost of centralised quarantine accounted for 19.68% of the increased public healthcare costs associated with COVID-19, including the Chinese government's reimbursements for medical expenses and the costs of the accommodation and meals provided during centralised quarantine (it is important to note that the provision of these items significantly improved compliance with centralised isolation and reduced the psychological stress of those in quarantine).

Health education is an essential measure that can increase people's knowledge, attitudes and practices (KAP) towards COVID-19.[30] Our study found that the making of videos and publicity materials by authorities and the healthcare system to increase public awareness of COVID-19 accounted for 1.85% of the public healthcare costs associated with COVID-19 and had a significant effect.[30]

Isolation within hospitals is necessary for patients with confirmed and suspected cases of COVID-19,[12,21] and the choice of treatment for patients was impacted by the method of compensation for hospitalisation expenses. To provide hospitalisation and treatment for every patient with a confirmed and suspected case, the Chinese government paid all medical expenses that would ordinarily have been paid by individuals, and our study found that the government provided 30.65% (nearly $0.11 billion) of the hospitalisation-associated costs for patients with confirmed cases (Supplementary Table S5). In contrast, out-of-pocket healthcare costs have placed an enormous burden on many patients with COVID-19 in some countries, preventing patients from receiving medical treatment[31] and exacerbating the spread of COVID-19. The average cost is 2.58 times that of the average medical expenses for inpatient treatment in general ($1468.78 in medical costs in 2020 values)[32] and 3.68 times that of the average medical expenses for bacterial pneumonia ($1039.71 in medical costs in 2020 values), which was similar to the results of Bartsch et al.[12] The direct medical costs are higher for COVID-19 than for other common infectious diseases because inpatients with COVID-19 have a longer average hospital stay (18 days vs 8.5 days) and higher mortality than patients with seasonal influenza and other infectious diseases.[32–34] Moreover, we found that the hospitalisation-associated costs for severe patients with COVID-19 (those treated in the NPIW, treated with non-invasive ventilation, treated in the ICU, and with two or more hospitalisations), patients from abroad and older patients were greater than those for their counterparts, which was in agreement with the findings of another published study.[17] The hospitalisation-associated costs in our study included only the expenses incurred during hospitalisation and did not consider the potential continued medical costs after the acute infection had run its course, including the cost of caring for those who had survived with major complications, such as cardiovascular disease and diabetes.[34] Furthermore, the costs of subsidies for emergency medical personnel (40,000 medical staff members supported the efforts to control COVID-19 in Wuhan), follow-up care and potential rehospitalisation are likely to be considerable because of the long-term effects of COVID-19,[35] making patients more susceptible to other health problems. These costs will further increase the cost of hospitalisation. The compensation policy for out-of-pocket hospitalisation costs for COVID-19 in China and the average hospitalisation cost in our study will provide references for other countries coping with the pandemic.

The current study has several limitations. First, we focused on the increased direct medical costs associated with COVID-19. Therefore, we did not consider the potentially substantial indirect medical costs that may be associated with COVID-19, such as those related to reduced economic activity and lost productivity owing to absenteeism and premature mortality, as we cannot contact the patients during the pandemic. In addition, we can only get the hospitalisation cost from the medical insurance information systems. Second, the results in this study may underestimate the direct medical costs because we only used the situation in Chongqing to calculate the costs for China as a whole. For example, we did not include the additional costs of building the mobile cabin hospitals in Wuhan or the tent hospitals in other places. Third, we did not include the financing of emergency medical equipment used for the control of COVID-19. Fourth, costs for environmental NAT sampling were not included in this study, which may underestimate the cost of public health care of COVID-19. Fifth, our analysis included only the subsidies paid to medical staff during the COVID-19 pandemic and did not include their regular salaries, which may have resulted in a significantly underestimation of the labour costs. Finally, we did not test the external validity of this study because we did not obtain the cost data from other areas of China.

However, the data regarding COVID-19 were from the National Health Commission of People's Republic of China (http://www.nhc.gov.cn/), which collected information from patients in all of China. In addition, the Jiulongpo District, from which we collected the COVID-19 public healthcare and hospitalisation cost data, is a middle-income area in China, which may partially, represent an average cost of hospitalisation and treatment in the whole of China. Furthermore, and different to other countries, the health policies (especially the policies on COVID-19 medication and public health) were exactly the same throughout mainland China. The facilities, equipment, drugs and health services were uniformly priced by the

Chinese government, so that even the cost data from a small part of China, such as Jiulongpo district, can represent the data for the whole of mainland China, which results in our conclusions having good external validity.

In conclusion, this study found that the COVID-19 pandemic has resulted in the expenditure of $6.83 billion in public health care and $0.37 billion in direct medical costs associated with hospitalisation. As large numbers of people must be tested and treated to prevent hospitalisation and potential death, the public healthcare costs were far greater than the hospitalisation costs. This suggests that governments should plan to increase the financial investment both in emergency public health care and hospitalisation during infectious disease outbreaks to effectively contain the spread of disease. Our study also highlights the magnitude of the resources needed to prevent the spread of the COVID-19 pandemic and to treat patients with COVID-19. Even when considering only the costs during the most severe pandemic period, and not those associated with routine surveillance and treatment following an acute outbreak, the increased medical costs related to the COVID-19 pandemic are likely to be substantially higher than those reported in this study. Therefore, tremendous health resources are needed to control the outbreak of infectious disease pandemics. However, at the beginning of pandemics, the medication and public healthcare costs of infectious diseases (such as SARS or COVID-19), are often not covered by health insurance, which will be an obstacle for the quick control of the pandemic. The quick control of the COVID-19 pandemic in China has been described in our previous study.[8] The estimated cost of pandemic control, especially the financial resources required from government to cover the medication and public health demand, will be of great help in achieving the goal to prevent the 'burst-out' situation of an infectious disease public health emergency.

Author statements

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Ethical approval

The Institutional Review Board at the Children's Hospital of Chongqing Medical University approved this study ((2020) No.59). Informed consent was provided by all patients.

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Competing interests

The authors declare that they have no competing interests.

Author contributions

An X and Xiao L conceived and designed the study; Yang X and Tang X participated in the acquisition and management of the data; An X analysed the data; Liang XH wrote the manuscript and all authors revised the manuscript. All authors took responsibility for the integrity of the data and the accuracy of the data analysis. All authors made critical revisions to the manuscript for important intellectual content and gave the final approval of the manuscript.

Data statement

Data are available on request owing to privacy/ethical restrictions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.12.001.

References

1. WHO. *Coronavirus disease (covid-19) pandemic*. 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
2. Chan-Yeung M, Xu RH. SARS: epidemiology. *Respirology (Carlton, Vic)* 2003;**8**(Suppl):S9–14.
3. National_Health_Commission_of_the_People's_Republic_of_China. *The latest situation of the COVID-19 epidemic situation as of 24:00 on May. 20*. 2020. Available from: http://www.nhc.gov.cn/xcs/yqtb/202005/7be4e0b23c9441dcb9d0f6e6c0b1f4ae.shtml.
4. Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. *J Trav Med* 2020;**27**.
5. Dickens BL, Koo JR, Wilder-Smith A, Cook AR. Institutional, not home-based, isolation could contain the COVID-19 outbreak. *Lancet* 2020;**395**:1541–2.
6. Meng Q, Yang H, Chen W. People's Republic of China health system review. *Health Syst Transit* 2015;**5**.
7. Wang J, Wang Z. Strengths, weaknesses, opportunities and threats (SWOT) analysis of China's prevention and control strategy for the COVID-19 epidemic. *Int J Environ Res Publ Health* 2020;**17**.
8. Liang XH, Tang X, Luo YT, Zhang M, Feng ZP. Effects of policies and containment measures on control of COVID-19 epidemic in Chongqing. *World J Clin Cases* 2020;**8**:2959–76.
9. Bartsch SM, Gorham K, Lee BY. The cost of an Ebola case. *Pathog Glob Health* 2015;**109**:4–9.
10. Lee BY, Alfaro-Murillo JA, Parpia AS, Asti L, Wedlock PT, Hotez PJ, et al. The potential economic burden of Zika in the continental United States. *PLoS Neglected Trop Dis* 2017;**11**:e0005531.
11. Alfaro-Murillo JA, Parpia AS, Fitzpatrick MC, Tamagnan JA, Medlock J, Ndeffo-Mbah ML, et al. A cost-effectiveness tool for informing policies on Zika virus control. *PLoS Neglected Trop Dis* 2016;**10**:e0004743.
12. Bartsch SM, Ferguson MC, McKinnell JA, O'Shea KJ, Wedlock PT, Siegmund SS, et al. The potential health care costs and resource use associated with COVID-19 in the United States. *Health Aff* 2020;**39**:927–35.
13. Ruhl AP, Huang M, Colantuoni E, Karmarkar T, Dinglas VD, Hopkins RO, et al. Healthcare utilization and costs in ARDS survivors: a 1-year longitudinal national US multicenter study. *Intensive Care Med* 2017;**43**:980–91.
14. Kraemer MUG, Yang CH, Gutierrez B, Wu CH, Klein B, Pigott DM, et al. The effect of human mobility and control measures on the COVID-19 epidemic in China. *Science* 2020;**368**:493–7.
15. Juni P, Rothenbuhler M, Bobos P, Thorpe KE, da Costa BR, Fisman DN, et al. Impact of climate and public health interventions on the COVID-19 pandemic: a prospective cohort study. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2020;**192**:E566–73.
16. Yang Z, Zeng Z, Wang K, Wong SS, Liang W, Zanin M, et al. Modified SEIR and AI prediction of the epidemics trend of COVID-19 in China under public health interventions. *J Thorac Dis* 2020;**12**:165–74.
17. Atherly A, Whittington M, VanRaemdonck L, Lampe S. The economic cost of communicable disease surveillance in local public health agencies. *Health Serv Res* 2017;**52**(Suppl 2):2343–56.
18. Esbin MN, Whitney ON, Chong S, Maurer A, Darzacq X, Tjian R. Overcoming the bottleneck to widespread testing: a rapid review of nucleic acid testing approaches for COVID-19 detection. *Rna* 2020;**26**:771–83.

19. Beeching NJ, Fletcher TE, Beadsworth MBJ. Covid-19: testing times. *Bmj* 2020;**369**:m1403.
20. Hong KH, Lee SW, Kim TS, Huh HJ, Lee J, Kim SY, et al. Guidelines for laboratory diagnosis of coronavirus disease 2019 (COVID-19) in Korea. *Ann Lab Med* 2020;**40**:351–60.
21. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res* 2020;**7**:4.
22. Lipsitch M, Swerdlow DL, Finelli L. Defining the epidemiology of Covid-19 - studies needed. *N Engl J Med* 2020;**382**:1194–6.
23. Wang J, Shen J, Ye D, Yan X, Zhang Y, Yang W, et al. Disinfection technology of hospital wastes and wastewater: suggestions for disinfection strategy during coronavirus Disease 2019 (COVID-19) pandemic in China. *Environ Pollut* 2020;**262**:114665.
24. Fathizadeh H, Maroufi P, Momen-Heravi M, Dao S, Kose S, Ganbarov K, et al. Protection and disinfection policies against SARS-CoV-2 (COVID-19). *Infezioni Med Le* 2020;**28**:185–91.
25. Hirschmann MT, Hart A, Henckel J, Sadoghi P, Seil R, Mouton C. COVID-19 coronavirus: recommended personal protective equipment for the orthopaedic and trauma surgeon. *Knee Surg Sports Traumatol Arthrosc – Off J ESSKA* 2020;**28**:1690–8.
26. Bin-Reza F, Lopez Chavarrias V, Nicoll A, Chamberland ME. The use of masks and respirators to prevent transmission of influenza: a systematic review of the scientific evidence. *Influenza Other Respir Viruses* 2012;**6**:257–67.
27. Liu M, Cheng SZ, Xu KW, Yang Y, Zhu QT, Zhang H, et al. Use of personal protective equipment against coronavirus disease 2019 by healthcare professionals in Wuhan, China: cross sectional study. *Bmj* 2020;**369**:m2195.
28. Pan A, Liu L, Wang C, Guo H, Hao X, Wang Q, et al. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. *Jama* 2020;**323**:1915–23.
29. Zhu Y, Wang C, Dong L, Xiao M. *Home quarantine or centralized quarantine, which is more conducive to fighting COVID-19 pandemic? Brain, behavior, and immunity*. 2020.
30. Zhong BL, Luo W, Li HM, Zhang QQ, Liu XG, Li WT, et al. Knowledge, attitudes, and practices towards COVID-19 among Chinese residents during the rapid rise period of the COVID-19 outbreak: a quick online cross-sectional survey. *Int J Biol Sci* 2020;**16**:1745–52.
31. Konrad W. *After battling COVID-19, survivors may have to fight big medical bills*. CBS NEWS; 2020. Available from: https://www.cbsnews.com/news/covid-19-health-care-costs-medical-treatment.
32. Ma X, Yu X, Jj Y, Wang H, Liu J, Xu S, et al. *China health statistics yearbook in 2019*. Peking Union Medical College Press; 2019.
33. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet (London, England)* 2018;**391**:1285–300.
34. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England)* 2020;**395**:1054–62.
35. Boldrini P, Garcea M, Brichetto G, Reale N, Tonolo S, Falabella V, et al. Living with a disability during the pandemic. "Instant paper from the field" on rehabilitation answers to the COVID-19 emergency. *Eur J Phys Rehabil Med* 2020;**56**:331–4.

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Short Communication

Excess deaths from COVID-19 in Japan and 47 prefectures from January through June 2021

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ABSTRACT

Objectives: In Japan, several studies have reported no excess all-cause deaths (the difference between the observed and expected number of deaths) during the coronavirus disease 2019 (COVID-19) pandemic in 2020. This study aimed to estimate the weekly excess deaths in Japan's 47 prefectures for 2021 until June 27.

Study design: Vital statistical data on deaths were obtained from the Ministry of Health, Labour and Welfare of Japan. For this analysis, we used data from January 2012 to June 2021.

Methods: A quasi-Poisson regression was used to estimate the expected weekly number of deaths. Excess deaths were expressed as the range of differences between the observed and expected number of all-cause deaths and the 95% upper bound of the one-sided prediction interval.

Results: Since January 2021, excess deaths were observed for the first time in the week corresponding to April 12–18 and have continued through mid-June, with the highest excess percentage occurring in the week corresponding to May 31–June 6 (excess deaths: 1431–2587; excess percentage: 5.95–10.77%). Similarly, excess deaths were observed in consecutive weeks from April to June 2021 in 18 of 47 prefectures.

Conclusions: For the first time since February 2020, when the first COVID-19 death was reported in Japan, excess deaths possibly related to COVID-19 were observed in April 2021 in Japan, during the fourth wave. This may reflect the deaths of non-infected people owing to the disruption that the pandemic has caused.

Introduction

Japan has so far had a relatively low number of deaths per population from coronavirus disease 2019 (COVID-19) compared with many high-income countries.[1] In Japan, several studies during the COVID-19 pandemic have reported no excess all-cause deaths (the difference between the observed and expected number of deaths) in 2020.[2] In April 2021, the fourth wave of COVID-19 started in Japan. Although the number of new cases showed a downward trend in June, the fifth wave began around July. This study provides estimates of weekly excess deaths in Japan's 47 prefectures from the start of 2021 until June 27, 2021, and reports the first observation of excess all-cause deaths in Japan that may be related to the pandemic.

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Methods

Estimating the expected number of deaths

Vital statistical data on deaths were obtained from the Ministry of Health, Labour and Welfare of Japan. For this analysis, we used data from 2012 (including the last few days of 2011 for weekly analysis) to June 2021. These data include information on the date of death, age at death, and place of residence (prefecture) of all persons who died in Japan, regardless of nationality, and those who had a residence card. Cause of death information was not available in the data. Those who died overseas, those who stayed in Japan for a short time (without a residence card), and those whose place of residence or date of birth was unknown were excluded. The conversion from daily data to weekly data was based on the categorization defined by the National Institute of Infectious Diseases' Infectious Diseases Weekly Report.[3]

To estimate the expected number of deaths and the associated prediction intervals, we used the Farrington algorithm,[4] which is commonly used to assess annual and seasonal trends in disease burden attributable to disease outbreaks.[5] The Farrington algorithm, which is based on a quasi-Poisson regression model, places restrictions on the time points of the data used for estimation (i.e. reference period). The expected number of deaths at a calendar week t is estimated using only data from $t - w$ to $t+ w$ weeks of years $h - b$ and $h - 1$, where w and b are prefixed values and h is the year of t. In the present study, we used $b = 5$ and $w = 3$, based on previous studies.[4] In addition, to incorporate seasonality into the model, data not included in the reference period are evenly divided and included in the regression model as dummy variables. The regression model is then given by

$$\log(E(Y_t)) = \alpha + \beta t + f^T(t)\gamma_f, \quad (1)$$

where Y_t is the number of deaths at a certain week t, α, and β are regression parameters, $\gamma_{f(t)}$ is a regression parameter vector representing seasonality, and $f(t)$ is a vector of dummies that equally divides the time points outside the reference period into nine periods. The parameters, including the regression coefficients and the overdispersion parameter ϕ, were estimated using the quasi-likelihood approach.

To estimate the baseline in Equation (1), we also used the data for 2020, which was during the pandemic period (e.g. the baseline estimate for 2021). To adjust for the impact of COVID-19 on the 2020 data and obtain a robust baseline estimate, the estimate was weighted by applying Anscombe residuals, as recommended in the original articles describing the Farrington algorithm. More details can be found in other reports.[4]

Using the estimated regression parameters, the expected number of deaths was predicted for the week of interest t_0. The one-sided 95% prediction interval was then estimated by assuming that the data follow a negative binomial distribution as $Y_{t_0} \sim NB(\widehat{Y_{t_0}}, \widehat{\nu_0})$, where $\widehat{Y_{t_0}}$ is the mean of the distribution and $\widehat{\nu_0} = \frac{\widehat{Y_{t_0}}}{\hat{\varphi}-1}$ is its dispersion parameter.

Adjusting for reporting delays

The observed number of deaths may differ from the actual number of deaths due to delays in reporting deaths. The delay in reporting deaths refers to any delay in submitting death notification to municipal offices, perhaps depending on where the death occurs. Nationally, the percentage of deaths reported with a one-month delay is about 1.5% of total deaths, a two-month delay is about 0.30%, and a three-month delay is about 0.11%. Therefore, in this study, we calculated the one-to three-month reporting delay rates of deaths in March 2021 for each prefecture and used them to adjust the observed number of deaths for the most recent three-month period (i.e. April to June 2021) to account for up to three months of reporting delay.

Results

Since January 2021, excess deaths were observed for the first time in the week corresponding to April 12–18 and have continued through mid-June, with the highest excess percentage occurring in the week corresponding to May 31–June 6 (excess deaths: 1431–2587; excess percentage: 5.95–10.77%) (Fig. 1). Similarly, excess deaths were observed in consecutive weeks from April to June in 18 of 47 prefectures. The largest cumulative number of excess deaths during this period was observed in Osaka Prefecture (1527–2629), followed by Hyogo Prefecture (839–1611) and Hokkaido Prefecture (652–1491). The highest excess percentage was observed in the week corresponding to May 3–9 (315–423; 18.44–24.77%) in Osaka Prefecture, in that corresponding to April 26–May 2 (187–268; 17.35–24.86%) in Hyogo Prefecture, and in that corresponding to June 7–13 (157–232; 13.38–19.78%) in Hokkaido Prefecture. The weekly observed and expected number of deaths for 47 prefectures can be found in the Supplementary Fig. 1, and the weekly excess number of deaths since April 2021 can be found in the Supplementary Table 1.

Discussion

For the first time since February 2020, when the first COVID-19 death was reported in Japan, excess deaths possibly related to COVID-19 were observed in April 2021, during the fourth wave. Osaka is the prefecture with the highest number of observed deaths from COVID-19 since the start of 2021 through June 27, 2021 ($n = 2068$), followed by Tokyo ($n = 1596$), Hyogo ($n = 1072$), and Hokkaido ($n = 932$).[6] The number of excess deaths during this period exceeded that of the observed COVID-19 deaths, possibly reflecting the deaths of non-infected people due to the disruption that the pandemic has caused. This is a very serious indication that Japan's healthcare system, which has coped so well with the past three waves, is finally unable to withstand COVID-19. In fact, it was reported that the healthcare systems in these prefectures were strained by the surge in COVID-19 cases during the fourth wave,[7] affecting urgent and emergency care for non-infected people, as well as general medical care and hospital services. It should be noted, however, that heterogeneity in excess deaths across prefectures is not necessarily explained by the resilience of the healthcare system alone[8] but that features outside the traditional healthcare system, such as leadership, social safety nets, and trust in the system to provide information and care, are also important.[9,10]

In the midst of the fifth wave of COVID-19, which surged again in July 2021 with the spread of the Delta variant,[11] many prefectures have issued requests to medical institutions to postpone hospitalization and surgery of non-urgent general patients as much as possible and to increase the number of beds for severely ill patients with COVID-19.[12] As of September 2021, when nearly half the population has received two doses of vaccine against COVID-19, the number of daily infections remains higher than during the fourth wave, and normal medical care remains limited. Continued monitoring of excess deaths is necessary to fully understand the impact of the COVID-19 pandemic, which varies by prefectures and has had a significant indirect impact on the population health.

The same limitations exist in this analysis as in other excess deaths studies,[13] including the reliance on provisional data

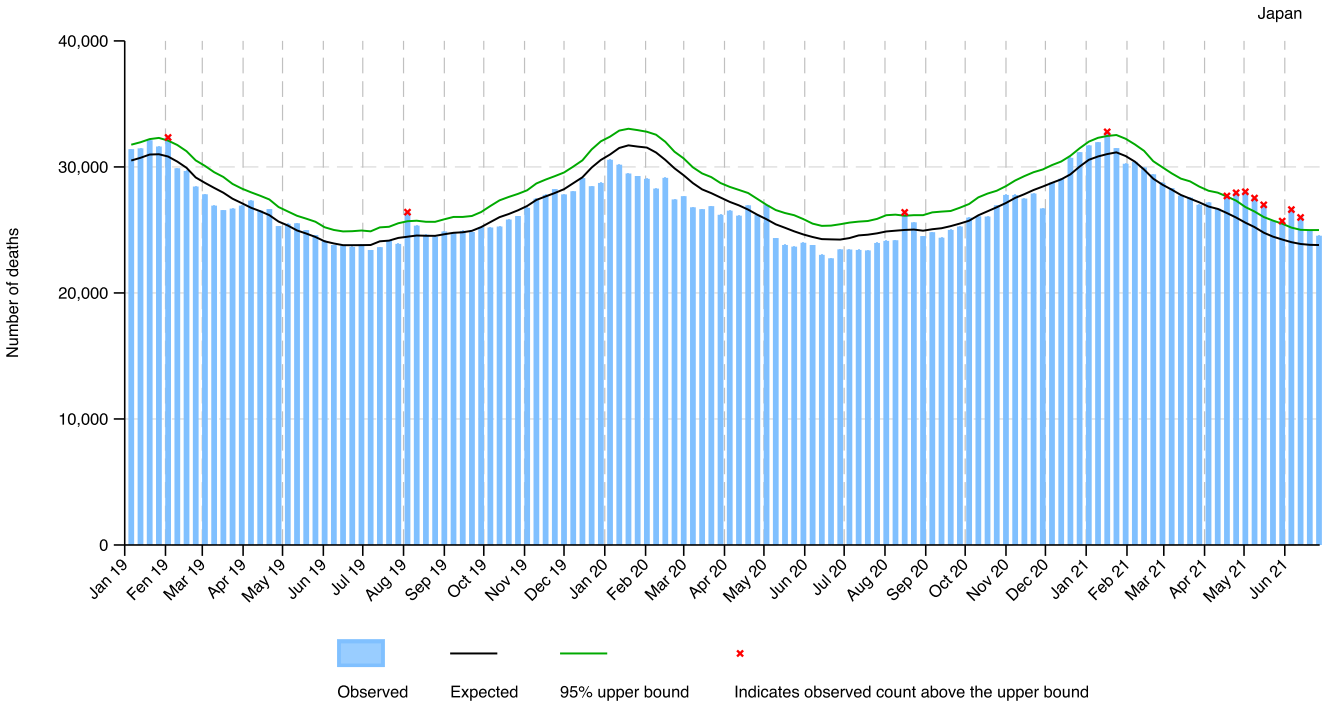

Fig. 1. Weekly observed and 95% upper bound of the expected weekly number of deaths in Japan from January 2019 through June 2021.

(although an attempt was made to adjust for reporting delays) and the assumptions applied in the model. It should be noted that the excess deaths presented in the study might be related to other factors unrelated to COVID-19.

Author statements

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Ethical approval

Ethical approval was granted by the Ethics Committee of the National Institute of Infectious Diseases, under authorization number 1174.

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Competing interests

None declared.

Author contributions

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Dr Nomura, Dr Eguchi.

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Statistical analysis: Dr Nomura, Dr Eguchi, Dr Tanoue, Dr Yoneoka, Dr Kawashima.

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Appendix A. Supplementary data

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References

1. World Health Organization. *WHO coronavirus (COVID-19) dashboard*. Geneva: World Health Organization; 2020 [cited 12 November 2021]; Available from: https://covid19.who.int/.
2. Sanmarchi F, Golinelli D, Lenzi J, Esposito F, Capodici A, Reno C, et al. Exploring the gap between excess mortality and COVID-19 deaths in 67 countries. *JAMA Netw Open* 2021;**4**:e2117359.
3. National Institute of Infectious Diseases. *Report week correspondence table [Japanese]*. Tokyo: National Institute of Infectious Diseases; 2021 [cited 12 November 2021]; Available from: https://www.niid.go.jp/niid/ja/calendar.html.
4. Noufaily A, Enki DG, Farrington P, Garthwaite P, Andrews N, Charlett A. An improved algorithm for outbreak detection in multiple surveillance systems. *Stat Med* 2013;**32**:1206–22.
5. Vestergaard LS, Nielsen J, Richter L, Schmid D, Bustos N, Braeye T, et al. Excess all-cause mortality during the COVID-19 pandemic in Europe - preliminary pooled estimates from the EuroMOMO network, March to April 2020. *Euro Surveill* 2020;**25**.
6. Toyo Keizai Online. *Coronavirus disease (COVID-19) situation report in Japan*. Tokyo: Toyo Keizai Inc.; 2020 [cited 12 November 2021]; Available from: https://toyokeizai.net/sp/visual/tko/covid19/en.html.
7. NHK WORLD-JAPAN. *Coronavirus surge strains Japan's medical system*. Tokyo: NHK; 2021 [cited 12 November 2021]; Available from: https://www3.nhk.or.jp/nhkworld/en/news/backstories/1645/.
8. Independent panel for pandemic preparedness and response. *Second report on progress for the WHO Executive Board. Geneva: Independent Panel for Pandemic*

Preparedness and Response. 2021 [cited 12 November 2021]; Available from: https://theindependentpanel.org/wp-content/uploads/2021/01/Independent-Panel_Second-Report-on-Progress_Final-15-Jan-2021.pdf.
9. Fukuyama F. *The pandemic and political order*. New York: Foreign Affairs; 2020 [cited 12 November 2021]; Available from: https://www.foreignaffairs.com/articles/world/2020-06-09/pandemic-and-political-order.
10. Bollyky TJ, Crosby S, Kiernan S. *Fighting a pandemic requires trust*. New York: Foreign Affairs; 2020 [cited 12 November 2021]; Available from: https://www.foreignaffairs.com/articles/united-states/2020-10-23/coronavirus-fighting-requires-trust.
11. Ito K, Piantham C, Nishiura H. Predicted dominance of variant Delta of SARS-CoV-2 before Tokyo olympic games, Japan, July 2021. *Euro Surveill* 2021:26.
12. The Japan Times. *Government ups pressure on Tokyo hospitals over accepting COVID-19 patients*. Tokyo: The Japan Times; 2021 [cited 12 November 2021]; Available from: https://www.japantimes.co.jp/news/2021/08/24/national/government-tokyo-hospital-beds-pressure/.
13. Weinberger DM, Chen J, Cohen T, Crawford FW, Mostashari F, Olson D, et al. Estimation of excess deaths associated with the COVID-19 pandemic in the United States, March to May 2020. *JAMA Intern Med* 2020;**180**(10):1336–44.

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Original Research

How Europeans move: a moderate-to-vigorous physical activity and sitting time paradox in the European Union

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ABSTRACT

Objectives: This study aimed to assess the interactions between physical activity (PA) and sedentary behaviour in a large population taking account of major sociodemographic characteristics.
Study design: Cross-sectional population-based study.
Methods: Data from 28,031 individuals living in the European Union who were aged ≥15 years were retrieved from a cross-sectional survey, the Eurobarometer 2017. Interactions among the four mobility components (vigorous, moderate, walking activity and sitting time) were assessed at the individual level across age, gender and place of residence, and at the country level by compositional data analysis, hierarchical linear regressions and principal component analysis.
Results: The most frequently reported PA was walking; however, sitting time represented >95% of the reported weekly times, whereas moderate-to-vigorous PA (MVPA) represented <1%. Women reported less PA and sitting time, age decreased total PA and increased sitting time, and individuals living in large urban areas reported lower PA and higher sitting times. MVPA decreased with age ($\beta = -0.047$, $P < 0.001$) and was lower in women ($\beta = -0.760$, $P < 0.001$) and those living in large urban areas ($\beta = -0.581$, $P < 0.001$), while walking and sitting times increased with age, being higher in women and lower in those living in rural areas. At the country level, sitting time was positively associated with moderate activity ($\beta = 0.389$, $P = 0.041$) and marginally non-significant with MVPA ($\beta = 0.330$, $P = 0.087$).
Conclusions: Walking was the highest contributor to weekly PA, whereas sitting time was paradoxically associated with higher MVPA. Specific measures to reduce sitting time are required to achieve an active lifestyle.

Introduction

Promoting active lifestyles in the population has important benefits, such as improving health status and preventing premature deaths.[1–4] The World Health Organisation (WHO) physical activity (PA) guidelines, established to improve population health, recommend 75 min of vigorous activity per week, 150 min of moderate activity per week or any equivalent combination of both.[5] However, lower volumes of PA have also been shown to increase life expectancy and quality of life (e.g. only 92 min per week or 15 min per day in a non-linear relationship), while increasing intensity may result in additional benefits.[6] As such, the study of PA patterns and their dissemination into different volumes and intensities (vigorous, moderate, light and very light) leads to a better understanding of their health-related impacts, interactions and the conditions that promote or limit PA.

Global health programmes to promote active lifestyles should include strategies to reduce sedentary behaviour. Many authors have described sedentary behaviour as an independent health risk factor.[7–10] Higher total PA levels seem to slightly decrease the detrimental effects of sitting time on health, although these are not eliminated completely.[7–9,11,12] Despite the rising role of sedentary behaviour in public health research, the available evidence linking sitting time with PA is scarce, and further research is required across different population groups. Increasing PA and reducing sedentary behaviours could play a critical role in health status by improving physical fitness and increasing energy expenditure.[13–16] Nonetheless, it remains debatable whether reducing sitting time results in a substantive increase in health status.[17] One perspective is that decreasing sitting time may improve health status by

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replacing it for light or very-light PA, increasing overall energy expenditure through muscle activity and energy costs.[10,18]

However, the interaction between PA and sedentary behaviour has not been rigorously investigated in large populations or taking into account sociodemographic factors, such as age, gender or place of residence. For example, age groups may interact with each other to modulate health-related lifestyle behaviours (e.g. parents' PA and sitting time could influence their children's PA),[19,20] and the relationship between activity patterns may differ across age and gender. Thus, this study aimed to identify the relationship between vigorous PA, moderate PA, walking PA and sitting time to gain a better understanding of how these behaviours are distributed and interact.

A representative sample of the European population was used in this study from the Eurobarometer 88.4, a cross-sectional survey conducted in the 28 European Union country members in 2017.[21] Reference values for total weekly energy expenditure and daily sitting time across age and gender for the European population are provided. A detailed analysis was subsequently performed of the relationship of PA pattern and sitting time, using both individual- and country-level approaches by age, gender and place of residence.

Methods

The present study was conducted according to the STROBE Statement for cross-sectional studies.[22]

Data

This study used data retrieved from the cross-sectional survey of Eurobarometer 88.4.[21] The survey was conducted between 2 December and 11 December 2017 and involved participants aged ≥15 years from the 28 European Union Member States, with approximately 1000 participants per country and a total sample size of 28,031 (54.77% women). By using a multistage random sampling method, in an iterative process, the sampling points were systematically drawn in each country according to population size and density by individual unit and type of area stratification, as well as age, gender, region and size of the locality. Finally, one participant (aged ≥15 years) in each household was randomly selected to complete a face-to-face survey by trained interviewers.

Physical activity and sedentary behaviour assessment

The International Physical Activity Questionnaire (IPAQ) was employed to assess the PA level of the population.[23] The IPAQ measures PA in a typical week according to its frequency (in days) and duration (the average minutes per day) at three different intensities (vigorous, moderate and walking). The Eurobarometer categorised the duration of PA into the following intervals: 'Never do any vigorous (or moderate) physical activity or never walk for 10 min at a time'; '30 min or less'; '31–60 min'; '61–90 min'; '91–120 min'; and 'More than 120 min'. Therefore, we applied the median values of each interval to obtain a continuous value to compute PA weekly time (note: for participants who responded 'Never do any physical activity or walk for 10 min' or 'More than 120 min', the values of 0 and 135 min were used, respectively).

In addition, we computed weekly moderate-to-vigorous physical activity (MVPA) as the sum between vigorous and moderate activity, excluding walking (despite that it is also considered a moderate activity), and total health-enhancing physical activity (HEPA, also as total PA) as the sum of the three intensities. HEPA was also expressed in metabolic equivalent of tasks (METs) per week as a relative measure of energy expenditure from resting values for percentile quantification across age groups, as detailed in the 'Statistical analyses' subsection. Each minute of vigorous, moderate and walking activity corresponds to 8, 4, and 3.3 METs, respectively. Further information related to METs for different activities is provided elsewhere.[24,25]

Last, individuals were classified into active or inactive categories according to the WHO PA recommendations.[5] To be active, individuals must accomplish at least one of the following criteria: 150 min of moderate PA per week; 75 min of vigorous PA per week; or any equivalent combination of vigorous and moderate PA.

Sedentary behaviour was assessed as sitting time in minutes per day, using the IPAQ. Sitting time was categorised into intervals ranging from '1 h or less', '1 h and 1 min to 1 h and 30 min', with subsequent increments of 1 h until 'more than 8 h and 30 min'. The median sitting time in minutes per day was computed, using 540 min (9 h) as the upper limit.

Statistical analyses

First, descriptive statistics (mean ± standard deviation [SD]) were calculated for weekly vigorous PA, moderate PA, walking PA, MVPA and HEPA, as well as daily sitting time across sociodemographic factors (i.e. gender, six age groups, place of residence, compliance with PA guidelines and country). HEPA expressed in MET-min/week were also reported by gender and age groups as mean, SD and percentiles (5th, 10th, 25th, 50th, 75th, 90th and 95th).

Second, two different approaches were carried out at the individual- and country-level to assess PA patterns. In the individual approach, compositional data analysis was executed among MVPA, walking and sitting time to analyse absolute and relative contributions to weekly IPAQ-reported activity, as well as interactions among the different and exclusive behaviours.[26] We transformed daily sitting time to weekly time to unify all variables in a weekly scale. Thus, we computed the absolute contribution means of the three components by using the geometric means. Subsequently, we obtained isometric log ratios, also called pivot coordinates, which represent the contribution of a given behaviour with respect to the overall PA pattern. Because many individuals do not perform MVPA, 0 values were imputed by pseudo-zeros of 0.01 min per week to allow these calculations. Hierarchical linear regressions were then modelled using the isometric log ratios to examine how the contributions differ by age, gender and place of residence. The models included a random intercept for the country and a random slope to age (level 1) for countries (level 2), as individuals are nested in countries. These models were also used to address the variability between countries.

Furthermore, at the country level, multiple linear regression models were carried out using vigorous PA, moderate PA, walking PA and sitting time as outcomes, using the others as predictors and adjusting for mean age per country. MVPA was also modelled against walking and sitting time, as well as HEPA against sitting time. Robust linear regression was applied using an 'M' estimation when any assumption was violated. Moreover, to assess multivariate interactions, two principal component analyses were performed scaling to unit variance: first with three weekly PA components (vigorous, moderate and walking) and second, using MVPA, walking and daily sitting time.

Individuals with missing data in any of IPAQ's questions or illogical answers were removed (n = 8269; 29.50%). Illogical answers included participants who selected multiple categories; for example, participants who reported that they perform PA '1 or more days per week' and 'Never do physical activity' in the intensity component, or 'zero days per week' and 'more than zero minutes' in the duration questions. The statistical significance level was set at

5%, and all statistical analyses were run employing Rstudio version 3.6.1.

Results

Population levels of physical activity and sitting time

Table 1 shows descriptive statistics of the different PA intensities and daily sitting times by sociodemographic factors.

For the total study population, an increase in the frequency of volume of PA was associated with a reduction in intensity, with an MVPA of 247.13 ± 367.16 min/week and a HEPA of 447.40 ± 488.59 min/week, whereas sitting time was 302.74 ± 147.22 min/day.

In terms of gender, men reported more PA and sitting time than women, excluding days of walking, which were higher in women than men (4.44 ± 2.56 vs 4.34 ± 2.56 days).

Vigorous PA decreased as age increased. There was a small increase in moderate activity levels and walking activity with age, but these decreased considerably in those aged ≥65 years. MVPA and HEPA also decreased with age, whereas sitting time slowly increased from the age of 25 years (285.13 ± 151. min/day) to those aged ≥65 years (321.99 ± 141.46 min/day). Further descriptive results of physical activity and sitting time levels across age and gender are provided in the supplementary material (Fig. S1).

Regarding the place of residence, participants living in large urban environments showed the lowest vigorous and moderate PA patterns but more walking frequency compared with those living in small urban environments. Moreover, MVPA was slightly higher in rural areas, while HEPA was higher in small urban areas. Sitting time was higher in large urban environments, but this study found no differences in sitting time between rural and small urban places.

It is interesting to note that the difference in daily sitting time between participants with an active lifestyle and those with an inactive lifestyle is smaller than the differences observed between these two lifestyle groups in all other categories of physical activity type (see Table 1).

Descriptive results of physical activity and sitting time across the 28 European Union country members are presented in the supplementary material (Table S1).

The asymmetric distribution of HEPA energy expenditure percentiles showed that, regardless of age and gender, most European individuals reported a low level of total PA (Fig. 1, Tables S2 and S3). With increasing age, HEPA percentiles decrease in both genders. Furthermore, the percentiles for women in all age groups were lower than for men; that is, women are more inactive and perform less PA.

Interactions between physical activity, walking and sitting time

In a typical week, the absolute and relative mean contributions to the analysed activity pattern were 4.584 min (0.25%) of MVPA, 43.276 min (2.37%) of walking and 1782.15 min (97.38%) of sitting. Ternary plots showed a high proportion of sitting time (>90%) for all age groups. MVPA decreases with age in men, and there is a corresponding increase in sitting time (Fig. 2a). In contrast, MVPA levels are low for women in all age groups. However, women reported more walking activity than men. For women of all ages, increases in sitting time were associated with reductions in levels of walking. In terms of place of residence, rural areas showed lower walking and higher sitting times (Fig. 2b).

Hierarchical linear regression models at the individual level (Table 2) revealed that MVPA decreased with age and was lower in women and individuals living in large urban areas. Walking

Table 1
Descriptive results at the individual level of physical activity and sitting time by sociodemographic factors and active/inactive status in the European Union-28, 2017.

Sociodemographic factors and active/inactive status	n (%)	Vigorous PA		Moderate PA		Walking		MVPA	HEPA	Sitting
		Days	Weekly time	Days	Weekly time	Days	Weekly time	Weekly time	Total weekly time	Daily time
Overall	19,762 (100)	1.52 ± 2.04	110.87 ± 196.99	2.11 ± 2.40	136.27 ± 215.18	4.40 ± 2.56	200.26 ± 220.42	247.13 ± 367.16	447.40 ± 488.59	302.74 ± 147.22
Gender										
Men	9047 (45.78)	1.79 ± 2.13	139.47 ± 218.31	2.27 ± 2.39	152.74 ± 224.51	4.34 ± 2.56	203.03 ± 229.53	292.22 ± 397.90	495.25 ± 525.17	308.05 ± 146.17
Women	10,715 (54.22)	1.30 ± 1.95	87.71 ± 173.37	1.98 ± 2.40	122.35 ± 205.97	4.44 ± 2.56	197.93 ± 212.42	209.07 ± 334.36	407.00 ± 451.51	298.26 ± 147.96
Age group (years)										
15–24	1653 (8.36)	2.20 ± 2.05	154.19 ± 196.92	2.57 ± 2.24	150.23 ± 189.36	5.02 ± 2.26	220.53 ± 223.36	304.42 ± 339.43	524.95 ± 454.58	318.16 ± 148.04
25–34	2541 (12.86)	2.00 ± 2.13	146.89 ± 218.21	2.43 ± 2.38	162.77 ± 231.50	4.71 ± 2.43	216.89 ± 225.19	309.66 ± 400.25	526.55 ± 514.96	285.13 ± 151.47
35–44	3021 (15.29)	1.76 ± 2.08	132.31 ± 215.59	2.21 ± 2.35	149.39 ± 229.50	4.36 ± 2.51	199.09 ± 223.41	281.70 ± 402.50	480.79 ± 527.74	284.70 ± 149.12
45–54	3272 (16.56)	1.62 ± 2.09	120.58 ± 207.41	2.13 ± 2.38	139.64 ± 221.44	4.35 ± 2.56	202.23 ± 227.85	260.23 ± 379.90	462.46 ± 503.53	295.06 ± 150.06
55–64	3568 (18.05)	1.41 ± 2.03	104.55 ± 197.17	2.13 ± 2.44	142.12 ± 223.08	4.40 ± 2.54	208.34 ± 228.19	246.67 ± 376.02	455.01 ± 503.57	299.70 ± 144.37
≥65	5707 (28.88)	1.00 ± 1.83	69.31 ± 158.84	1.78 ± 2.41	107.88 ± 194.25	4.11 ± 2.69	181.42 ± 204.64	177.20 ± 311.46	358.61 ± 429.43	321.99 ± 141.46
Place of residence[a]										
Rural	5708 (28.88)	1.61 ± 2.15	121.12 ± 213.63	2.19 ± 2.46	146.95 ± 229.67	4.14 ± 2.66	189.60 ± 218.08	268.07 ± 397.16	457.67 ± 521.71	292.88 ± 146.96
Small urban	6525 (33.02)	1.56 ± 2.04	112.95 ± 196.63	2.20 ± 2.41	144.85 ± 223.20	4.32 ± 2.59	207.02 ± 231.67	257.80 ± 372.19	464.82 ± 502.22	295.59 ± 147.03
Large urban	7529 (38.10)	1.42 ± 1.96	101.29 ± 183.25	1.98 ± 2.33	120.73 ± 194.92	4.66 ± 2.44	202.49 ± 211.76	222.02 ± 336.41	424.51 ± 448.15	316.43 ± 146.57
Physical Activity status[b]										
Active	13,460 (68.11)	2.20 ± 2.15	162.17 ± 220.69	2.98 ± 2.40	197.53 ± 236.80	5.19 ± 2.10	272.59 ± 232.49	359.70 ± 397.51	632.29 ± 492.27	288.36 ± 139.32
Inactive	6302 (31.89)	0.07 ± 0.33	1.30 ± 5.93	0.28 ± 0.88	5.41 ± 17.08	2.69 ± 2.63	45.78 ± 43.38	6.71 ± 19.20	52.49 ± 45.23	333.48 ± 158.53

PA, physical activity; MVPA, moderate-to-vigorous physical activity; HEPA, health-enhancing physical activity.
[a] Residence place was classified according to European Commission.
[b] Physical status active or inactive was determined according to the WHO guidelines.

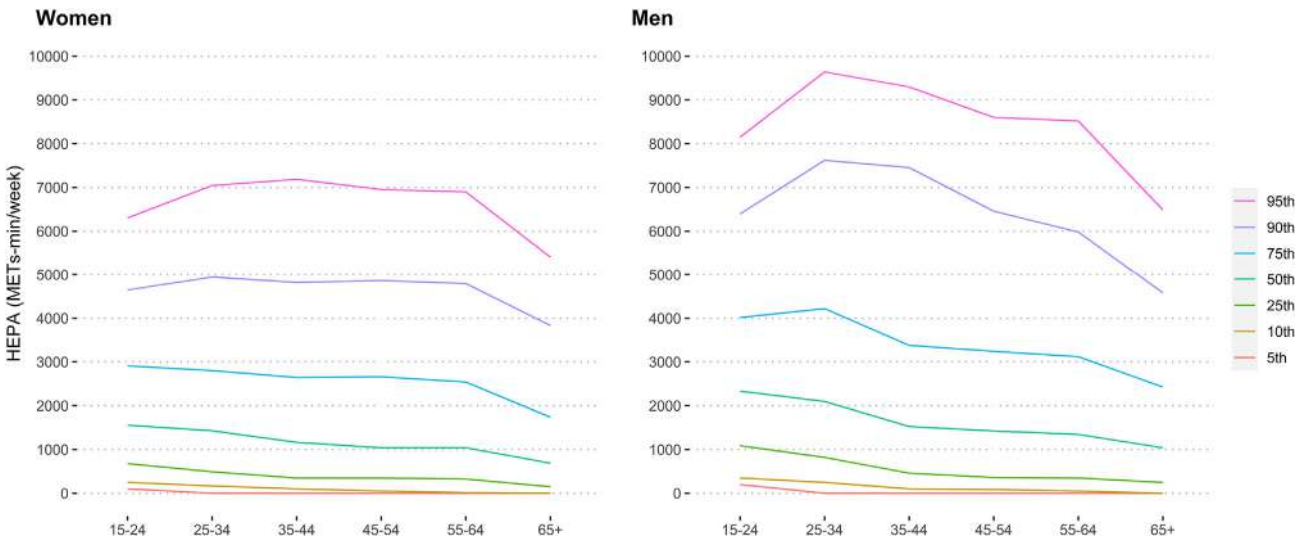

Fig. 1. Percentiles of Health-Enhancing Physical Activity (HEPA) across age groups and gender expressed as Weekly Metabolic Equivalents of Task (METs) in minutes. HEPA is the sum of vigorous, moderate and walking activity's METs. European Union-28, 2017.

increased with age and was higher in women and those living in small and large urban areas. Finally, sitting time also increased with age and was higher in women but lower in participants living in small urban areas.

At the country level (Table 3), the association between physical activity type and sitting time was analysed. Vigorous PA and moderate PA were associated, and walking was only associated with MVPA. Daily sitting time was not associated with total PA (HEPA) in the European population.

The principal component analysis among PA components (i.e. vigorous, moderate and walking activity) showed that all variables are towards the same direction (i.e. right, indicating higher activity), and moderate and vigorous PA are closely aligned (Fig. S2a). The second principal component analysis (Fig. S2b) showed that MVPA and walking activity behaviour are not inversely related with mean daily sitting time.

Discussion

We found that daily sitting time was paradoxically associated with HEPA as there are countries with high PA and sedentary behaviour, such as the Netherlands. In this study, sitting time is shown to be a persistent behaviour, whereas walking is the predominant PA type at the individual level, with higher volume and frequency compared with other types of PA. Consistent with other studies, walking contributes significantly to HEPA level.[27,28] This study also established that, at the country level, vigorous PA and moderate PA are strongly associated. However, the results of the compositional analysis showed that, on average, 97.38% of the reported weekly activity patterns were sitting time, and MVPA did not reach 1%. The current analyses revealed that sitting time could not be explained by changes in the amount of weekly PA pattern. This noteworthy finding indicates that sitting time is a very widespread behaviour and is not influenced by an increase in weekly PA.

The unexpected lack of association between sitting time and overall PA contradicts previous studies that have shown increased walking and MVPA levels to be associated with reduced sitting times.[29] As such, this study has observed an activity-sedentary paradox among European countries and populations. Furthermore, we must consider that there is little evidence of the combined impact of PA and sedentary behaviour on health. Some researchers have found that the harmful effects of sitting time can be offset by a high PA level (>35.5 MET-h/week);[30] although other authors have found that it can be only partially offset.[8,9,11] Therefore, future studies of PA should also include sedentary behaviours as an independent risk factor.

Moreover, age, gender and other sociodemographic factors impact daily PA,[31–33] but little is known about their influence on sitting time. This study has found that all types of PA decrease with age, whereas sitting time increases. In addition, being a woman or living in large urban areas are associated with a lower HEPA and higher sitting time. Rural areas also reported a higher proportion of sitting and a lower proportion of walking, showing a gradient from rural to large urban areas. Previous reports have described lower PA and higher sitting time in older adults, women and rural settings.[34–39] Place of residence and environmental factors that impact sitting time and light-intensity PA may become more relevant because leisure-time PA is socially biased, and it is not the main source of daily energy expenditure for the whole population.[40,41] Some studies have reported that changes in moderate-to-vigorous leisure-time PA levels do not always reduce obesity nor increase energy expenditure.[42] Also, most populations describe only modest contributions by these MVPAs to daily energy expenditure[41] and, according to the results of the current study, increased walking could improve PA in the European population.

These PA levels and differences among population groups may correspond to individual particularities, such as lack of motivation, lack of time, or work and family barriers and their characteristics (e.g. time of the day, venue, the social condition of the activity, among others).[43] However, social determinants and better living conditions (e.g. educational level, social class, income or gender equality), in particular, may help achieve the goal of increasing walking by means of daily commuting and other non-leisure PA.[27,44–49] Light PA may also contribute significantly to total daily PA because, at these intensities, the population can maintain large volumes of PA and, more importantly, can replace sitting time. Several experimental studies indicate that under prolonged and continuous sitting time, brief breaks to a standing position may counter adverse effects to the metabolism and breaks, including light PA, could even improve health status.[16,50,51]

Future research should analyse the combination of sedentary behaviour with PA using both experimental and epidemiological approaches. Current experimental research conducted on breaks

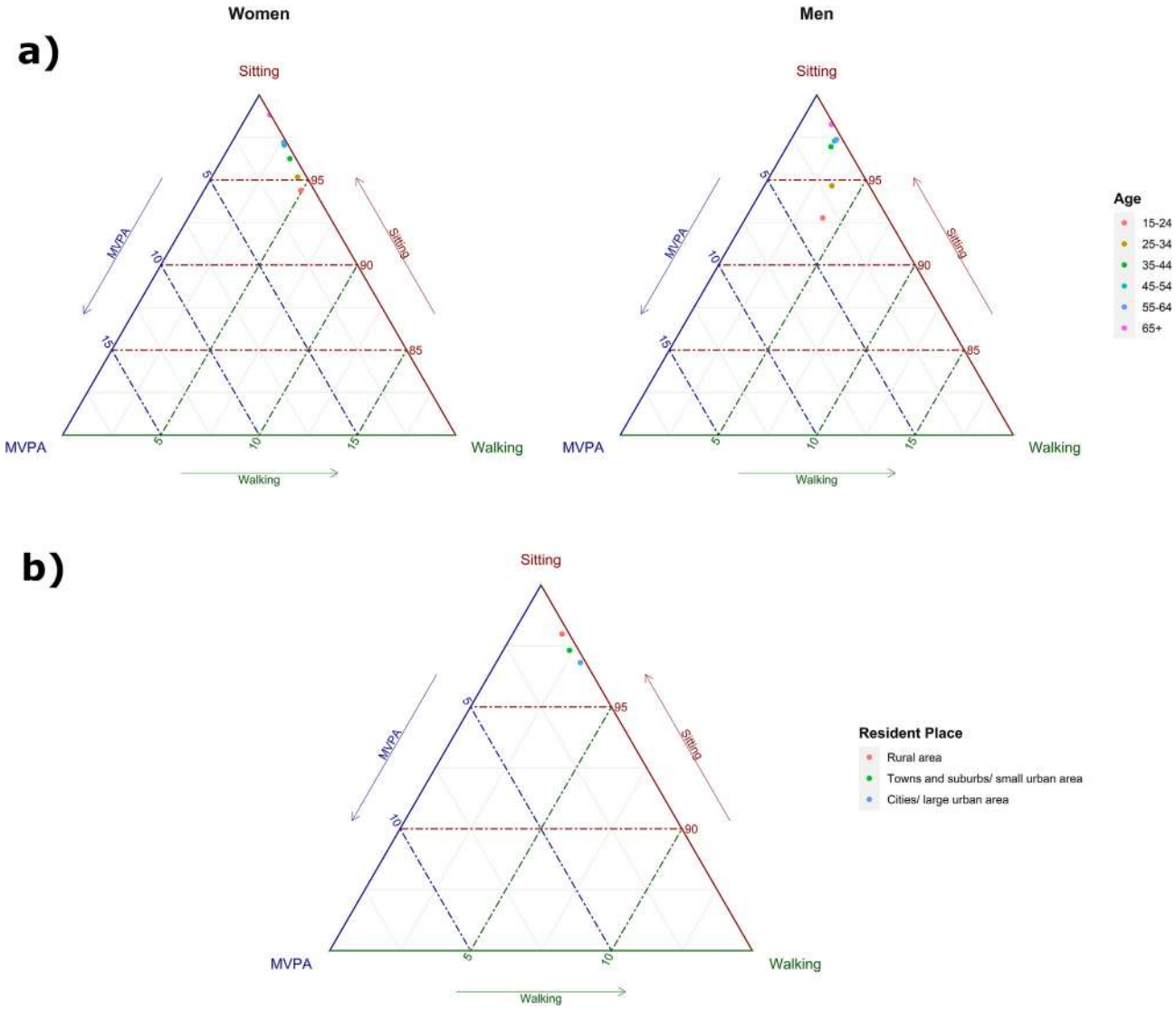

Fig. 2. Ternary plots of weekly compositional data analysis among moderate-to-vigorous physical activity (MVPA), walking and sitting total time in minutes across (a) age groups and gender, and (b) different places of residence. The residence place was classified according to European Commission. Points represent the centre using geometric means from each pattern component. European Union-28, 2017.

Table 2
Contributions to weekly activity and sociodemographic factors by age-adjusted hierarchical linear regression's unstandardised beta coefficients in the European Union-28, 2017.

Sociodemographic factor[a]	MVPA		Walking		Sitting	
	β (95% CI)	*P*-Value	β (95% CI)	*P*-Value	β (95% CI)	*P*-Value
Age	−0.047 (−0.053, −0.042)	<0.001	0.007 (0.003, 0.011)	0.002	0.041 (0.036, 0.045)	<0.001
Gender						
Women	−0.760 (−0.861, −0.658)	<0.001	0.431 (0.353, 0.508)	<0.001	0.329 (0.255, 0.404)	<0.001
Place of residence[b]						
Small urban	−0.089 (−0.223, 0.045)	0.192	0.291 (0.189, 0.393)	<0.001	−0.204 (−0.302, −0.106)	<0.001
Large urban	−0.581 (−0.711, −0.452)	<0.001	0.673 (0.574, 0.771)	<0.001	−0.094 (−0.189, 0.001)	0.053

CI, confidence interval; MVPA, moderate-to-vigorous physical activity.
[a] Reference groups were men and rural residence place.
[b] Residence place was classified according to European Commission.

during the sitting time are providing evidence about those 'sedentary' physiological pathways that can have harmful effects on health.[7,16,52] In addition, new epidemiological studies are showing how and why PA and sedentary behaviours are formed, their factors, determinants and correlates.[53]

The current study has some limitations. First, the cross-sectional study design excludes cause-effect implications. Second, the use of the IPAQ implies a subjective assessment based on memory and recall. The IPAQ was validated to evaluate PA in large samples, but its application tends to overestimate PA and underestimate sitting

Table 3
Associations between physical activity types and sitting time at the country level by age-adjusted multiple linear regression's unstandardised beta coefficients in the European Union-28, 2017.

Physical activity type	Vigorous PA		Moderate PA		Walking		Sitting		MVPA		HEPA	
	β (95% CI)	*P*-Value	β (95% CI)	*P*-Value	β (95% CI)	*P*-Value	β (95% CI)	*P*-Value	β (95% CI)	*P*-Value	β (95% CI)	*P*-Value
Vigorous PA			1.052 (0.748, 1.355)	<0.001	0.316 (−0.447, 1.079)	0.402	−0.359 (−1.139, 0.359)	0.316				
Moderate PA	0.646 (0.484, 0.808)	<0.001			0.586 (−0.003, 1.174)	0.050	0.538 (−0.016, 1.092)	0.072				
Walking	0.077 (−0.071, 0.225)	0.309	0.139 (−0.075, 0.353)	0.191			−0.135 (−0.440, 0.171)	0.400	1.183 (0.738, 1.627)	<0.001		
Sitting	−0.076 (−0.274, 0.122)	0.461	0.286 (0.011, 0.561)	0.042	−0.229 (−0646, 0.187)	0.300			0.708 (−0.097, 1.513)	0.082	0.951 (−0.855, 2.756)	0.289

CI, confidence interval; PA, physical activity; MVPA, moderate-to-vigorous physical activity; HEPA, health-enhancing physical activity.

time.[23] Additionally, self-reported PA assessments may undervalue the actual amount of activity energy expenditure on ill and old-aged populations, leading to profile misclassification (active/inactive).[54] The IPAQ's estimations also vary between countries[55] according to residence location, with lower validity results in rural populations.[56] Third, light PA (<3 METs) could not be measured by the IPAQ; hence, we used walking activity as a proxy. Therefore, compositional analysis of mobility patterns consisted of an incomplete spectrum of total weekly activity data, in addition to previous biases, such as duration interval. Last, other social determinants may alter activity and sedentary patterns as active prevalence and total PA. Education attainment, occupational social class, subjective social class and household incomes are strong social determinants, showing a descending social gradient of health and PA from high to low social status.[33,47,57,58] Nonetheless, the objective of this study was to provide an initial overview of PA patterns in Europe.

In summary, higher daily PA is not necessarily associated with lower sitting time. In fact, countries could present both high PA and sitting time. Sitting time appears to be a consistent behaviour across sociodemographic characteristics in European countries. The relationship between MVPA and sitting time differs across sociodemographic characteristics, such as age, gender and place of residence. Moreover, walking behaviour was the highest contributor to weekly PA, showing narrower sociodemographic differences among population groups. Public health policies should consider not only promoting PA, but also reducing sitting time because sitting time could not be explained by changes in PA patterns.

Author statements

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Ethical approval

Not applicable.

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Competing interests

The authors have no conflict of interest to declare.

Availability of data and materials

Data are from the GESIS Leibniz Institute for the Social Sciences.

Authors' contributors

A.M.L contributed to performing the study and data analysis. J.G.M contributed to performing the study. E.D.C.S participated in the design of the study and contributed to performing the study and data analysis. All authors contributed to the writing of the manuscript. All authors have read and approved the final version of the manuscript and agree with the order of the presentation of the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.11.016.

References

1. Shiroma EJ, Sesso HD, Moorthy MV, Buring JE, Lee IM. Do moderate-intensity and vigorous-intensity physical activities reduce mortality rates to the same extent? *J Am Heart Assoc.* 2014;**3**(5):7–9.
2. Foulds HJA, Bredin SSD, Charlesworth SA, Ivey AC, Warburton DER. Exercise volume and intensity: a dose-response relationship with health benefits. *Eur J Appl Physiol* 2014;**114**(8):1563–71.
3. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol* 2017;**32**(5):541–56.
4. Rhodes RE, Janssen I, Bredin SSD, Warburton DER, Bauman A. Physical activity: health impact, prevalence, correlates and interventions. *Psychol Health* 2010;**32**(8):942–75.
5. World Health Organization. *Global recommendations on physical activity for health*. Geneva. 2010. Available from: https://apps.who.int/iris/bitstream/handle/10665/44399/9789241599979_eng.pdf;jsessionid=2D26B672A1A89A911289DEB5248F036F?sequence=1.
6. Wen CP, Wai JPM, Tsai MK, Yang YC, Cheng TYD, Lee MC, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 2011;**378**(9798):1244–53.
7. Tremblay MS, Healy GN, Owen N, Colley RC, Saunders TJ. Physiological and health implications of a sedentary lifestyle. *Appl Physiol Nutr Metabol* 2010;**35**(6):725–40.
8. Chau JY, Grunseit AC, Chey T, Stamatakis E, Brown WJ, Matthews CE, et al. Daily sitting time and all-cause mortality: a meta-analysis. *PLoS One* 2013;**8**(11):e80000.
9. Patel AV, Bernstein L, Deka A, Feigelson HS, Campbell PT, Gapstur SM, et al. Leisure time spent sitting in relation to total mortality in a prospective cohort of US adults. *Am J Epidemiol* 2010;**172**(4):419–29.
10. van der Ploeg HP, Hillsdon M. Is sedentary behaviour just physical inactivity by another name? *Int J Behav Nutr Phys Activ* 2017;**14**(1):1–8.
11. Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia* 2012;**55**(11):2895–905.
12. Ding D, Mutrie N, Bauman A, Pratt M, Hallal PRC, Powell KE. Physical activity guidelines 2020: comprehensive and inclusive recommendations to activate populations. *Lancet* 2020;**396**(10265):1780–2.
13. Gebel K, Ding D, Bauman AE. Volume and intensity of physical activity in a large population-based cohort of middle-aged and older Australians: prospective relationships with weight gain, and physical function. *Prev Med* 2014;**60**:131–3.
14. Knaeps S, Bourgois JG, Ch6arlier R, Mertens E, Lefevre J. Associations between physical activity and health-related fitness–volume versus pattern. *J Sports Sci* 2016;**35**(6):539–46.
15. Raichlen DA, Pontzer H, Zderic TW, Harris JA, Mabulla AZP, Hamilton MT, et al. Sitting, squatting, and the evolutionary biology of human inactivity. *Proc Natl Acad Sci U S A* 2020;**117**(13):7115–21.
16. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population-health science of sedentary behavior. *Exerc Sport Sci Rev* 2010;**38**(3):105–13.
17. Du Y, Liu B, Sun Y, Snetselaar LG, Wallace RB, Bao W. Trends in adherence to the physical activity guidelines for Americans for aerobic activity and time spent on sedentary behavior among US adults, 2007 to 2016. *JAMA Netw Open* 2019;**2**(7):e197597.
18. Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. *Diabetes* 2007;**56**:2655–67.
19. Boente-Antela B, Leirós-Rodríguez R, García-Soidán JL. Son los adultos un modelo de conducta influyente en los hábitos de actividad física en los menores. *Retos* 2021;**2041**(39):306–11.
20. García-Soidán JL, Leirós-Rodríguez R, Romo-Pérez V, Arufe-Giráldez V. Evolution of the habits of physical activity and television viewing in Spanish children and pre-adolescents between 1997 and 2017. *Int J Environ Res Publ Health* 2020;**17**(18):1–14.
21. European Commission. Eurobarometer 88.4. In: *TNS opinion, brussels [internet]*. Cologne: GESIS Data Archive; 2017. https://doi.org/10.4232/1.13065. 2018. Available from:.
22. STROBE Statement. STROBE Statement – checklist of items that should be included in reports of observational studies (© STROBE Initiative). *Int J Publ Health* 2008;**53**(1):3–4.
23. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-Country reliability and validity. *Med Sci Sports Exerc* 2003;**35**(8):1381–95.
24. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. 2011 compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011;**43**(8):1575–81.
25. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of Physical Activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;**32**(Supplement):S498–516.
26. Dumuid D. Pediši Ž, palarea-albaladejo J, martín-fernández JA, hron K, olds T. *Compositional Data Analysis in Time-Use Epidemiology: What, Why, How. Int J Environ Res Public Health* 2020;**17**(7):2220.
27. Westerterp KR. Pattern and intensity of physical activity. *Nature* 2001;**410**(6828):539.
28. Rutten A, Abu-Omar K. Prevalence of physical activity in the European Union. *Sozial-und Praventivmedizin* 2004;**49**(4):281–9.
29. Farrahi V, Niemelä M, Kärmeniemi M, Puhakka S, Kangas M, Korpelainen R, et al. Correlates of physical activity behavior in adults: a data mining approach. *Int J Behav Nutr Phys Activ* 2020;**17**:94.
30. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet* 2016;**388**(10051):1302–10.
31. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJF, Martin BW, et al. Correlates of physical activity: why are some people physically active and others not? *Lancet* 2012;**380**(9838):258–71.
32. Althoff T, Sosič R, Hicks JL, King AC, Delp SL, Leskovec J. Large-scale physical activity data reveal worldwide activity inequality. *Nature* 2017;**547**(7663):336–9.
33. O'Donoghue G, Kennedy A, Puggina A, Aleksovska K, Buck C, Burns C, et al. Socio-economic determinants of physical activity across the life course: a "DEterminants of DIet and Physical ACtivity" (DEDIPAC) umbrella literature review. *PLoS ONE* 2018;**13**:e0190737.
34. Smith L, Gardner B, Fisher A, Hamer M. Patterns and correlates of physical activity behaviour over 10 years in older adults: prospective analyses from the English Longitudinal Study of Ageing. *BMJ Open* 2015;**5**:e007423.
35. Moreno-Llamas A, García-Mayor J. De la Cruz-Sánchez E. Urban-rural differences in trajectories of physical activity in Europe from 2002 to 2017. *Health Place* 2021;**69**:102570.
36. Fan JX, Wen M, Kowaleski-Jones L. Rural-urban differences in objective and subjective measures of physical activity: findings from the national health and nutrition examination survey (NHANES) 2003-2006. *Prev Chronic Dis* 2014;**11**:8–10.
37. Parks SE, Housemann RA, Brownson RC. Differential correlates of physical activity in urban and rural adults of various socioeconomic backgrounds in the United States. *J Epidemiol Community Health* 2003;**57**(1):29–35.
38. Owen N, Sugiyama T, Eakin EE, Gardiner PA, Tremblay MS, Sallis JF. Adults' sedentary behavior: determinants and interventions. *Am J Prev Med* 2011;**41**(2):189–96.
39. Varo JJ, Martínez-González MA. Irala-Estévez J de, Kearney J, Gibney M, Martínez JA. Distribution and determinants of sedentary lifestyles in the European Union. *Int J Epidemiol* 2003;**32**(1):138–46.
40. Straker L, Holtermann A, Lee I-M, van der Beek AJ, Stamatakis E. Privileging the privileged: the public health focus on leisure time physical activity has contributed to widening socioeconomic inequalities in health. *Br J Sports Med* 2021;**55**(10):525–6.
41. Strain T, Wijndaele K, Garcia L, Cowan M, Guthold R, Brage S, et al. Levels of domain-specific physical activity at work, in the household, for travel and for leisure among 327 789 adults from 104 countries. *Br J Sports Med* 2020;**54**(24):1488–97.
42. Bauman A, Allman-Farinelli M, Huxley R, James WPT. Leisure-time physical activity alone may not be a sufficient public health approach to prevent obesity - a focus on China. *Obes Rev* 2008;**9**(SUPPL. 1):119–26.
43. Iolascon G, Gimigliano F, Di Pietro G, Moretti A, Paoletta M, Rivezzi M, et al. Personalized paths for physical activity: developing a person-centered quantitative function to determine a customized amount of exercise and enhancing individual commitment. *BMC Sports Sci Med Rehabil* 2021;**13**(1):1–15.
44. Sallis JF, Cerin E, Conway TL, Adams MA, Frank LD, Pratt M, et al. Physical activity in relation to urban environments in 14 cities worldwide: a cross-sectional study. *Lancet* 2016;**387**(10034):2207–17.
45. Hallal PC, Bauman AE, Heath GW, Kohl HW, Lee I-M, Pratt M. Physical activity: more of the same is not enough. *Lancet* 2012;**380**(9838):190–1.
46. Brown WJ, Mielke GI, Kolbe-Alexander TL. Gender equality in sport for improved public health. *Lancet* 2016;**388**(10051):1257–8.
47. Moreno-Llamas A, García-Mayor J. De la Cruz-Sánchez E. Physical activity barriers according to social stratification in Europe. *Int J Publ Health* 2020 Sep 28;**65**:1477–84.
48. García-Mayor J, Moreno-Llamas A. De la Cruz-Sánchez E. High educational attainment redresses the effect of occupational social class on health-related lifestyle: findings from four Spanish national health surveys. *Ann Epidemiol* 2021;**58**:29–37.
49. Stringhini S, Carmeli C, Jokela M, Avendaño M, McCrory C, D'Errico A, et al. Socioeconomic status, non-communicable disease risk factors, and walking speed in older adults: multi-cohort population based study. *BMJ* 2018;**360**:1–10.
50. Winkler EAH, Chastin S, Eakin EG, Owen N, Lamontagne AD, Moodie M, et al. Cardiometabolic impact of changing sitting, standing, and stepping in the workplace. *Med Sci Sports Exerc* 2018;**50**(3):516–24.
51. Hadgraft NT, Winkler E, Climie RE, Grace MS, Romero L, Owen N, et al. Effects of sedentary behaviour interventions on biomarkers of cardiometabolic risk in

adults: systematic review with meta-analyses. *Br J Sports Med* 2021;**55**(3):144–54.
52. Larsen R, Ali H, Dempsey PC, Grace M, Dillon F, Kingwell BA, et al. Interrupting sitting time with simple resistance activities lowers postprandial insulinemia in adults with overweight or obesity. *Obesity* 2019;**27**(9):1428–33.
53. Werneck AO, Sadarangani KP, Ramírez-Vélez R, Baldew SS, Gomes TN, Ferrari G, et al. Macroeconomic, demographic and human developmental correlates of physical activity and sitting time among South American adults. *Int J Behav Nutr Phys Activ* 2020;**17**(1):1–13.
54. Dibben GO, Gandhi MM, Taylor RS, Dalal HM, Metcalf B, Doherty P, et al. Physical activity assessment by accelerometry in people with heart failure. *BMC Sports Sci Med Rehabil* 2020;**12**(1):1–12.
55. Cerin E, Cain KL, Oyeyemi AL, Owen N, Conway TL, Cochrane T, et al. Correlates of agreement between accelerometry and self-reported physical activity. *Med Sci Sports Exerc* 2016;**48**(6):1075–84.
56. Lachat CK, Verstraeten R, Khanh LNB, Hagströmer M, Khan NC, Van NDA, et al. Validity of two physical activity questionnaires (IPAQ and PAQA) for Vietnamese adolescents in rural and urban areas. *Int J Behav Nutr Phys Activ* 2008;**5**(37).
57. Marmot M. Social determinants of health inequalities. *Lancet* 2005;**365**(9464):1099–104.
58. Marmot M. Understanding social inequalities in health. *Perspect Biol Med* 2003;**46**(3 SUPPL).

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Original Research

Investigating the association between COVID-19 vaccination and care home outbreak frequency and duration

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ABSTRACT

Objectives: At the end of 2020, many countries commenced a vaccination programme against SARS-CoV-2. Public health authorities aim to prevent and interrupt outbreaks of infectious disease in social care settings. We aimed to investigate the association between the introduction of the vaccination programme and the frequency and duration of COVID-19 outbreaks in Northern Ireland (NI).
Study design: We undertook an ecological study using routinely available national data.
Methods: We used Poisson regression to measure the relationship between the number of RT-PCR confirmed COVID-19 outbreaks in care homes, and as a measure of community COVID-19 prevalence, the Office for National Statistics COVID-19 Infection Survey estimated the number of people testing positive for COVID-19 in NI. We estimated the change in this relationship and estimated the expected number of care home outbreaks in the absence of the vaccination programme. A Cox proportional hazards model estimated the hazard ratio of a confirmed COVID-19 care home outbreak closure.
Results: Care home outbreaks reduced by two-thirds compared to expected following the introduction of the vaccination programme, from a projected 1625 COVID-19 outbreaks (95% prediction interval 1553 −1694) between 7 December 2020 and 28 October 2021 to an observed 501. We estimated an adjusted hazard ratio of 2.53 of the outbreak closure assuming a 21-day lag for immunity.
Conclusions: These findings describe the association of the vaccination with a reduction in outbreak frequency and duration across NI care homes. This indicates probable reduced harm and disruption from COVID-19 in social care settings following vaccination. Future research using individual level data from care home residents will be needed to investigate the effectiveness of the vaccines and the duration of their effects.

Introduction

COVID-19 has caused a disproportionately high number of deaths among the residents of care homes in the UK;[1] an experience shared by other countries.[2–5] In Northern Ireland (NI), there

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have been 1127 COVID-19-related deaths among care home residents by the week ending 5 November 2021.[6] Care home residents may be at high risk of exposure to SARS-CoV-2 because of outbreaks in these closed settings and greater vulnerability to severe outcomes because of age and comorbidities.[2,3] A range of factors contribute to the risk, size and duration of outbreaks in care homes, including the background community incidence of infection, the prevalence of infection in care home staff, care home size, the use of bank and agency staff, regional variation and whether homes provided sick pay to their staff.[5,7] Although comparison of mortality rates across different stages of the pandemic is difficult, international evidence demonstrates a lower level of excess deaths among care home residents in the second wave of the pandemic.[8] This suggests that the enhancement of infection prevention and control measures, including the restriction of visiting, cohorting of staff and/or the increased testing of staff and residents may have reduced transmission compared to the earlier period, although there may also have been some displacement of the timing of deaths, bringing deaths forwards in time during the first wave.

In light of the exposure and vulnerability of care home residents to SARS-CoV-2, the UK Joint Committee on Vaccination and Immunisation recommended that residents and staff of the care home should be the first group to be offered vaccination when it became available in late 2020.[9] On 8 December 2020, Health and Social Care (HSC) Trusts (public healthcare providers) began a vaccination programme for staff and residents in care homes in NI. The programme primarily used Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 (with a small number of exceptions for *ad hoc* doses of the AstraZeneca COVID-19 vaccine given to those who missed vaccination at the time of the visit to the care home by those delivering the vaccination programme). In contrast to the other parts of the UK, NI delivered the great majority of the care home vaccination programme with a 21-day interval between doses, as most implementation occurred before the change in policy to a 12-week dosing interval, which was announced on 31 December 2020. In advance of individual-level data being available, we sought to investigate the association between the COVID-19 vaccination programme on the COVID-19 outbreak frequency and duration. The vaccination programme was introduced at a time when there were changes in non-pharmaceutical interventions (including a period of 'lockdown') in NI, which were associated with considerable changes in the growth of the epidemic. Investigation of the association between the vaccination programme and changes in COVID-19 outcomes, therefore, needed to use methods that would not be confounded by this changing context. The aim of our study was to assess the association of the COVID-19 vaccine programme and the frequency and duration of confirmed COVID-19 outbreaks in care homes.

Methods

Research ethics

This study was undertaken using routine data, accessed under pre-existing information governance arrangements, for the purpose of health protection surveillance and health and social care service delivery and evaluation. Research ethics approval was not required.

Study population

There were 480 operational care homes in NI on 18 November 2021 (Table 1).[10] Care home occupancy is dynamic over time, although occupancy is high. The majority of homes were independent, with some directly operated by HSC Trusts.

Table 1
Number and size of care homes registered in NI on 18 November 2021.

Care home type	Number	Maximum approved places
Residential	235	5344
Nursing	245	10,710
Total	480	16,054

Definitions

Possible case of COVID-19

Any resident (or staff) with symptoms of COVID-19 (high temperature, new continuous cough or loss of taste/smell), or new onset of influenza-like illness or worsening shortness of breath. Symptoms may be more nuanced in older people with co-morbidities in care homes who may present with Flu-Like Illness (FLI), respiratory illness, new-onset confusion, reduced alertness, reduced mobility, or diarrhoea and sometimes do not develop fever. This may be true for COVID-19, so such changes should alert staff to the possibility of new COVID infection.

Confirmed case of COVID-19

Any resident (or staff) with Reverse Transcription Polymerase Chain Reaction (RT-PCR) laboratory-confirmed diagnosis of COVID-19.

COVID-19 outbreak

Two or more cases in a facility, which meet the case definition of a possible or confirmed case of COVID-19, within a 14-day period among either residents or staff in the care home.

Confirmed COVID-19 outbreak

Identification of two or more confirmed COVID-19 cases (both symptomatic and asymptomatic detection), among either residents or staff in the care home, within a 14-day period.

Closed outbreaks

An outbreak was closed when there had been no new cases for 14 days after symptom onset of the most recent case, and a terminal clean was complete.

Data sources and preparation

Daily returns from care homes to the Regulation and Quality Improvement Authority

All care homes in NI participated in a monitoring scheme through which they submitted daily aggregate data to the Regulation and Quality Improvement Authority (RQIA). Summary information from these reports was made available to us in the Public Health Agency (PHA). The submissions from each care home for the previous calendar month, along with the maximum number of staff employed and the number of beds occupied during that month, were used to estimate the number of staff and residents for each care home.

Care home outbreak surveillance

The PHA health protection (HP) team was notified by care homes of cases of COVID-19. An outbreak was declared when two or more cases among care home residents or staff in a facility meet the case definition of a possible or confirmed case of COVID-19 within a 14-day period, according to the definitions above.[11] Once an outbreak was notified, the information was entered into the management information system, HP Zone. Data were extracted

from HP Zone by the HP surveillance team, cleaned and entered into a database.

Office for National Statistics (ONS) COVID-19 Infection Survey (CIS)

The ONS CIS tests approximately 5000 people for COVID-19 in NI over two-week time windows and provides openly available modelled estimates of the number of people in NI who would test positive if tested.[12] This is an estimate of community prevalence of COVID-19, which does not include care homes or hospitals. Full details of the survey methods are available from the ONS.[12] We used the 'Estimated number of people testing positive for COVID-19' from 'Official reported estimates of the percentage of the population testing positive for COVID-19, NI', from 17 October 2020 to 23 October 2020, to 31 October 2021 to 6 November 2021, which was the full range of results available that used a consistent method.

Testing practices

A regular programme of COVID-19 testing (screening) for all care home residents and staff in NI commenced on 3 August 2020. All asymptomatic residents were tested for COVID-19 every 28 days, and all asymptomatic staff were tested every 7 days with an RT-PCR test. Health and Social Care Trusts offered Loop-mediated isothermal amplification (LAMP) tests for residents for whom RT-PCR testing was unsuitable, but we were advised by the responsible team in PHA that this was used very rarely. If a single case was identified through a positive test result, the whole home was tested. Detailed guidance was provided to homes about the pattern of testing during and after outbreaks.

Statistical methods

Outbreak frequency

We used the ONS CIS estimated number of people testing positive for COVID-19 as a measure of the severity of the epidemic in the general population. We explored the relationship between this measure and the weekly frequency of new PCR-confirmed COVID-19 care home outbreaks by plotting these in a scatter plot. We used *ccf* in R v 4.0.2 for the cross-correlation function to assess the time lag between the variables and applied the time lag associated with the maximum correlation before fitting a Poisson regression model using *glm* in R v 4.0.2. We chose a Poisson model because the dependent variable was a count of events, and the low-value daily counts of care home outbreaks did not meet the assumptions required for linear regression. We divided the time series into a pre-vaccination period, before 7 December 2020, a 'washout' period from 7 December 2020 to 28 February 2021 inclusive, and a post-vaccination period from 1 March 2021 to 3 November 2021. The majority of care homes had their first vaccinations delivered during December 2020 (Fig. S1). Staff and residents were offered vaccination at the same time. Those that were in an outbreak at the time vaccination was due were deferred. By the end of December 2020, at least 356 (74%) had their first dose, and by the end of January 2021, at least 404 (84%) had their first dose (for these estimates, any incompleteness in reporting will bias the estimate downwards). This three-month 'washout' period conservatively allowed the great majority of care homes to have been given two visits for vaccination (with the 21-day dosing interval), with time for an immune response to the second dose. ONS CIS results were reported weekly as midpoint estimates of the reported week, so we added three to the first day of the reporting window to make the value represent the middle of the time period, and interpolated daily estimates using *spline(method = "fmm")* in R v4.0.2. Poisson generalised linear regression models were created for the pre-vaccination and postvaccination time periods separately to investigate the relationship in each time period, then in a single multivariable model with the prevaccination time period as the reference category. This was conducted for all care homes and for nursing and residential homes separately. The expected number of care home outbreaks in the absence of the vaccination programme was projected from the observed number of community-acquired COVID-19 hospitalisations using *predict.glm* to estimate the daily and the total number of new care home outbreaks that would have been expected if the conditions of the prevaccination time period had continued. The total projected number of outbreaks for the time and its confidence limits were estimated by 1000 simulations that used *rpois* for random daily projections, summing the projected number of outbreaks in the time period for each simulation, and taking the median and the 2.5% and 97.5% quantiles of the simulated total outbreak counts.

Outbreak closure

A Cox proportional hazards model was used to produce the hazard ratios (HR) and 95% confidence intervals (CIs) to measure the hazard ratio for a care home COVID-19 outbreak being declared over. The likelihood of an outbreak is known to be directly related to care home size.[5,13] For this analysis, residents in each home ranged from one to 100 and staff from three to 280. Community prevalence of COVID-19 affects the prevalence of the virus in care home settings.[13] To adjust for this, the rolling 7-day prevalence of COVID-19 at Super Output Level (SOA) and care home size were adjusted for in the model.

Each of the homes with a reported outbreak represented a case with the time since the first visit at which COVID-19 vaccination was administered to staff and/or residents as the exposure and duration of the outbreak as the outcome. The exposure time was lagged by 21 days from the first visit to vaccinate the staff and residents to account for the lead time from vaccination to immunity. The 21-day lag period was chosen as a time point by which vaccine would be in effect (69% vaccine effectiveness at 14–20 days and 79% at 21–28 days after the first dose in people aged 80 years or older).[14] A Kaplan Meier plot was produced showing 'survival' of outbreaks by care home vaccination status. The time lag was altered to 14, 28 and 35 days as a sensitivity analysis for the Cox regression (which includes the time period of the second dose of vaccine for most care homes). We considered only the effect of time from the first vaccine (rather than whether there was a second vaccine visit) as we had no way of separating any changes associated with the passage of time from the first dose from any change associated with a second dose. Most homes received their second visit at 21 days, and the presence of an outbreak was a potential reason for the second vaccine being delayed.

Results

Study population

The Northern Ireland Statistics and Research Agency (NISRA) estimated the population of NI on 30 June 2019 to be 1,893,700, of which 38,700 (2%) were over the age of 85.[15] Total care home residents and staff were estimated to be 12,884 and 20,537, respectively. Using aggregate data provided by RQIA as of 8 April 2021, the overall vaccination coverage for residents was estimated to be 11,608 (90.1%) and 10,368 (80.5%) for first and second vaccines and 14,524 (70.7%) and 13,173 (64.1%) for staff respectively.

The frequency of COVID-19 outbreaks in care homes

There was a 7-day time lag between care home outbreaks and the estimated number of people who would have tested positive in

the community according to the ONS CIS (Fig. S2). The trends in care home outbreaks happened earlier than the community prevalence. The association between the number of people who would have tested positive and the daily number of new care home outbreaks with confirmed COVID-19 is shown, adjusted for the 7-day time lag. The gradient of this relationship was different in the prevaccination and postvaccination time periods (Fig. 1). The pattern was very similar in nursing and residential homes when shown separately (Figs. S3 and S4).

Poisson regression models for the prevaccination and postvaccination time periods are shown (Table 1), illustrating a change in the relationship. A multivariable Poisson regression model of the number of new care home outbreaks per day as the dependent variable and the modelled number of people who would have tested positive for COVID-19 showed a significant association between the postvaccination period and reduced care home outbreaks (incidence rate ratio [IRR] 0.28 (0.23–0.35)). When investigated separately, nursing homes (IRR 0.27 (0.21–0.35)) and residential homes (IRR 0.27 (0.19–0.40)) showed the same relative effect.

We used the relationship between the number of people who would have tested positive for COVID-19 in the Office for National Statistics COVID-19 Infection Survey and care home outbreaks from the prevaccination period to project the number of outbreaks expected in the washout and postvaccination period. The projection estimated 1625 (95% prediction interval 1553–1694) outbreaks would occur between 7 December 2020 and 28 October 2021, and we observed 501 outbreaks in that time period. The observed and projected number of care home outbreaks are shown as a time series (Fig. 2).

The duration of COVID-19 outbreaks in care homes

We used a Cox proportional hazards model to investigate whether care homes that had been offered the vaccination had a higher likelihood of outbreak closure than those homes that had not reached that immunity threshold. Between 7 December 2020 and 8 April 2021, there were 179 confirmed COVID-19 outbreaks in care homes following the first vaccination, 175 of which had ended at the time of analysis. The median outbreak duration was 29 days from notification to closure (Table S1). A Kaplan Meier plot illustrates the divergence of the outbreak duration in vaccinated compared to unvaccinated care homes (Fig. 3).

The findings indicate that vaccinated homes had a significantly higher hazard ratio of experiencing outbreak closure over time than homes in which the vaccination programme had not yet been implemented (Table 2). These findings remain after adjusting for care home size and measures of community prevalence of COVID-19. The daily hazard ratios analysis illustrating the effect of using different time lags for immunity from vaccination shows the effect days postvaccination the likelihood of outbreak closure increases and appears to stabilise by day 28 (Fig. S5).

Discussion

The COVID-19 pandemic has had a severe impact on care home residents and staff worldwide. Consequently, residents and staff were amongst the first groups to be offered vaccination. Our findings suggest that the introduction of the COVID-19 vaccination programme in NI was associated with a two-thirds reduction in the frequency of confirmed COVID-19 outbreaks in care homes compared to the expected number. This relative effect was the same in nursing and residential homes. We showed that the outbreak duration was shorter in homes where the vaccine had been delivered. These findings provide evidence that the vaccination programme had a positive impact on outbreaks in care homes.

Outbreaks occurred in the postvaccination period, and there are many potential explanations for this. Not all residents and staff will have been vaccinated, and not all those vaccinated will have been fully protected against infection. Furthermore, the care home population is dynamic, with new residents arriving, many of whom would not have been vaccinated. The workforce is also dynamic, and staff may frequently move between care homes and not all were vaccinated. The social care working group of the Scientific Advisory Group for Emergencies (SAGE) have advised that in order to protect against outbreaks in care homes, vaccination uptake rates of 90% of residents and 80% of staff are required.[16] As of 4 April 2021, 94% of all eligible people living in older adult care homes and 78.9% of all eligible workers in all in England have received at least their first vaccination.[16] This had led the English Department of Health and Social Care to launch a consultation on COVID-19

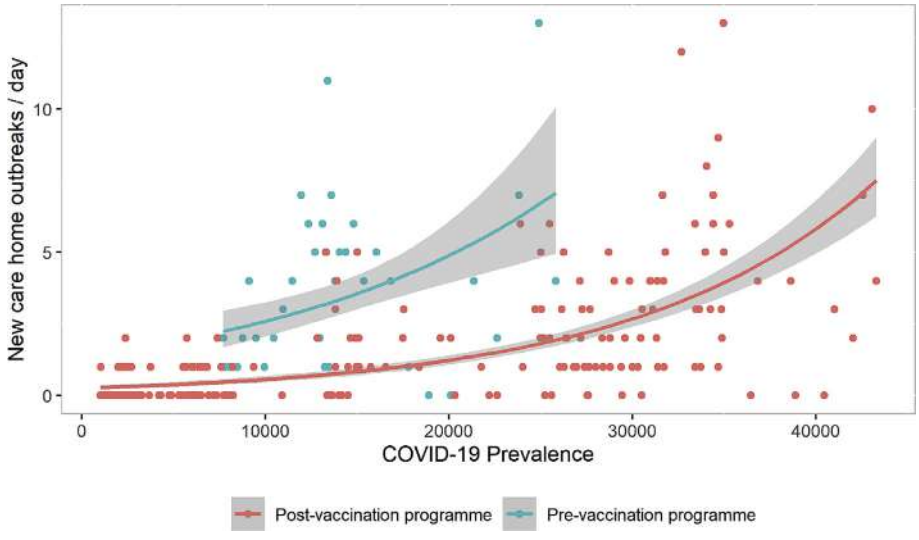

Fig. 1. Number of people who would have tested positive for COVID-19 in the Office for National Statistics COVID-19 Infection Survey (COVID-19 Prevalence) and incident care home outbreaks per day prevaccination and postvaccination programme.

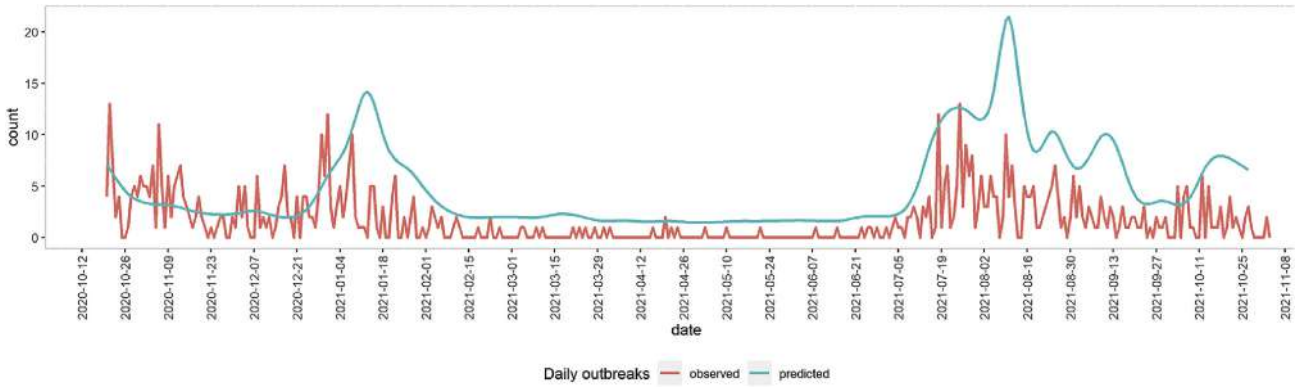

Fig. 2. Observed and predicted care home outbreaks per day.

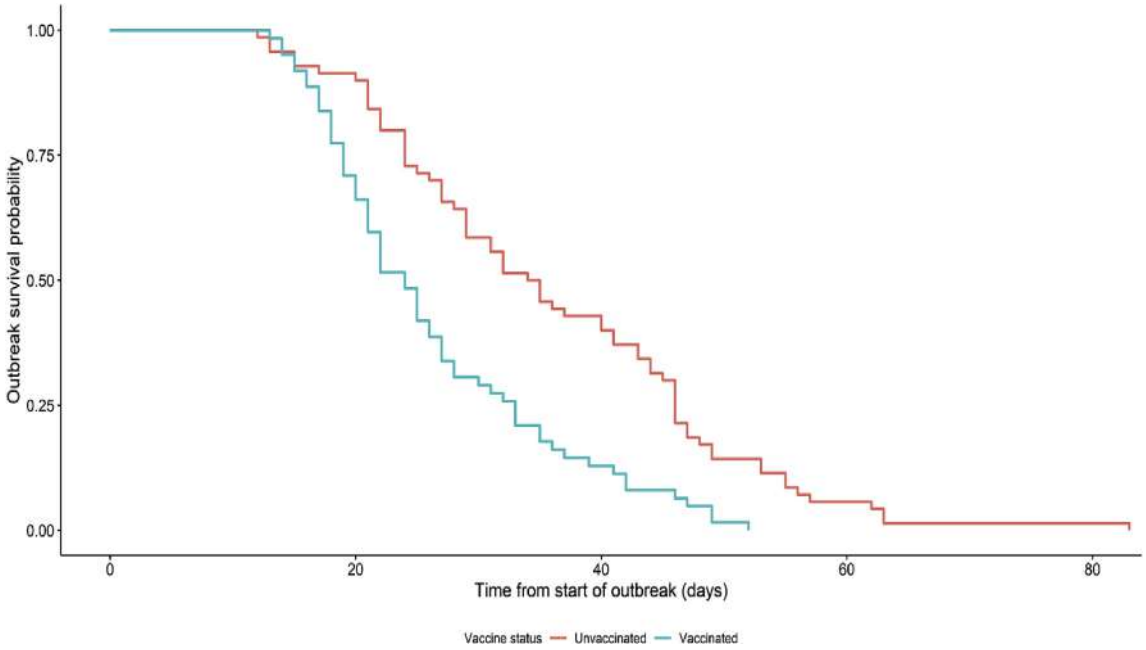

Fig. 3. Kaplan Meier plot illustrating survival of outbreaks by vaccination status.

vaccination as a condition of work for people who work in care homes.[16] Other jurisdictions can be expected to observe these developments with interest.

The findings of this study should be interpreted in the context of its methodological limitations. We did not have access to individual vaccination status at the time of writing, and future work on individual-level data will be needed to validate our findings. We chose not to use aggregate counts of the number of individuals vaccinated within homes or the number of cases within outbreaks. Although these aggregate data were reported and collected, we were advised by PHA that these data were not suitable for statistical analysis due to variation in the completeness and quality of these between and within homes and over time. Therefore, we used the dates of events, which were considered more robust. Outbreak dates were recorded by PHA. We did not attempt to account for the potentially complex interactions between past outbreaks, delays to vaccination, and the resulting synergistic effects of vaccination on a background of recent infection, which would reduce the chance of future outbreaks. This warrants deeper exploration in future. Individual-level data would enable linkage across a range of administrative datasets to assess the effectiveness of the vaccination programme against a range of outcomes. Reliable information about whether individuals are in a specific care home is elusive in administrative information systems, and the challenges of accurately identifying and following these individuals have been well-documented.[17,18] The pandemic has also highlighted how investment in the development of minimum dataset for care home residents is needed to understand the health needs and outcomes of this vulnerable population. The association between community

Table 2
Hazard ratios and 95% confidence intervals for outbreak closure in homes according to time since first vaccination.

Time after vaccination	N (112)	Unadjusted Model		Adjusted Model[a]	
		HR (95% CI)	*P*	HR (95% CI)	*P*
14 days	79	2.22 (1.52–3.24)	<.001	2.44 (1.64–3.63)	<.001
21 days	62	2.24 (1.56–3.22)	<.001	2.53 (1.88–4.31)	<.001
28 days	42	2.57 (1.75–3.78)	<.001	2.84 (1.88–4.34)	<.001
35 days	32	2.27 (1.51–3.43)	<.001	2.55 (1.63–3.99)	<.001

Note: HR = hazard ratio; CI confidence interval.
[a] =models adjusted for care home size and community prevalence.

prevalence and care home outbreaks measured in the prevaccination status might be sensitive to the fact that the ONS CIS data were not available for a period of very low community prevalence. Although we did not aim to measure the incremental benefit of the second dose that was delivered after a 21-day interval, there was no obvious increase at 28 or 35 days in sensitivity analyses or in the estimates of hazard ratio with time beyond 21 days in Fig. S5. This might be explained by the wide confidence limits (our study was not designed or powered to directly compare the effect of the second to first doses) that infection prevention and control measures in place during this period may have been sufficiently robust to mask the incremental benefit of the second dose, or that the benefit of the first dose may give a level of protection due to network effects that, at a group level, makes the effect of the second dose less evident.

By the end of 2020, the UK Medicines and Healthcare products Regulatory Agency (MHRA) approved two vaccines, Pfizer-BioNTech and Oxford-AstraZeneca, for administration. The speed with which these vaccines were available has been unprecedented. In the UK, as of 1 December 2021, 116 million COVID-10 vaccines have been administered.[19] Public Health England recently reported that a single dose of the Pfizer vaccine was approximately 60–70% effective at preventing symptomatic disease, which increased to approximately 85–90% following two doses in over 70-year-olds.[20] For those vaccinated who later developed COVID-19 there was a 44% lower risk of hospitalisation and a 51% lower risk of death compared to unvaccinated people.[20] In looking specifically at care home residents, a large UK cohort study of 10,400 residents reported vaccine effectiveness estimates of 62% against PCR-confirmed infection following first vaccination.[21] Furthermore, a recent preliminary study suggests that a single dose of vaccine may be sufficient to obtain a high level of S-protein IgG antibody in nursing home residents previously diagnosed with COVID-19.[22] Collectively, these findings are encouraging and demonstrate the success of the vaccination programme in the early stages in reducing outbreaks across NI care homes. This evidences a significant degree of protection among a vulnerable and at-risk population against the severe consequences of COVID-19. Future research using individual-level data and across longer periods postvaccination will be needed to determine the magnitude and duration of this protection.

Author statements

Ethical approval

None declared.

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Competing interests

DTB is jointly employed by Queen's University Belfast and the Public Health Agency, NI; he is seconded to the NI Department of Health.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.12.010.

References

1. Schultze A, Nightingale E, Evans D, et al. Mortality among Care Home Residents in England during the first and second waves of the COVID-19 pandemic: an analysis of 4.3 million adults over the age of 65. *medRxiv* 2021. https://doi.org/10.1101/2021.07.07.21253295.
2. Salcher-Konrad M, Jhass A, Naci H, et al. COVID-19 related mortality and spread of disease in long-term care: a living systematic review of emerging evidence. *medRxiv* 2020. https://doi.org/10.1101/2020.06.09.20125237.
3. Comas-Herrera A, Zalakaín J, Litwin C et al. Mortality associated with COVID-19 outbreaks in care homes: Early International Evidence. Retrieved from https://alzheimeriberoamerica.org/wp-content/uploads/2020/04/Mortality-associated-with-COVID-12-April-3.pdf.
4. Morciano M, Stokes J, Kontopantelis E, et al. Excess mortality for care home residents during the first 23 weeks of the COVID-19 pandemic in England: a national cohort study. *BMC Med* 2021;**19**:1–11.
5. Burton JK, Bayne G, Evans C, et al. Evolution and effects of COVID-19 outbreaks in care homes: a population analysis in 189 care homes in one geographical region of the UK. *Lancet Healthy Longev* 2020;**1**:e21–31.
6. Northern Ireland Statistics and Research Agency (NISRA). *Weekly deaths in Northern Ireland*. 2021. Retrieved from, https://www.nisra.gov.uk/system/files/statistics/Deaths-Registered-in-NI-Week-44-2021.pdf.
7. Office of National Statistics. *Impact of coronavirus in care homes in England: 26 May to 19 June*. 2020. Retrieved from, https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/impactofcoronavirusincarehomesinenglandvivaldi/26mayto19june2020.
8. Ioannidis JP, Axfors C, Contopoulos-Ioannidis DG. Second versus first wave of COVID-19 deaths: shifts in age distribution and in nursing home fatalities. *Environ Res* 2021;**195**:110856. https://doi.org/10.1016/j.envres.2021.110856.
9. *Joint Committee on Vaccination and Immunisation: advice on priority groups for COVID-19 vaccination*. 2020. Retrieved from, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950113/jcvi-advice-on-priority-groups-for-covid-19-vaccination-30-dec-2020-revised.pdf.
10. The Regulation and Quality Improvement Authority: Services registered with RQIA. Retrieved from https://www.rqia.org.uk/what-we-do/register/services-registered-with-rqia/. Accessed 18 November 2021.
11. Public Health England. *COVID-19: epidemiological definitions of outbreaks and clusters in particular settings*. 2020. Retrieved from, https://www.gov.uk/government/publications/covid-19-epidemiological-definitions-of-outbreaks-and-clusters/covid-19-epidemiological-definitions-of-outbreaks-and-clusters-in-particular-settings.
12. Office for National Statistics. *Coronavirus (COVID-19) infection survey*. UK. 12 November 2021. Retrieved from, https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurveypilot/12november2021.
13. Abrams HR, Loomer L, Gandhi A, et al. Characteristics of US nursing homes with COVID-19 cases. *J Am Geriatr Soc* 2020;**68**:1653–6.
14. Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet* 2021 May 1;**397**(10285):1646–57. https://doi.org/10.1016/S0140-6736(21)00677-2.
15. Northern Ireland Statistics and Research Agency (NISRA). *2019 Mid-year population estimates for Northern Ireland*. 2020. Retrieved from, https://www.nisra.gov.uk/sites/nisra.gov.uk/files/publications/MYE19-Bulletin.pdf.
16. Department of Health and Social Care. Making vaccination a condition of deployment in older adult care homes. Retrieved from https://www.gov.uk/government/consultations/making-vaccination-a-condition-of-deployment-in-older-adult-care-homes.
17. Burton JK, Goodman C, Guthrie B, et al. Closing the UK care home data gap–methodological challenges and solutions: closing the UK care home data gap. *Int J Popula Data Sci* 2020. https://doi.org/10.23889/ijpds.v5i4.1391.
18. Housley G, Lewis S, Usman, et al. Accurate identification of hospital admissions from care homes; development and validation of an automated algorithm. *Age Ageing* 2018;**47**:387–91.
19. UK Government: Coronavirus (COVID-19) in the UK. Retrieved from https://coronavirus.data.gov.uk/details/vaccinations.
20. Bernal JL, Andrews N, Gower C, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. *medRxiv* 2021. https://www.medrxiv.org/content/medrxiv/early/2021/03/02/2021.03.01.21252652.full.pdf.
21. Shrotri M, Krutikov M, Palmer T, et al. Vaccine effectiveness of the first dose of ChAdox1 nCOV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long term care facilities (VIVALDI study). *medRxiv* 2021. https://doi.org/10.2139/ssrn.3814794.
22. Blain H, Tuaillon E, Gamon L, et al. Spike antibody levels of nursing home residents with or without prior COVID-19 3 Weeks after a single BNT162b2 vaccine dose. *JAMA* 2021. https://doi.org/10.1001/jama.2021.6042.

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Original Research

Investigation of the prevalence of non-COVID-19 infectious diseases during the COVID-19 pandemic

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ABSTRACT

Objectives: This study aimed to investigate non-COVID-19-related upper respiratory tract infections (URTIs), gastrointestinal infections (GIIs) and urinary tract infections (UTIs) during the COVID-19 pandemic in Germany.
Study design: Cross-sectional study.
Methods: Patients with diagnoses of URTIs, GIIs and UTIs from 994 general practitioners (GP) and 192 paediatric practices that routinely send anonymous data to the Disease Analyzer database (IQVIA) were investigated. We studied the differences in recorded URTIs, GIIs and UTIs between April 2019–March 2020 (non-pandemic period) and April 2020–March 2021 (pandemic period) in terms of rates and baseline characteristics by comparing absolute frequencies.
Results: Compared with the non-pandemic period, the total number of patients with defined diagnoses was lower in the pandemic period (URTIs: 810,324 vs 520,800; GIIs: 253,029 vs 142,037; UTIs: 132,425 vs 117,932). The number of patients per practice with URTIs (683 vs 439, −36%, $P < 0.001$) and GIIs (213 vs 120, −44%, $P < 0.001$) decreased significantly during the pandemic period; the decrease in the number of recorded UTIs was smaller (112 vs 99, −11%, $P < 0.05$). The decrease in diagnoses was more pronounced among paediatricians than GPs (URTIs: −39% vs −35%; GIIs: −57% vs −39%; UTIs: −15% vs −9%). The decrease in URTIs varied between −35% and −40% depending on the age group.
Conclusions: Measures introduced during the COVID-19 pandemic to reduce transmission of the virus also helped to reduce the spread of non-COVID-19-related URTIs and GIIs. UTIs were impacted to a lesser extent, with rates seeing a slight decrease. An increase in awareness of infectious diseases may have also contributed to the reduction in recorded diagnoses.

Introduction

The implementation of strict worldwide measures to combat the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a dramatic impact on individual behaviours and interactions between individuals. Measures, such as reducing indoor seating, social distancing, the wearing of masks and stay-at-home orders, helped to reduce SARS-CoV-2 infection rates.[1,2] In addition to these fundamental changes in social behaviours, the coronavirus disease 2019 (COVID-19) pandemic has also led to the general public having an increased awareness of the importance of hygiene and a better understanding of the transmission and spread of infectious diseases.

COVID-19 mitigation measures may have also influenced the occurrence of non-COVID-19-related infectious diseases. The spread of viruses and bacteria with similar transmission properties to those of SARS-CoV-2 and which also cause upper respiratory tract infections (URTIs) and/or gastrointestinal infections (GIIs) might be most significantly affected by anti-SARS-CoV-2 measures.[3–5] For other infectious diseases, such as urinary tract infections (UTIs), medical structural abnormalities (e.g. metabolic disorders) may be more relevant than measures intended to reduce social contact.[6] However, considering the general increase in awareness of infectious diseases and hygiene during the pandemic, it is reasonable to expect the rates for all non-COVID-19 infectious diseases to decrease (to varying extents).

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Thus, the present study aimed to investigate the change in reported non-COVID-19 URTIs, GIIs and UTIs between the non-pandemic period and the pandemic period using data from a large database, supplied with data from general practitioners (GPs) and paediatricians in Germany.

Methods

Database

This cross-sectional study was based on electronic medical record data from the Disease Analyzer database (IQVIA), which compiles drug prescriptions, diagnoses, and general medical and demographic data obtained directly (in an anonymous format) from computer systems used in GP practices and specialist departments.[7] Diagnoses, prescriptions and the quality of reported data are monitored by IQVIA based on an array of criteria. The coverage of this database is around 3% of all private practices in Germany. In Germany, the sampling methods used to select physicians' practices have been shown to be appropriate for obtaining a database of primary and specialised care that is representative of the German population.[7] The study was carried out in accordance with the latest version of the Declaration of Helsinki.

Study population

The analysis included patients who received at least one diagnosis of URTI (ICD-10: J01-J09, J20-J22), GII (ICD-10: A08, A09) or UTI (ICD-10: N39.0) between April 2019 and March 2021 in one of 994 GP or 192 paediatric practices that routinely send data to IQVIA. A total of 1,976,547 individuals were studied.

Study outcomes

The primary outcomes of this study were the number of URTIs, GIIs and UTIs documented by GPs and paediatricians between April 2019 and March 2020 (the non-pandemic period) compared with the number recorded between April 2020 and March 2021 (the pandemic period).

Statistical analyses

To assess changes in the number of reported infectious diseases, we compared the results for April 2020–March 2021 with April 2019–March 2020 and calculated the percentage change between both periods. To demonstrate practitioners' perceived changes, we also used the mean number of documented infection diagnoses per practice. A one-sample Kolmogorov–Smirnov test was used to check whether the data (patient number per practice) were distributed normally. As there was evidence that the data were not normally distributed, the number of patients with diagnoses per practice was compared for the two time periods using a non-parametric Wilcoxon signed-rank test. This test was also used to compare the average ages of patients diagnosed in the non-pandemic and pandemic periods. The proportions of women and men, patients in GP and paediatric practices, and age groups were compared using Chi-squared tests. Finally, we estimated a Pearson correlation coefficient to measure the strength of a linear association between COVID-19 and non-COVID-19-related URTIs. *P*-values of <0.05 were considered statistically significant. Analyses were carried out using SAS version 9.4 (Cary, NC: SAS Institute Inc).

Results

Patient characteristics

Compared with the non-pandemic period, the total number of patients with defined diagnoses was lower in the pandemic period (URTIs: 810,324 vs 520,800; GIIs: 253,029 vs 142,037; UTIs: 132,425 vs 117,932). Patient characteristics are presented in Table 1. The average age of individuals with infectious disease diagnoses was slightly higher in the pandemic period than in the non-pandemic period. In addition, the proportion of patients diagnosed by GPs increased slightly, especially for GIIs.

Infectious diseases documented in the non-pandemic period compared with the pandemic period

Table 2 shows the difference between the number of patients diagnosed with infections in the non-pandemic period and those diagnosed in the pandemic period. The number of patients per practice with URTIs (683 vs 439, −36%, $P < 0.001$) and GIIs (213 vs 120, −44%, $P < 0.001$) decreased significantly from April 2019–March 2020 to April 2020–March 2021; the decrease in the number of recorded UTIs was smaller (112 vs 99, −11%, $P < 0.05$).

The decrease in the number of URTIs diagnosed in GP and paediatric practices was similar (−35% and −39%). GII diagnoses decreased in paediatric practices much more than in GP practices (−57% vs −39%). The decrease in the number of patients with URTIs varied between −35% and −40% depending on age group, but no clear tendency could be identified. The greatest decrease in diagnoses of GIIs during the pandemic was seen in young children (−60% in the age group <6 years), and the decrease was least pronounced in the oldest age group (−19% in the age group >80 years). There was no significant change in the number of patients with UTIs in the age groups <6, 51–65, 66–80 and > 80 years.

Fig. 1 shows the monthly trends in COVID-19 and non-COVID-19-related URTI diagnoses (per practice) in GP and paediatric practices from April 2019 to March 2021. The Pearson correlation coefficient was 0.10 ($P = 0.172$) in GP practices and 0.08 ($P = 0.321$) in paediatric practices.

Discussion

In the current study, the largest decrease in non-COVID-19-related infections during the pandemic was detected for GIIs (−44%), followed by URTIs (−36%) and UTIs (−11%). For all three infectious diseases, the decrease was slightly more pronounced when diagnoses were made by paediatricians. Accordingly, during the pandemic period, diagnoses were less frequent among the younger age groups (6–17 years old). No specific trend for the change in diagnoses of infectious diseases was observed for gender. There was no significant correlation between diagnoses of COVID-19 and non-COVID-19 URTIs.

Many studies have reported that fewer diagnoses of various disorders were recorded during the pandemic period compared with previous time periods.[8–11] This could be interpreted as a general reduction in reporting during the pandemic, with patients being reluctant to seek medical help because of the risk of being infected with SARS-CoV-2 when visiting a physician.[8–11] Another possible reason that may influence the results of the current study could be the decrease in diagnoses observed in children (URTIs, GIIs and UTIs); children may recover more rapidly from infections than adults,[12] but both adolescents and their parents may avoid visits to paediatricians due to the risk of being infected with SARS-CoV-2. In contrast, for adults, no specific age-dependent trend could be identified for any of the three infectious diseases investigated.

Table 1
Sociodemographic characteristics of patients diagnosed with upper respiratory tract infections (URTIs), gastrointestinal infections (GIIs) and urinary tract infections (UTIs) in April 2019–March 2020 (non-COVID-19 pandemic period) and in April 2020–March 2021 (COVID-19 pandemic period)[a].

Sociodemographic characteristics	URTIs			GIIs			UTIs		
	April 2019–March 2020 (n = 810,324)	April 2020–March 2021 (n = 520,800)	*P*-value	April 2019–March 2020 (n = 253,029)	April 2020–March 2021 (n = 142,037)	*P*-value	April 2019–March 2020 (n = 132,425)	April 2020–March 2021 (n = 117,932)	*P*-value
Specialty									
GPs	70.2	71.5	<0.001	75.6	81.3	<0.001	70.4	71.8	<0.001
Paediatricians	29.8	28.5		24.4	18.7		29.6	28.2	
Age in years [mean (SD)]	30.5 (23.2)	30.8 (22.9)	<0.001	30.3 (21.7)	33.8 (22.2)	<0.001	40.9 (29.1)	42.6 (29.3)	<0.001
<6	18.9	17.6	<0.001	15.4	11.0	<0.001	16.6	15.8	<0.001
7–12	11.5	11.4		9.1	6.9		10.3	9.5	
13–17	7.2	7.4		8.0	7.5		5.9	5.6	
18–30	15.9	16.1		23.8	25.4		9.1	8.4	
31–50	23.5	25.8		24.2	25.2		15.4	15.1	
51–65	15.3	15.4		12.9	14.9		16.7	17.4	
66–80	5.3	4.9		4.1	5.4		15.8	16.4	
>80	2.4	2.4		2.6	3.7		10.2	11.7	
Gender									
Male	48.5	48.7	0.024	52.4	53.1	<0.001	29.3	28.7	0.003
Female	51.5	51.3		47.6	46.9		70.7	71.3	

SD, standard deviation.
[a] Data are percentages unless otherwise specified.

These combined reporting effects may partially explain the results of the current study.

On the other hand, the increased awareness of hygiene and the spread of infectious diseases during the pandemic may have resulted in behavioural changes in many individuals, also causing a decrease in the incidence of infections. In particular, specific measures targeting the spread of viruses or bacteria transmitted by aerosols and/or by oral transmission that were primarily intended to combat SARS-CoV-2 may have also influenced our findings regarding URTIs and GIIs diagnosed during the pandemic. The lower reduction of reported UTIs might also support this hypothesis. For UTIs, measures for reducing infectious disease transmission via aerosols may be less relevant as the occurrence of UTIs is facilitated by structural abnormalities as well as other hygiene deficits.[6,13]

Some authors have discussed the COVID-19 pandemic as a favourable opportunity for effective education in good hygiene practice, speculating that this could have a lasting impact on controlling the spread of infectious diseases.[14] In this context, it is necessary to mention the decline observed in influenza cases, in both adults and children, as the global seasonal spread for this disease is comparable to that of COVID-19.[15] Some reports even indicate the complete collapse of influenza epidemics during the 2020–2021 season.[16,17] This observation can be regarded as a welcome effect, since a dramatic drop in cases of seasonal influenza could preserve healthcare systems in critical phases of the pandemic, thus reserving resources for COVID-19 patients.

With regard to the decrease in incidence rates detected in our study, gender was not identified as a determinant factor. This was observed for all three infectious diseases investigated. Some pandemic reports described a more pronounced decline in vascular events (e.g. strokes and myocardial infarctions) in men compared with women, resulting in speculation about gender-specific differences in coping strategies with regard to these illnesses during the

Table 2
Total annual change in infection diagnoses (per practice) in GP and paediatric practices (April 2019–March 2020 [non-COVID-19 pandemic period] compared with April 2020–March 2021 [COVID-19 pandemic period]).

Characteristic	URTIs			GIIs			UTIs		
	April 2019–March 2020	April 2020–March 2021	change	April 2019–March 2020	April 2020–March 2021	change	April 2019–March 2020	April 2020–March 2021	change
	[n mean (SD)]	[n mean (SD)]	(%)	[n mean (SD)]	[n mean (SD)]	(%)	[n mean (SD)]	[n mean (SD)]	(%)
Total	683 (515)	439 (453)	−36***	213 (174)	120 (102)	−44***	112 (127)	99 (113)	−11[a]
Specialty									
GPs	572 (393)	375 (406)	−35***	192 (162)	116 (103)	−39***	94 (95)	85 (84)	-9[a]
Paediatricians	1259 (668)	774 (531)	−39***	322 (192)	138 (97)	−57***	204 (208)	173 (192)	−15[a]
Gender									
Male	331 (267)	214 (232)	−35***	112 (95)	64 (56)	−43***	33 (56)	29 (50)	−13[a]
Female	352 (253)	225 (224)	−36***	102 (81)	56 (47)	−45***	79 (77)	71 (69)	−10**
Age groups in years									
<6	129 (307)	77 (195)	−40***	33 (81)	13 (34)	−60***	19 (64)	16 (57)	−15
7–12	78 (165)	50 (115)	−36***	19 (43)	8 (20)	−57***	12 (36)	9 (31)	−17[a]
13–17	49 (58)	32 (45)	−34***	17 (20)	9 (12)	−47***	7 (15)	6 (15)	−16***
18–30	109 (107)	71 (90)	−35***	51 (59)	30 (38)	−40***	10 (13)	8 (11)	−17**
31–50	160 (142)	109 (131)	−32***	52 (54)	30 (33)	−42***	17 (22)	15 (19)	−13[a]
51–65	105 (87)	67 (83)	−36***	28 (26)	18 (18)	−35***	19 (25)	17 (22)	−7
66–80	36 (34)	22 (34)	−40***	9 (9)	6 (7)	−26***	18 (23)	16 (20)	−7
>80	17 (17)	11 (19)	−35***	6 (7)	5 (6)	−19***	12 (14)	12 (14)	1

GIIs, gastrointestinal infections; GP, general practitioner; SD, standard deviation; URTIs, upper respiratory tract infections; UTIs urinary tract infections.
[a] p <0.05, **P < 0.01, ***P < 0.001.

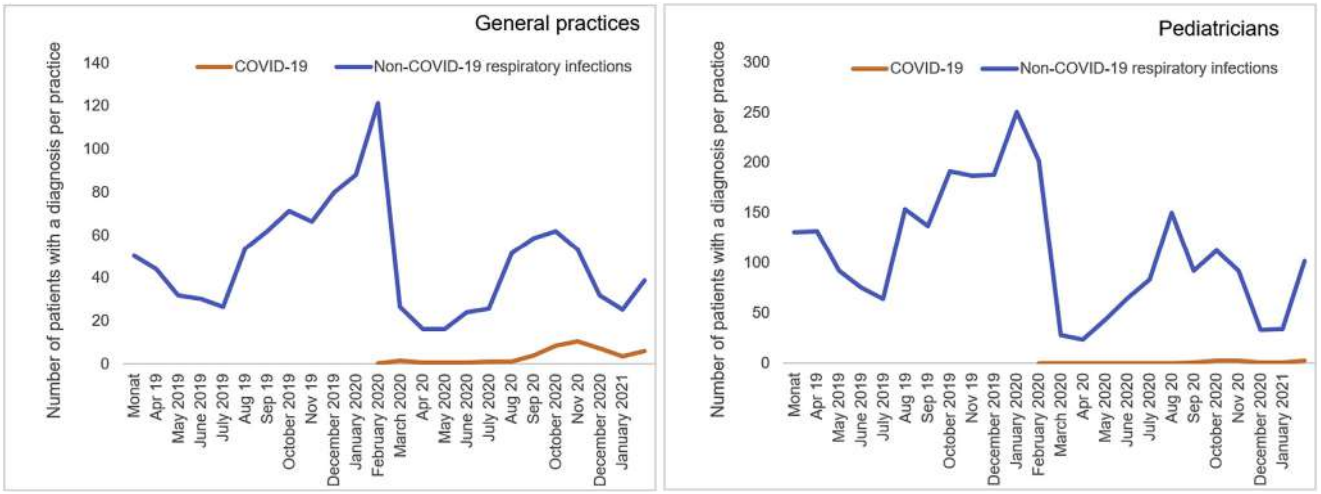

Fig. 1. Monthly trend in COVID-19 and non-COVID-19 upper respiratory tract infection diagnoses (per practice) in general and paediatric practices (April 2019–March 2021).

pandemic.[18–20] For infectious diseases such as those addressed in the present study, it appears that the pandemic environment influenced both genders similarly. However, while men may be more likely to avoid seeking medical care, our observations support the assumption that the decline in infectious disease rates depicted in our study might be determined by individual hygiene-related behavioural changes rather than a reluctance to book medical consultations.

Interestingly, a decrease in common respiratory viral infections during the COVID-19 pandemic has been reported in other countries. Parry et al. reported that in the United States, the difference in respiratory viral infections in April and May 2020 was significantly lower than during the same period in the previous 4 years. The authors attributed this result to the widespread use of public health interventions, including wearing face masks, social distancing, hand hygiene and stay-at-home orders.[21] Olsen et al. cited that influenza data reported to the World Health Organisation from Australia, Chile and South Africa showed very low influenza activity during June–August 2020. The authors assumed that the use of community mitigation measures for the COVID-19 pandemic, plus influenza vaccination, reduced the incidence of influenza during this time.[22]

The current study is subject to several limitations that need to be acknowledged. First, no information was available on any other potential reasons for the decrease in the number of medical consultations. Second, medical services may only have been able to accommodate a reduced number of non-COVID-19 consultations during the pandemic period. Third, URTI, GII and UTI diagnosis data relied solely on ICD-10 codes, and no data were available on the diagnosis process or the severity/activity of the disease. Fourth, no information was available on behavioural factors (e.g. alcohol use, smoking and sedentary lifestyle), and the role played by these factors, therefore, could not be examined. Fifth, no hospital data were available, and only outpatients were analysed.

The two major strengths of this study are the number of patients available for analysis and the detailed analyses using real-world data. The latter is particularly relevant, as the main medical point of contact for the diseases analysed in this study is the GP for adults and the outpatient paediatrician for children.

Conclusions

For all three infectious diseases investigated (URTIs, GIIs and UTIs), we detected a relevant decrease in incidence rates during the COVID-19 pandemic within the outpatient medical care sector, specifically GPs and outpatient paediatricians. The decrease in reported UTIs was less pronounced than that in GIIs and URTIs, supporting the hypothesis that pandemic mitigation measures to combat the spread of SARS-CoV-2 and increased hygiene awareness helped reduce the spread of these diseases.

Author statements

Ethical approval

German law allows the use of anonymous electronic medical records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data.

Because patients were only queried as aggregates and no protected health information was available for queries, no Institutional Review Board approval was required for the use of this database or the completion of this study.

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Competing interests

None declared.

Author contributions

CT and KK developed the idea for the study, and KK analysed the data. CT and KK wrote the manuscript. All authors contributed to and reviewed the final version of the manuscript.

References

1. Rizvi RF, Craig KJT, Hekmat R, Reyes F, South B, Rosario B, Kassler WJ, Jackson GP. Effectiveness of non-pharmaceutical interventions related to social distancing on respiratory viral infectious disease outcomes: a rapid evidence-based review and meta-analysis. *SAGE Open Med* 2021 Jun 6;**9**. 20503121211022973. https://doi.org/10.1177/20503121211022973. PMID: 34164126; PMCID: PMC8188982.
2. Kucharski AJ, Klepac P, Conlan AJK, Kissler SM, Tang ML, Fry H, Gog JR, Edmunds WJ. CMMID COVID-19 working group. Effectiveness of isolation, testing, contact tracing, and physical distancing on reducing transmission of SARS-CoV-2 in different settings: a mathematical modelling study. *Lancet Infect Dis* 2020

Oct;**20**(10):1151–60. https://doi.org/10.1016/S1473-3099(20)30457-6. Epub 2020 Jun 16. PMID: 32559451; PMCID: PMC7511527.
3. To KK, Chan JF, Yuen KY. Viral lung infections: epidemiology, virology, clinical features, and management of avian influenza A(H7N9). *Curr Opin Pulm Med* 2014 May;**20**(3):225–32. https://doi.org/10.1097/MCP.0000000000000047. PMID: 24637225.
4. Sopena N, Sabrià M, Pedro-Botet ML, Manterola JM, Matas L, Domínguez J, Modol JM, Tudela P, Ausina V, Foz M. Prospective study of community-acquired pneumonia of bacterial etiology in adults. *Eur J Clin Microbiol Infect Dis* 1999 Dec;**18**(12):852–8. https://doi.org/10.1007/s100960050419. PMID: 10691195.
5. Ahn SY, Park JY, Lim IS, Chae SA, Yun SW, Lee NM, Kim SY, Choi BS, Yi DY. Changes in the occurrence of gastrointestinal infections after COVID-19 in Korea. *J Kor Med Sci* 2021 Jun 21;**36**(24):e180. https://doi.org/10.3346/jkms.2021.36.e180. PMID: 34155841; PMCID: PMC8216988.
6. Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *Dis Mon* 2003 Feb;**49**(2):71–82. https://doi.org/10.1067/mda.2003.8. PMID: 12601338.
7. Rathmann W, Bongaerts B, Carius HJ, Kruppert S, Kostev K. Basic characteristics and representativeness of the German Disease Analyzer database. *Int J Clin Pharmacol Therapeut* 2018 Oct;**56**(10):459–66. https://doi.org/10.5414/CP203320. PMID :30168417.
8. Gold N, Hu XY, Denford S, Xia RY, Towler L, Groot J, Gledhill R, Willcox M, Ainsworth B, Miller S, Moore M, Little P, Amlôt R, Chadborn T, Yardley L. Effectiveness of digital interventions to improve household and community infection prevention and control behaviours and to reduce incidence of respiratory and/or gastro-intestinal infections: a rapid systematic review. *BMC Publ Health* 2021 Jun 21;**21**(1):1180. https://doi.org/10.1186/s12889-021-11150-8. PMID: 34154553; PMCID: PMC8215628.
9. Tanislav C, Jacob L, Kostev K. Consultations decline for stroke, transient ischemic attack, and myocardial infarction during the COVID-19 pandemic in Germany. *Neuroepidemiology* 2021 Feb 2:1–8. https://doi.org/10.1159/000513812. Epub ahead of print. PMID: 33530092; PMCID: PMC7900477.
10. Mueller TM, Kostev K, Gollwitzer S, Lang JD, Stritzelberger J, Westermayer V, Reindl C, Hamer HM. The impact of the coronavirus disease (COVID-19) pandemic on outpatient epilepsy care: an analysis of physician practices in Germany. *Epilepsy Behav* 2021 Apr;**117**:107833. https://doi.org/10.1016/j.yebeh.2021.107833. PMID: 33618316; PMCID: PMC7895474.
11. Slagman A, Behringer W, Greiner F, Klein M, Weismann D, Erdmann B, Pigorsch M, Möckel M, AKTIN Emergency Department Registry. German forum of university emergency departments (FUN) in the society of university clinics of Germany E.V. Medical emergencies during the COVID-19 pandemic. *Dtsch Arztebl Int* 2020 Aug 17;**117**(33–34):545–52. https://doi.org/10.3238/arztebl.2020.0545. PMID: 32865489; PMCID: PMC8171546.
12. Seifert G, Brandes-Schramm J, Zimmermann A, Lehmacher W, Kamin W. Faster recovery and reduced paracetamol use - a meta-analysis of EPs 7630 in children with acute respiratory tract infections. *BMC Pediatr* 2019 Apr 23;**19**(1):119. https://doi.org/10.1186/s12887-019-1473-z. PMID: 31014293; PMCID: PMC6477747.
13. M Hassan M, Lagha R, Mabrouk I, Alhomrani M, Alorabi JA, Gaber A, Ben Abdallah F. Molecular investigation of multidrug-resistant Escherichia coli clinical isolates from patients with urinary tract infections. *Pakistan J Biol Sci* 2021 Jan;**24**(5):636–45. https://doi.org/10.3923/pjbs.2021.636.645. PMID: 34486339.
14. McNeil JC, Flores AR, Kaplan SL, Hulten KG. The indirect impact of the SARS-CoV-2 pandemic on invasive group a Streptococcus, Streptococcus pneumoniae and Staphylococcus aureus infections in houston area children. *Pediatr Infect Dis J* 2021 Aug 1;**40**(8):e313–6. https://doi.org/10.1097/INF.0000000000003195. PMID: 34250979.
15. Laris-González A, Avilés-Robles M, Domínguez-Barrera C, Parra-Ortega I, Sánchez-Huerta JL, Ojeda-Diezbarroso K, Bonilla-Pellegrini S, Olivar-López V, Chávez-López A, Jiménez-Juárez R. Influenza vs. COVID-19: comparison of clinical characteristics and outcomes in pediatric patients in Mexico city. *Front Pediatr* 2021 Jun 24;**9**:676611. https://doi.org/10.3389/fped.2021.676611. PMID: 34249813; PMCID: PMC8264261.
16. Sawakami T, Karako K, Song P. Behavioral changes adopted to constrain COVID-19 in Japan: what are the implications for seasonal influenza prevention and control? *Glob Health Med* 2021 Jun 30;**3**(3):125–8. https://doi.org/10.35772/ghm.2021.01066. PMID: 34250286; PMCID: PMC8239374.
17. Kim JH, Roh YH, Ahn JG, Kim MY, Huh K, Jung J, Kang JM. Respiratory syncytial virus and influenza epidemics disappearance in Korea during the 2020-2021 season of COVID-19. *Int J Infect Dis* 2021 Jul 7. https://doi.org/10.1016/j.ijid.2021.07.005. S1201-S9712(21)00560-9. Epub ahead of print. PMID: 34245886.
18. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth* 2013;**111**(1):52–8. https://doi.org/10.1093/bja/aet127.
19. Hodes GE, Epperson CN. Sex differences in vulnerability and resilience to stress across the life span. *Biol Psychiatr* 2019;**86**(6):421–32. https://doi.org/10.1016/j.biopsych.2019.04.028.
20. Fletcher K, Prigerson HG, Paulk E, Temel J, Finlay E, Marr L, et al. Gender differences in the evolution of illness understanding among patients with advanced cancer. *J Support Oncol* 2013;**11**(3):126–32. https://doi.org/10.12788/j.suponc.0007.
21. Parry MF, Shah AK, Sestovic M, Salter S. Precipitous fall in common respiratory viral infections during COVID-19. *Open Forum Infect Dis* 2020 Oct 23;**7**(11). https://doi.org/10.1093/ofid/ofaa511. ofaa511. PMID: 33269297; PMCID: PMC7665739.
22. Olsen SJ, Azziz-Baumgartner E, Budd AP, Brammer L, Sullivan S, Pineda RF, Cohen C, Fry AM. Decreased influenza activity during the COVID-19 pandemic - United States, Australia, Chile, and South Africa, 2020. *MMWR Morb Mortal Wkly Rep* 2020 Sep 18;**69**(37):1305–9. https://doi.org/10.15585/mmwr.mm6937a6. PMID: 32941415; PMCID: PMC7498167.

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Original Research

Learning about COVID-19 across borders: public health information and adherence among international travellers to the UK

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ABSTRACT

Objective: Public health control measures at borders have long been central to national strategies for the prevention and containment of infectious diseases. Travel was inevitably associated with the rapid global transmission of COVID-19. In the UK, public health authorities tried to reduce the risks of travel-associated spread by providing public health information at ports of entry. This study investigates risk assessment processes, decision-making and adherence to official advice among international travellers, to provide evidence for future policy on the provision of public health information to facilitate safer international travel.
Study design: This study is a qualitative study evaluation.
Method: International air passengers arriving at the London Heathrow Airport on scheduled flights from China and Singapore were approached for interview after consenting to contact in completed surveys. Semi-structured interviews were conducted by telephone, using two topic guides to explore views of official public health information and self-isolation. Interview transcripts were coded and analysed thematically.
Results: Participants regarded official advice from Public Health England as adequate at the time, despite observing differences with intervention measures implemented in their countries of departure. Most participants also described adopting precautionary measures, including self-isolation and the use of face coverings that went beyond official advice, but reported adherence to guidance on contacting health authorities was more variable. Adherence to the official guidance was informed by the perceived salience of specific transmission possibilities and containment measures assessed in relation to participants' local social and institutional environments.
Conclusion: Analysis of study findings demonstrates that international air travellers' responses to public health advice constitute a proactive process of risk assessment and rationalised decision-making to guide preventive action. This process incorporates consideration of the current living situation, trust in information sources, correspondence with cultural logics and willingness to accept potential risk to self and significant others. Our findings concerning international passengers' understanding of, and compliance with, official advice and mitigation measures provide valuable evidence to inform future policy and generate recommendations on the presentation of public health information to facilitate safer international travel. Access to a central source of regularly updated official information would help minimise confusion between different national guidelines. Greater attention to the differentiated

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information needs of diverse groups in creating future public-facing guidance would help to minimise the uncertainties generated by the receipt of generic information.

Introduction

The significant transmission risks associated with travel mean that public health disease control measures at borders have long been central to national strategies for the prevention and containment of infectious diseases. COVID-19 has surged across successive countries and continents since early 2020,[1] despite various cross-border travel restrictions. The socio-economic impact of COVID-19 may be causing the largest global recession in history,[2] with decades of progress and development at risk.[3]

Although interventions such as mass vaccination may ultimately succeed in containing COVID-19, behavioural measures based on public health guidance remain vital, particularly while national health systems remain under pressure and new variants with increased transmissibility constitute threats to effective vaccination.[4,5] Knowledge and information can support the public to adopt measures that will mitigate or prevent transmission and these behavioural non-pharmaceutical interventions remain key to controlling the spread of COVID-19.

As the first cases of COVID-19 were reported, public health authorities in the UK took action to reduce the risk of travel-associated spread by monitoring travel and providing public health advice at ports of entry. On 25 January 2020, Public Health England (PHE) activated the Airport Public Health Monitoring Operations Centre to monitor all direct flights from China to the London Heathrow Airport (LHR) and subsequently all international direct flights to London (Heathrow and Gatwick) and Manchester. Measures directed at passengers travelling from affected countries to England included (see Supplementary material online):

- a broadcast message to passengers made on incoming aircraft, to encourage travellers to report relevant symptoms,
- posters containing COVID-19 related public health advice displayed at arrival terminals and
- leaflets containing the same advice distributed to passengers by airlines on board flights and/or made available on arrival.

These measures remained in place until extensive travel restrictions were implemented on 23rd March as part of a national lockdown, with UK residents prohibited from travelling abroad unless they had a permitted reason to do so, while returning travellers were required to quarantine for 14 days.

As vaccination programmes progress and lockdown measures in certain countries are eased, international travel has again become a pressing concern. Amid discussion of vaccine passports and pressure from the travel industry and national economies dependent on tourism to ease restrictions, passengers are left to navigate differing rules, guidance and social norms between countries. International passengers' views on, and compliance with, official advice and mitigation measures can provide valuable evidence to inform policy. Our previous evaluation of official COVID-19 guidance for international travellers reported on the impact and effectiveness of these communication materials in the early stage of the pandemic.[6] Drawing on qualitative data collected prior to the implementation of travel restrictions, this paper considers risk assessment, decision-making and adherence practices among air travellers arriving in the UK. Our findings provide wider insights into the interactions between official advice and individual behaviour and indicate possible improvements in the presentation of public health information to facilitate safer international travel.

Methods

A mixed-methods study was conducted to evaluate the public health information provided to international travellers arriving in the UK. Passengers aged 18 years and over from any nationality, arriving at LHR on three scheduled flights from China and Singapore in March 2020 were recruited for a cross-sectional survey and semi-structured interviews regarding their experience and understanding of the official guidance they received, as well as their subsequent actions. A total of 121 passengers consented and completed the survey (results reported separately).[6] Of the respondents, 15 indicated a willingness to take part in the follow-up interviews, by recording their contact details on the questionnaire and consenting to participate when contacted on arrival, and subsequently participated in semi-structured interviews.

One-to-one semi-structured telephone interviews were conducted in April 2020 in either English or Mandarin, according to participant preference. All interviews were audio-recorded with consent. Two topic guides were used; one which explored participants' experience and views regarding COVID-19 information they had received during travel was used with all participants, and the second was used to elicit details of experiences relating to self-isolation if a participant reported having self-isolated due either to potential exposure or to having developed COVID-19 symptoms.

Key information was summarised by researchers in field notes either during or immediately after the completion of each interview. Prior to data analysis, interviews in English were transcribed verbatim and those in Mandarin were transcribed directly into English.

Data analysis

Interview transcripts were initially coded independently (by TZ, SC, CS and WR) using open coding, followed by collaborative development of an initial coding framework that was then used to index each transcript in NVivo 12 Pro. Codes that represented similar concepts were assembled into conceptual categories and themes. Common categories emerging across the transcripts indicated that all themes reached saturation.

Results

Participants ranged from 20 to 80 years of age; five were male and ten were female. Ten were permanent residents in the UK while five were visitors or temporary residents. Six participants were retired; five worked full-time, three were full-time students and one was unemployed (Table 1). Most participants were British; all three Chinese participants spoke Mandarin and English and had read the official PHE guidance in both languages, while other participants only knew English and accordingly, only read the English version. One participant reported symptoms of COVID-19 after arrival.

Table 1
Demographic background of participants in follow-up interviews, arriving at the London Heathrow airport from COVID-19 affected countries in March 2020.

Participant No.	Age	Gender	Language
P01	50–59	Male	English
P02	60–69	Male	English
P03	60–69	Female	English
P04	20–29	Male	English, Chinese
P05	70–79	Male	English
P06	30–39	Female	English
P07	20–29	Female	English
P08	60–69	Female	English
P09	70–79	Female	English
P10	70–79	Male	English
P11	60–69	Female	English
P12	70–79	Female	English
P13	70–79	Female	English
P14	20–29	Female	English, Chinese
P15	40–49	Female	English, Chinese

Summarised from qualitative research data.

Perceptions of public health measures

Fourteen participants recalled obtaining the official information from PHE on COVID-19 (leaflets and/or posters) in flight or at the airport, while one participant reported only receiving local information at the port of departure. Most participants stated that they considered the UK official guidance to be adequate. However, they also reported finding the situation on disembarkation dramatically different from their experience at their departure airport; extensive public health border control measures were implemented in most Asian countries within weeks of the first reports of COVID-19. In Singapore, inbound flights from Wuhan were cancelled from 23rd January and all passengers returning from mainland China were required to quarantine or self-isolate from 19th February onwards. In China, exit and entry health supervision was implemented on 25th February 2020, including body temperature monitoring, health check, epidemiological history survey and medical sample monitoring.

> "At China's airport… you need to fill in a Health Declaration Card… they will check your temperature; all the [airport] staff were fully equipped with PPE… [in the UK] only when I went through the customs that I saw the hand sanitiser there. They [airport staff] didn't wear face masks…So, in China, the official advice is wearing face masks and washing hands as often as possible. In the UK, as no one was wearing a face mask, it gave you the impression that things were not bad here." (P1, young female travelling from China)

Although posters and leaflet stands giving COVID-19 information had been set up at LHR, 12 participants had no recollection of seeing such posters or leaflets at all. Direct observation by our research team verified that these were unobtrusive and their visibility was very limited due to the print size, colour and positioning.[6] Only two participants recalled seeing hand sanitisers placed at the airport. Participants emphasised the amount of information and measures being reported in the media or displayed at the airport in their departure country, as well as the protection measures that were applied on board their flight, in contrast with the situation at the arrival airport. A British participant also expressed frustration and concern that airport staff at the disembarkation point did not provide detailed instructions regarding the COVID-19 situation in the UK and possible protection measures.

Most participants expressed uncertainty about the COVID-19 situation in the UK, having seen little evidence of interventions to actively contain travel-associated transmission on arrival. An airport without visible containment measures was considered to signal good containment of the virus in the UK; participants also described their desire for reassurance in the absence of detailed instructions and protection measures.

> "At Heathrow, it was like nothing was wrong in the UK, so I think that causes a false sense of security, maybe if there was more of a presence, like information, temperature check, personnel etc, people might take it more seriously. I think a lot of people probably didn't take it seriously at the time." (P2, older male, Singapore)[1]

> "They could have had thermal imaging cameras, they could have had medical staff in protective clothing there to talk to people whose temperature came up as above the norm, they could have then asked people in those conditions, if they met those conditions to isolate them." (P3, older female, Singapore)

> "When we came back through in March the taxi driver said that there hadn't really been too many more cases. So, at the time, how silly, it didn't seem to be as serious as we all now know it is." (P4, older male, Singapore)

All participants were eager to acquire information regarding the pandemic and official advice about how to protect themselves and their families. Participants reported proactively searching for advice and information in traditional and social media to understand the changing situation at ports of departure and arrival, evaluate potential risks and identify measures they should take for international travel.

> "We'd kind of already sort of lived with it, listened to it out there probably all through February [on the television], we were a bit ahead of the game if you like in terms of that we'd already seen it." (P5, older female, Singapore)

> "I think we found out enough ourselves and heard enough and talked about it between ourselves and came to the decisions that we did, so yeah, so I don't really think that there could have been any more advice at that time that would have made any difference because as I say that advice if you like that was coming out later on we were already doing because of being where we'd been I suppose." (P3, older female, Singapore)

Based on their experience in the country of departure, some participants also pointed out that following official advice was voluntary in the UK and noted that, 'advice and rules imposed by the British government are already very loose'. Participants also stated awareness of the vacuum of scientific knowledge and detailed guidance at this early stage of the pandemic, which provided a space for interpretation of official advice regarding actions people should take.

> "Even if you self-isolate I think nobody quite realised how contagious this virus is, so when it means self-isolate it means self-isolate, it means don't touch anyone, you know, wear a mask. I think at the time little was really known about the virus. If you're going to redesign the leaflet again it might not only say to self-isolate but wear a mask, do not come into contact with each other, self-isolate but also practice social distancing as well to make sure that you do not give the virus to anybody else." (P6, older male, Singapore)

[1] In this and subsequent quotes, placename denotes the flight origin, not nationality, of the quoted passenger.

"It was difficult because we'd had no idea what was going on anyway, because at that point it definitely felt a bit over the top, we didn't know how many cases were in the UK and you don't know if you've actually contracted it or not. I do know people that have come back from Italy, I think the advice then was you need to isolate yourself for a week but they just kind of took it as oh well I'll stay in my house, but I'll still be around my housemates and my family and stuff like that, so I think they need to actually take it seriously and just get used to not doing anything, being ok with not doing anything." (P7, older male, Singapore)

"I can't think why you would not follow the official advice, at the time the number of people who had died from Coronavirus was rising and the numbers were unclear, but they were talking about one to two percent of the people who got infected may die." (P8, younger male, China)

Precautionary measures

Although participants described the official advice as adequate, based on their experience of public health responses to outbreaks in Asia, some participants took actions beyond those recommended in official advice to reduce the risk of infection and transmission. On arrival, some participants voluntarily self-isolated or tried to maintain social distance by skipping social activities and gatherings (not required under PHE guidelines). Participants expressed their concerns over the seemingly 'business as usual' situation in the UK, which contradicted their experiences in areas with established outbreaks, and chose to take extra precautions such as staying indoors, socially distancing, wearing masks and monitoring their body temperatures daily, despite not being symptomatic.

"We sort of self-isolated anyway when we came back. Nobody told us to do it. Because of the precautions we had taken and because we hadn't really hardly been with anybody; the chances of us giving others anything were miniscule." (P5, older female, Singapore)

"I felt scared when I came back here. Because everyone in China took it seriously, but no one took it seriously here in the UK. When I go out, I wear a face mask, a pair of goggles and a pair of disposable gloves. I cover myself tight." (P1, younger female, China)

Several participants also mentioned their reasons for these precautionary behaviours as being in part related to the potential stigma associated with the possibility of being seen as 'contagious' due to being travellers who had just returned from epidemic hotspots. They expressed willingness to adopt these measures voluntarily to avoid such stigma and to protect their family and friends.

"We wouldn't have put anybody at risk if we really thought that were was a chance, but we just didn't want it on us. We knew the chances were absolutely miniscule, but we took the decision that we wouldn't see anybody, so that was family and friends, for over a week after we got back." (P5, older female, Singapore)

"There was a kind of stigma with Singapore and South Korea and a few other Southeast Asian countries. We wanted to make everybody aware that if they did get something it possibly wouldn't have come from us because we'd been self-isolating." (P9, older female, Singapore)

Study participants were asked whether they knew what they should do if they had developed symptoms or visited pandemic hotspots and whether they were familiar with the NHS 111 service. All participants mentioned difficulties accessing the service, while those who were visitors or temporary residents in the UK were more concerned about the vagueness of advice itself and uncertain whether formal support was available for non-citizens.

"I think they [official advice] were only saying like contact 111 basically if your symptoms get worse but obviously, they're inundated, but certainly had we got symptoms on those first few days after we got back then that's what we would have done because as I say at that time it was still quite a new thing here." (P5, older female, Singapore)

"Someone told me it [NHS 111] is constantly engaged. I would have hoped to know how to contact the NHS effectively in the case that I was infected. Maybe I could have been given a few more telephone numbers? This kind of information enabling me to have access to medical treatment would have given me a sense of security." (P8, younger male, China)

Alongside calling NHS 111, British participants noted that they had additional options such as contacting their GP or seeking support from their local communities. They considered it easy to access any help they might need to follow the official advice, such as support from their local authority or community organisations and were appreciative of this. However, interviewees who were visitors or temporary residents (such as foreign citizens travelling on business or studying in the UK) reported relying on personal or social networks, social media and employers, as well as NHS 999 in case of emergency, and stated that they had limited contact with and support from local authorities and communities.

"We're luckier than most and if I want to go down and take a walk, I sort of can. I think if somebody is locked up in a one-bedroom flat in London it will be horrible." (P4, older male, Singapore)

"I think providing they have sufficient support in their communities there is no reason at all why anybody should not self-isolate." (P9, older female, Singapore)

"I don't think so [received any official support]. But the school sent us emails. It offered a backup option. If we encountered any problem, we could contact the school in the case of need. The school made us feel that they are quite protective." (P10, older female, Singapore)

Participants also differed in their views of which official guidelines they should follow, especially regarding the use of face coverings. Some were concerned that airport staff did not wear face coverings and attributed this to cultural and policy differences from their departure countries. Having already adopted face coverings as a daily health protection measure, they argued that wearing masks should be included in official UK guidance:

"The quarantine officer [at Heathrow airport] told me: don't worry, it is ok, don't be nervous; it is no use to wear a face mask. Social distancing was not taken at that time. I felt there would be loopholes and hidden risk. The outbreak has worsened in the UK, I think it has something to do with the measures taken then. [The UK] Airports were free zones at that time, hidden risk reveals itself when you entirely depend on voluntary [adherence]." (P8, younger male, China)

Conversely, some participants noted that they did not believe in the value of face coverings, due to official announcements from New Zealand and Singapore on the lack of evidence for their effectiveness. Others shared an ambivalent 'wait-and-see' attitude towards face coverings.

"We've seen [on the TV] about the mask doing more harm than good so we had to keep saying no, we're not going to get one because it's going to do more harm than good." (P5, older female, Singapore)

"There wasn't any clear evidence to say an ordinary mask would prevent you picking up germs and if you did pick up a germ it would multiply inside the mask. So even though we had masks in our bags, but we decided we'd use the hand gel, but we didn't want to wear the masks." (P11, older female, Singapore)

"The concern is, are you depriving the NHS of masks, when you're buying them for yourself when there is such a short global supply. So, there's a difficulty and a dilemma in just do I wear a mask. There is also a flipside to wearing masks, if you happen to have the mask and if your mask happens to pick up droplets from somebody else, your mask might become contagious." (P6, older male, Singapore)

Discussion

Clear and actionable official information can help to shape the public's understanding of COVID-19 and promote adherence to official advice.[6–8] The transnational experiences of international travellers in this study exposed them to multiple versions of official information and interventions to contain transmission that became sources both of valued knowledge and of uncertainty or confusion. This was exacerbated at this early stage of the pandemic by frequent changes in public health guidance and implementation of control measures.[9,10]

This study indicates that early in the pandemic, international travellers arriving in LHR were relatively confident about their knowledge of appropriate behavioural measures and proactively used information acquired from multiple international sources to minimise exposure and transmission risks. In taking additional precautions beyond those recommended by UK authorities at the time, many of the international travellers in our study were not following official PHE guidance, albeit because they were 'ahead of the game'. Arriving from countries that had already instituted robust public health control measures in response to COVID-19, these travellers had acquired knowledge from the places where their travel originated and adopted additional precautionary measures that went beyond local recommendations.

The apparent lack of control measures at arrival ports led many arriving passengers to question the seriousness of the UK government's response to the pandemic. The explicit public health information they received was less comprehensive than, and in some areas contradicted, official responses in countries where their travel originated. One consequence of these cross-national discrepancies was that international travellers had to rely on their own judgement to navigate the salience and appropriateness of differing rules, guidance and social norms across borders.

Participants responded to the need to assimilate and interpret sometimes inconsistent information from multiple sources by 'customising' the available guidance to inform action. Their responses constituted a proactive risk assessment and rationalised decision-making process whereby living situation in the UK, trust in information sources, correspondence with cultural logic and degree of willingness to accept potential risk to self and significant others all contributed to choosing what advice to follow. Some interviewees took actions that were not aligned with PHE guidance at the time but constituted effective precautionary measures. Although study participants repeatedly described their actions while manoeuvring across borders as "common sense", their interpretations of multiple versions of official information and consequent behaviour were context-based and consistent with sociocultural affiliation.

These tailored responses are informed population-level determinants of vulnerability, such as viral prevalence within specific population groups and geographies. Participants with a British background reported relative confidence in following official PHE advice, while visitors or temporary residents reported greater uncertainty and were more likely to maintain transmission-minimising precautions by adopting protective actions such as mask-wearing and non-mandated self-isolation, drawing on knowledge derived from their countries of origin and their own social networks. Younger visitors and temporary residents without pre-existing health issues who lacked knowledge about national health services in particular expressed uncertainty about the guidance to 'call NHS 111' in the event of experiencing symptoms. They also reported lacking connections with local communities and being highly reliant on members of their own networks for support. There were no significant differences in participants' awareness and knowledge about COVID-19 symptoms and self-protection measures,[6] but compared with other travellers, those who were visitors or temporary residents had willingly adopted additional preventive measures that were not required according to the UK official guidance at the time and maintained such caution after arrival. Such measures might have helped to reduce infection and transmission risks; however, as the pandemic continued, longer stay visitors may have faced other adverse impacts due to their limited integration into local structures for practical, social and emotional support, as well as difficulties in accessing health care. These difficulties which heighten potential vulnerability may also apply to resident minority communities in the UK and especially to more recent migrants. Studies have shown higher rates of COVID-19 exposure among minority communities due to socio-economic disparities,[11,12] and individuals from these communities have faced more barriers in adhering to official advice during self-isolation and national lockdowns.[8,13]

Several limitations exist in this study. First, our sample of international travellers was limited due to the rapid changes in travel restrictions and border closures. Also, all interviewees reported having essential business or reasonable needs to travel abroad, so our findings may not be generalisable to those travelling for leisure. However, the study does provide early evidence on responses to public health guidance among international travellers in the uncertain first phase of the pandemic. It provides an opportunity to learn about how people navigate between differing national rules and guidance across borders at the start of an international health emergency. This evidence can inform recommendations for improving information provision and hence individual adherence for public health benefits.

Public health implications

International travellers in this study were conscious of the potential risks associated with travel and keen to mitigate them. The provision of a centralised and regularly updated official national information hub would help to minimise possible confusion between different sources of guidance. Additionally, incorporating into public health guidance an explicit recognition that international travel inevitably entails exposure to public health containment measures, regulations and knowledge sources that differ across national jurisdictions may itself help to reassure travellers.

Our findings suggest that, information consistency, sociocultural norms, perceived risks and benefits and availability of support from both official and unofficial sources all affect adherence to official public health advice. In line with Denford et al. (2021),[8] we found individual adherence to involve a decision-making process to select

the health threats and containment measures that are most salient in the social context and institutional environment within which people are living. Greater attention to the differentiated information requirements of diverse groups of international travellers in the design of future public health guidance – for example, through the provision of tailored information for dual residents, short-stay business and leisure travellers and long-stay migrant workers and students – would help to minimise the uncertainties generated by receipt of generic advice which does not necessarily fit with individual circumstances. These categories of travellers could be anticipated in preparation for future cross-border epidemics and key aspects predesigned to facilitate rapid generation of tailored guidance when needed. Clarification of financial and other support measures available in the destination country for both short- and long-stay travellers would enhance adherence to requirements, such as mandatory self-isolation periods supported by testing, that are not institutionally provided but depend on voluntary action.

Author statements

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Ethical approval

This study was a form of service evaluation; therefore, no ethics committee approval was required. This was confirmed by the PHE Research Ethics and Governance Group.

All participants were informed about the purpose of this study and their participation was voluntary. The participants were told they could withdraw at any time without giving any reasons or if they are facing any consequences. They agreed to the interview being recorded and that any identifiable information would be removed. Consent was obtained from participants to use anonymous quotes to be published. Signed and verbal consent were obtained at the beginning of both the survey and interviews.

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Competing interests

No potential conflict of interest was reported by the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.11.015.

References

1. World Health Organisation (WHO). *Timeline of WHO's response to COVID-19*. 2020. https://www.who.int/news-room/detail/29-06-2020-covidtimeline. [Accessed 24 May 2021].
2. World Bank. *Global economic prospects 2020: pandemic, recession: the global economy in crisis*. 2020. https://www.worldbank.org/en/publication/global-economic-prospects. [Accessed 24 May 2021].
3. United Nations (UN). *The sustainable development goals report 2020*. 2020. https://unstats.un.org/sdgs/report/2020/. [Accessed 24 May 2021].
4. Thiagarajan K. Why is India having a COVID-19 surge? *BMJ* 2021;**373**:n1124. https://doi.org/10.1136/bmj.n1124.
5. World Health Organisation (WHO). *SARS-CoV-2 variants*. 2020. https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/. [Accessed 24 May 2021].
6. Zhang T, Robin C, Cai S, Sawyer C, Rice W, Smith LE, et al. Public health information on COVID-19 for international travellers: lessons learned from a mixed-method evaluation. *Public Health* 2021;**193**:116–23. https://doi.org/10.1016/j.puhe.2021.01.028.
7. Habersaat KB, Betsch C, Danchin M, Sunstein CR, Böhm R, Falk A, et al. Ten considerations for effectively managing the COVID-19 transition. *Nat Hum Behav* 2020;**4**:677–87. https://doi.org/10.1038/s41562-020-0906-x.
8. Denford S, Morton KS, Lambert H, Zhang J, Smith LE, Rubin GJ, et al. Understanding patterns of adherence to COVID-19 mitigation measures: a qualitative interview study. *J Public Health* 2021:fdab005. https://doi.org/10.1093/pubmed/fdab005.
9. Scally G, Jacobson B, Abbasi K. The UK's public health response to COVID-19. *BMJ* 2020;**369**:m1932. https://doi.org/10.1136/bmj.m1932.
10. Galvão J. COVID-19: the deadly threat of misinformation. *Lancet Infect Dis* 2021;**21**:E114. https://doi.org/10.1016/S1473-3099(20)30721-0.
11. Coetzee BJ, Kagee A. Structural barriers to adhering to health behaviours in the context of the COVID-19 crisis: considerations for low- and middle-income countries. *Global Public Health* 2020;**15**:1093–102. https://doi.org/10.1080/17441692.2020.1779331.
12. Public Health England. *Understanding the impact of COVID-19 on BAME groups*. 2020. https://www.gov.uk/government/publications/covid-19-understanding-the-impact-on-bame-communities. [Accessed 24 May 2021].
13. Raisi-Estabragh Z, McCracken C, Bethell MS, Cooper J, Cooper C, Caulfield MJ, et al. Greater risk of severe COVID-19 in Black, Asian and Minority Ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25(OH)-vitamin D status: study of 1326 cases from the UK Biobank. *J Public Health (Oxf)* 2020;**42**:451–60. https://doi.org/10.1093/pubmed/fdaa095.

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Original Research

Long-term trends in the incidence of congenital anomalies in Central China from 1997 to 2019

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ABSTRACT

Objective: The aim of the study was to investigate the incidence of, and trends in, congenital anomalies in Central China from 1997 to 2019.
Study design: This was a descriptive study.
Methods: We collected data describing 4,134,098 births from 75 hospital monitoring sites in Henan Province, Central China, from 1997 to 2019. A joinpoint regression model was used to analyze the continuous changes.
Results: There were 4,134,098 births recorded from 1997 to 2019, of which 50,646 noted the presence of congenital anomalies (incidence: 122.5 per 10,000). The incidence of congenital anomalies was found to have increased over time (P-trend <0.05). Congenital anomaly incidence in urban areas was higher than that in rural areas (155.3 per 10,000 vs 100.7 per 10,000; $P < 0.001$). Moreover, incidence was higher in males than in females (129.1 per 10,000 vs 112.9 per 10,000; $P < 0.001$). The incidence of neural tube defects significantly reduced from 1997 to 2019 (39.3 per 10,000 in 1997 vs 0.92 per 10,000 in 2019, P-trend <0.001), whereas the incidence of congenital heart disease (CHD) increased (5.56 per 10,000 in 2010 to 136.46 per 10,000 in 2019), which meant that CHD was the most common congenital anomaly post-2013.
Conclusion: In Henan province, the incidence of congenital anomalies increased by 115% from 1997 to 2019. Notably, the incidence of CHD is rising.

Introduction

Congenital anomalies are defined as functional, structural, and/or metabolic disorders occurring because of abnormal embryonic and/or fetal development and are the leading cause of infant mortality globally.[1–3] Approximately 7.9 million newborns are affected by congenital anomalies every year, accounting for 6% of live births worldwide. Among these newborns, 3.3 million do not survive past 5 years of age, whereas 3.2 million will live with life-long disabilities.[4] In China, congenital anomalies are the leading cause of infant and perinatal death, as they account for 20–25% of newborn deaths each year.[5]

A population-based survey in Inner Mongolia found that the incidence of congenital anomalies was 156.1 cases per 10,000 births, with the most common congenital anomalies being neural tube defects (NTDs) and congenital heart disease (CHD). Children of mothers aged <25 years were more likely to have congenital anomalies (relative risk = 2.22, 95% confidence interval [CI]: 2.05–2.41).[6] A study in Dalian reported a cumulative incidence of congenital anomalies of 101.14 per 10,000 live births from 2006 to 2010, with the incidence in 2010 being 29% lower than that in 2006 (incidence:81.16 per 10,000 vs 115.49 per 10,000). The incidence of congenital anomalies in urban areas was higher, with the most common congenital anomalies being CHD, cleft lip (CL) and/or palate, and polydactyly (PD) or syndactyly.[7] A study on the occurrence of congenital anomalies in Hainan reported a 27% increase in

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birth defects from 2000 (incidence: 98.93 per 10,000) to 2010 (incidence: 77.99 per 10,000). The most common congenital anomalies were PD, CL, congenital hydrocephalus (CH), CHD, and limb shortening. The prevalence of congenital anomalies was higher in rural areas (incidence: 112.34 per 10,000) than in urban areas (incidence: 87.11 per 10,000).[8] In the past decade, several risk factors for congenital anomalies, such as environmental pollution and older maternal age, have been changing. However, no study has focused on the prevalence of congenital anomalies in Central China.[8–10] Therefore, a more recent study of the prevalence of congenital anomalies is warranted.

Our study aimed to study the long-term trends in congenital anomalies in Henan, Central China, from 1997 to 2019. We analyzed the changing trends in both total and disease-specific incidence of congenital anomalies, which provides a comprehensive reference for the development of novel preventative strategies.

Methods

Study population

Participant data were collected from a population-based congenital anomaly surveillance system in Henan province, Central China. The surveillance system includes 75 hospital-based congenital anomaly surveillance sites and two congenital anomaly population-based surveillance locations (Gongyi city and the Yuanhui District of Luohe city). The data describe all live births recorded in the surveillance system from January 1, 1997, to December 31, 2019. Of the 75 hospital surveillance sites, 40 are located in urban areas and 35 are in rural areas.

The congenital anomaly hospital surveillance data describe perinatal infants with birth defects from 28 weeks of gestation to 7 days postpartum. This population was monitored from 28 weeks of gestation (including live births and stillbirths) to 42 days postpartum when the birth defect was officially diagnosed. This paper focuses on 23 different congenital anomalies identified according to the guidelines of the International Classification of Diseases and Related Health Problems, 10th revision.[11] A pediatrician or neonatologist recorded and verified information describing the infant, such as his/her date of birth, birth weight, sex, maternal age, place of residence, gestational age, and abnormal diagnosis. The occurrence of congenital anomalies was calculated annually and classified according to different parameters, including residence (rural or urban), sex (male or female), and maternal age. The incidence of various congenital anomalies was statistically analyzed, and variation in the trends of major congenital anomalies was analyzed.

This study was approved by the ethical committee of the third hospital of Zhengzhou University (Approve number: 2021-WZ-011).

Statistical analysis

We used Joinpoint Regression Program 4.8.0.1 to analyze time-dependent trends in the incidence of congenital anomalies.[12,13] This method divides long periods into several shorter periods and then analyzes changing trends across these periods to reveal whether the changes seen in these trends are statistically significant. The average annual percentage change (AAPC) for the segments, or time partitions, was calculated. The AAPC is a novel measure that uses the annual percentage changes from piecewise analyses to summarize and compare trends over a specific time partition. It avoids the disadvantage of conventional annual percentage analyses, which does not consider transitional periods.[14] The incidence of congenital anomalies and the 95% CIs were calculated, and the chi-squared statistics and odds ratios were calculated. Differences were considered statistically significant when the two-sided *P*-value was <0.05. SPSS 23.0 was used.

Results

From 1997 to 2019, 4,134,098 infants were born in the 75 surveillance sites in Henan Province, 50,646 of which were born with congenital anomalies. The incidence of congenital anomalies was thus calculated as 122.5 per 10,000 births (95% CI: 121.5–123.5). Of the 1,651,539 and 2,482,559 infants born in urban and rural areas, respectively, there were 25,644 and 25,002 cases of congenital anomalies recorded. Thus, the incidence of congenital anomalies was 155.3 per 10,000 births (95% CI: 153.4–157.2) in urban areas and 100.7 per 10,000 births (95% CI: 99.5–102.0) in rural areas. A total of 2,238,566 males and 1,893,392 females were born during the surveillance period, of which 28,900 males and 21,370 females were born with congenital anomalies, resulting in an incidence of 129.1 per 10,000 births (95% CI: 127.6–130.6) in males and 112.9 per 10,000 births (95% CI: 111.4–114.4) in females.

Geographical location differences in the incidence of congenital anomalies

The incidence of congenital anomalies in urban areas increased from 72.10 per 10,000 in 1997 to 339.70 per 10,000 in 2019, with a significant increase seen from 2012 to 2015 (per 10,000 births: 90.13 in 2012 to 233.48 in 2015, AAPC 33.1%, *P*-trend <0.05) and from 2015 to 2019 (233.48 in 2015 to 339.70 in 2019, AAPC 12.4%, *P*-trend <0.05; Fig. 1B; Table 1). From 1997 to 2011, the incidence of congenital anomalies in rural areas decreased, with a significant decrease from 1997 to 2003 (per 10,000 births: 172.30 in 1997 to 82.16 in 2003, AAPC −10.4%, *P*-trend <0.05) and from 2003 to 2011 (per 10,000 births: 82.16 in 2003 to 77.15 in 2011, AAPC −2.5%, *P*-trend <0.05). The incidence of congenital anomalies in rural areas increased from 77.15 per 10,000 in 2011 to 154.24 per 10,000 in 2019, with a significant increase from 2017 to 2019 (per 10,000 births: 105.56 in 2017 to 154.24 in 2019, AAPC 0.4%, *P*-trend <0.05; Fig. 1C; Table 1).

Sex-specific differences in the incidence of congenital anomalies

The incidence of congenital anomalies in males increased from 83.80 per 10,000 in 1997 to 254.04 per 10,000 in 2019 (AAPC 4.9%, *P*-trend<0.05) with a significant increase from 2011 to 2019 (per 10,000 births: 84.71 in 2011 to 254.04 in 2019, AAPC 14.7%, *P*-trend <0.05; Fig. S1A [Fig. S means supplementary Fig.]; Table 1). From 1997 to 2019, the incidence of congenital anomalies in females increased from 140.20 per 10,000 to 215.12 per 10,000 (AAPC 2.0%, *P*-trend<0.05). The incidence of congenital anomalies decreased from 140.20 per 10,000 in 1997 to 70.38 per 10,000 in 2010 (AAPC −5.5%, *P*-trend<0.05). However, a significant increase occurred from 2010 to 2019 (per 10,000 births: 70.38 in 2010 to 215.12 in 2019, AAPC 13.9%, *P*-trend <0.05; Fig. S1B; Table 1).

Maternal age-specific risk of congenital anomalies

No significant difference in congenital anomaly incidence for mothers aged <20 years was seen from 1997 to 2019 (per 10,000 births: 250.0 in 1997 to 187.7 in 2019, AAPC −3.4%, *P*-trend = 0.1; Fig. S2A; Table 2). The overall incidence of congenital anomalies for mothers aged 20–24 years increased from 1997 to 2019 (per 10,000 births: 121.0 in 1997 to 199.90 in 2019, AAPC 2.3%, *P*-trend <0.05). The incidence of congenital anomalies decreased from 121.0 per 10,000 in 1997 to 76.86 per 10,000 in 2011 (AAPC −3.0%, *P*-trend <0.05) but increased from 2011 to 2019 (per 10,000 births: 76.86 in

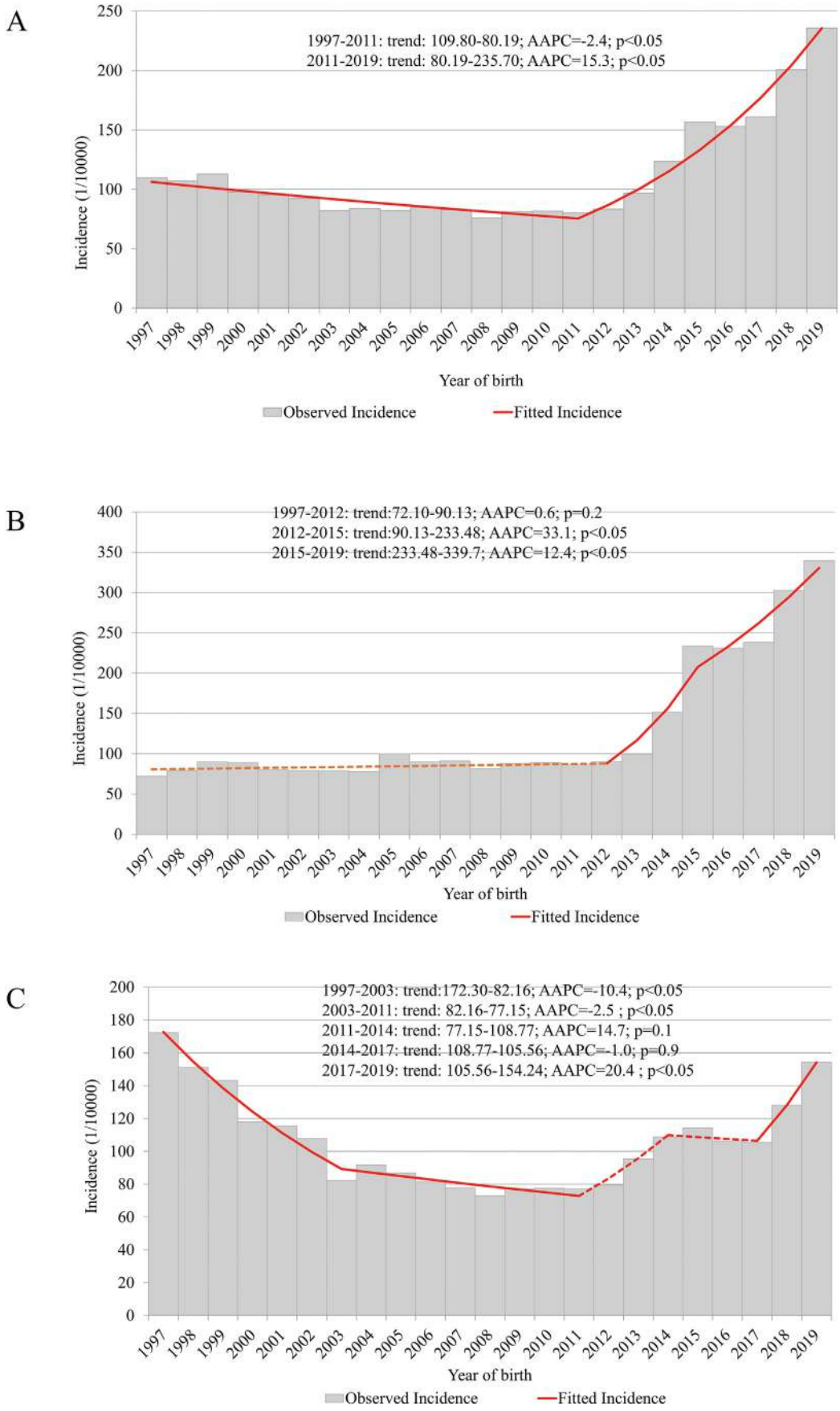

Fig. 1. Long-term trends in congenital anomalies in Henan, China, from 1997 to 2019. Observed and fitted total incidence of congenital anomalies (A) in total, (B) in urban areas, and (C) in rural areas, by year of birth. A bold line represents a significant joinpoint fit for the incidence, with markers indicating the join points, whereas a dashed line represents no significance.

Table 1
Long-term trends in congenital anomalies in Henan, China, from 1997 to 2019.

Condition	*n*	Period	Trend in proportion (1/10,000)	AAPC[a]	*P*
Total	4,134,098	1997–2019	109.8–235.7	3.7[b]	<0.05
		1997–2011	109.8–80.19	−2.4[b]	<0.05
		2011–2019	80.19–235.7	15.3[b]	<0.05
Areas					
Urban	1,651,539	1997–2019	72.10–339.70	6.6[b]	<0.05
		1997–2012	72.10–90.13	0.6	0.2
		2012–2015	90.13–233.48	33.1[b]	<0.05
		2015–2019	233.48–339.70	12.4[b]	<0.05
Rural	2,482,559	1997–2019	172.30–154.24	−0.5	0.7
		1997–2003	172.30–82.16	−10.4[b]	<0.05
		2003–2011	82.16–77.15	−2.5[b]	<0.05
		2011–2014	77.15–108.77	14.7	0.1
		2014–2017	108.77–105.56	−1.02	0.9
		2017–2019	105.56–154.24	0.4[b]	<0.05
Gender					
Male	2,204,268	1997–2019	83.80–254.04	4.9[b]	<0.05
		1997–2011	83.80–84.71	−0.4	0.4
		2011–2019	84.71–254.04	14.7[b]	<0.05
Female	1,929,830	1997–2019	140.20–215.12	2.0[b]	<0.05
		1997–2010	140.20–70.38	−5.5[b]	<0.05
		2010–2019	70.38–215.12	13.9[b]	0.05

[a] Average annual percent change.
[b] AAPC is significantly different from zero at $\alpha = 0.05$.

Table 2
Long-term trends in congenital anomalies in Henan, China, from 1997 to 2019.

Condition	Period	Trend in proportion (1/10,000)	AAPC[a]	*P*
Maternal age				
<20	1997–2019	250.0–187.7	−3.4	0.1
20–24	1997–2019	121.0–199.90	2.3[b]	<0.05
	1997–2011	121.0–76.86	−3.0[b]	<0.05
	2011–2019	76.86–199.90	12.4[b]	<0.05
25–29	1997–2019	99.10–228.04	4.5[b]	<0.05
	1997–2011	99.10–57.43	−1.8[b]	<0.05
	2011–2019	57.43–228.04	19.6[b]	<0.05
30–34	1997–2019	125.50–243.69	3.3[b]	<0.05
	1997–2011	125.50–74.57	−3.6[b]	<0.05
	2011–2019	74.57–243.69	16.5[b]	<0.05
35~	1997–2019	140.10–293.32	3.1[b]	<0.05
	1997–2011	140.10–96.13	−3.3[b]	<0.05
	2011–2019	96.13–293.32	15.5[b]	<0.05
Common congenital anomalies				
NTDs	1997–2019	39.3–0.92	−14.8[b]	<0.05
	1997–2006	39.3–14.36	−10.1[b]	<0.05
	2006–2019	14.36–0.92	−17.8[b]	<0.05
CL	1997–2019	14.33–3.52	−5.7[b]	<0.05
	1997–2012	14.33–10.51	−1.2	0.1
	2012–2019	10.51–3.52	−14.7[b]	<0.05
PD	1997–2019	6.46–17.14	4.7[b]	<0.05
	1997–2000	6.46–10.92	24.5[b]	<0.05
	2000–2003	10.92–3.84	−21.7[b]	<0.05
	2003–2019	3.84–17.14	7.1[b]	<0.05
CHD	1997–2019	4.64–136.46	19.7[b]	<0.05
	1997–2010	4.64–5.56	4.4	0.1
	2010–2019	5.56–136.46	45.8[b]	<0.05
CH	1997–2019	10.13–1.83	−6.0[b]	<0.05

NTD, neural tube defects; CL, cleft lip; PD, polydactyly; CHD, congenital heart disease; CH, congenital hydrocephalus.
[a] Average annual percent change.
[b] AAPC is significantly different from zero at $\alpha = 0.05$.

2011 to 199.90 in 2019, AAPC 12.4%, *P*-trend <0.05; Fig. S2B; Table 2). The incidence of congenital anomalies for mothers aged 25–29 years increased from 99.10 per 10,000 in 1997 to 228.04 per 10,000 in 2019 (AAPC 4.5%, *P*-trend<0.05). A decrease was observed from 1997 to 2011 (per 10,000 births: 99.10 in 1997 to 57.43 in 2011, AAPC −1.8%, *P*-trend <0.05), whereas a significant increase was seen from 2011 to 2019 (per 10,000 births: 57.43 in 2011 to 228.04 in 2019, AAPC 19.6%, *P*-trend <0.05; Fig. S2C; Table 2). From 1997 to 2019, the incidence of congenital anomalies for mothers aged 30–34 years increased from 125.50 per 10,000 to 243.69 per 10,000 (AAPC 3.3%, *P*-trend <0.05). The incidence of congenital anomalies in this group decreased from 1997 to 2011 (per 10,000 births: 125.50 in 1997 to 74.57 in 2011, AAPC change −3.6%, *P*-trend <0.05), whereas a significant increase was seen from 2011 to 2019 (per 10,000 births: 74.57 in 2011 to 243.69 in 2019, AAPC 16.5%, *P*-trend <0.05; Fig. S2D; Table 2). The incidence of congenital anomalies for mothers aged >35 years increased from 1997 to 2019 (per 10,000 births: 140.10 in 1997 to 293.32 in 2019, AAPC 3.1%, *P*-trend <0.05). A decrease occurred from 1997 to 2011 (per 10,000 births: 140.10 in 1997 to 96.13 in 2011, AAPC −3.3%, *P*-trend <0.05), whereas a significant increase occurred from 2011 to 2019 (per 10,000 births: 96.13 in 2011 to 293.32 in 2019, AAPC 15.5%, *P*-trend <0.05; Fig. S2E; Table 2).

Most common congenital anomalies

Fig. S3 indicates that the most common congenital anomalies seen during the period of monitoring were NTDs (including anencephalia, myelomeningocele, and encephalocele), total CL, PD, CHD, and CH. The incidence of NTDs decreased from 1997 to 2019, with rates of 39.3 per 10,000 in 1997, 14.36 per 10.000 in 2006, and 0.92 per 10,000 in 2019 (AAPC −10.1%, *P*-trend <0.05 and AAPC −17.8%, *P*-trend <0.05, respectively; Fig. S4A; Table 2). The incidence of total CL decreased from 1997 to 2019 (per 10,000 births: 14.33 in 1997 to 3.52 in 2019, AAPC −5.7%, *P*-trend<0.05), with the incidence decreasing most significantly from 2012 to 2019 (per 10,000 births: 10.51 in 2012 to 3.52 in 2019, AAPC −14.7%, *P*-trend <0.05; Fig. S4B; Table 2). The incidence of PD increased from 6.46 per 10,000 in 1997 to 17.14 per 10,000 in 2019 (AAPC 4.7%, *P*-trend <0.05). A significant increase in PD was seen from 1997 to 2000 (per 10,000 births: 6.46 in 1997 to 10.92 in 2000, AAPC 24.5%, *P*-trend <0.05) and from 2003 to 2019 (per 10,000 births: 3.84 in 2003 to 17.14 in 2019, AAPC 7.1%, *P*-trend <0.05), whereas a significant decrease was seen from 2000 to 2003 (per 10,000 births: 10.92 in 2000 to 3.84 in 2003, AAPC −21.7%, *P*-trend <0.05; Fig. S4C; Table 2). The incidence of CHD increased from 4.64 per 10,000 in 1997 to 136.46 per 10,000 in 2019 (AAPC 19.7%, *P*-trend <0.05), and this increase was particularly significant from 2010 to 2019 (per 10,000 births: 5.56 in 2010 to 136.46 in 2019, AAPC 45.8%, *P*-trend<0.05; Fig. S4D; Table 2). The

incidence of CH decreased gradually from 1997 to 2019 (per 10,000 births: 10.13 in 1997 to 1.83 in 2019, AAPC −6.0%, *P*-trend <0.05; Fig. S4E; Table 2).

Discussion

The incidence of total congenital anomalies in Henan province and within the different subgroups displayed similar trends. The average incidence of congenital anomalies during the monitoring period was 122.5 per 10,000 births (95% CI: 121.5–123.5). The overall incidence decreased from 1997 to 2011 and subsequently increased from 2011 to 2019. The incidence of congenital anomalies in urban areas and males showed an upward trend, with the incidence of congenital anomalies in urban areas and males increasing by 371% and 203%, respectively, from 1997 to 2019. In contrast, the incidence of congenital anomalies in rural areas and females initially decreased, but then subsequently increased. From 1997 to 2019, the incidence in rural areas decreased by 10%, whereas it increased by 53% in females. Overall, the incidence of congenital anomalies for mothers aged >20 years gradually decreased from 1997 to 2011, with the incidence subsequently increasing after 2011. The most common congenital anomalies seen were PD, CL, CH, CHD, and NTDs. From 1997 to 2019, there was a significant increase in the incidence of CHD (per 10,000 births: 4.64 to 136.46), whereas there was a significant reduction in the incidence of NTDs (per 10,000 births: 39.3 to 0.92).

Over the study period, an increase in the incidence of congenital anomalies in urban resulted in an overall increase of 115% for the province. This increased incidence was predominantly observed in urban areas and in males. Among the most common anomalies, the incidence of PD and CHD increased while the incidence of CH, CL, and NTDs decreased. PD was one of the top five most common congenital anomalies for many years, with the incidence of PD rising steadily since 2003. Indeed, PD incidence increased by 165% from 1997 to 2019. Similarly, CHD has ranked in the top five most common anomalies since 2008 and has been the most common overall since 2013. The incidence of CHD increased rapidly after 2010, with the incidence of CHD in 2019 being 29.4 times that in 1997. The incidence of CH has been decreasing, with an 82% decrease seen in its incidence from 1997 to 2019. Moreover, CH ranked second after PD in terms of overall incidence. In addition to these common congenital anomalies, syndactyly and hypospadias have been ranked among the top five most common anomalies in recent years, which may be because of the decreasing incidence of other previously more common congenital anomalies and an increase in the incidence of dactylions and hypospadias. The incidence of NTDs continued to decline during the survey period, moving from its position as the most common anomaly in 1997 to 10th place in 2019. The overall decline in the incidence of NTDs may be attributed to increased folic acid supplementation and improved prenatal diagnostic techniques in recent years.[15–17] CHD is the most common congenital anomaly in infants and is the most common birth defect–related cause of infant mortality.[19] Chromosomal anomalies are responsible for a small number of cases; however, the cause of most cases of CHD remains unknown.[20] In our study, we found that the incidence of CHD has been increasing since 2010 and has consistently ranked as the most common abnormality since 2013. The incidence of atrial septal defect/patent foramen oval and patent ductus arteriosus (per 10,000 births: 53.66 to 122.61; 26.76 to 70.67, respectively) has similarly been increasing between 2015 and 2019; they are the two most common subtypes of CHD and may be related to the increased incidence of mild CHD. However, improvements in CHD diagnostics may also have led to an increase in the rate of detection of CHD. Timely fetal and infant heart examination is gradually being adopted across the whole province, with some districts and counties popularizing infant CHD screening, which increases the rate of detection of CHD. In addition, in 2013, national standards for the detection of CHD were adopted. In recent years, there have also been increasing reports of novel micro-heart diseases. These may indeed be the causal factors driving the increasingly high incidence of CHD.

Previous studies have reported a differential incidence of congenital anomalies between urban and rural areas.[7,8,10,20] In this study, we found that the incidence of congenital anomalies in rural areas was higher than that in urban areas from 1997 to 2005, whereas the incidence in urban areas was higher than that in rural areas after 2005. Although the incidence of congenital anomalies in both areas showed an upward trend, the rate of increase was higher in urban areas. These results are consistent with previous studies.[7,10,20] This difference may be because of the increasing availability of prenatal diagnostics and monitoring techniques in rural areas. Improved diagnostics mean that the number of babies born with certain life-limiting or fatal congenital anomalies can be reduced, by means of abortion, thus reducing the overall incidence of congenital anomalies in rural areas.[21] Improved maternal health in rural areas, potentially because of increasing use of multivitamins and folic acid supplementation during pregnancy, may also help to reduce the incidence of congenital anomalies.[15–17] Pollution and other risk factors associated with modern lifestyles, such as indirect smoking, alcohol consumption during pregnancy, and maternal obesity, may contribute to the increase in congenital anomalies seen in urban areas.[22–26]

Previous studies have reported sex-specific differences in the incidence of congenital anomalies.[10,15,16] We identified a higher incidence of congenital anomalies in males than in females, which may be attributable to the increased incidence of hypospadias and PD. Hypospadias and PD are known to be more common in males. This higher incidence may also be because of an overall decline in the incidence of NTDs, as the incidence of NTDs is thought to be higher in females than in males.[27–29] It is an indisputable fact that maternal age has a substantial influence on the occurrence of congenital anomalies.[8,10,17] In our study, we found that the proportion of infants born to women aged >35 years has increased in recent years, which may be because of the implementation of the universal two-child policy in China.[30]

Compared with previous studies in China, this study had a longer study period, a larger sample size, and more recent data. The limitations of this study include that there were only 23 congenital anomalies reported by the surveillance system, whereas 110 congenital anomalies are known to frequently occur. In addition, the study lacked an individual database for each pregnancy, meaning that confounding factors such as smoking, drinking alcohol, and medical history could not be accounted for.

Conclusion

In general, the incidence of congenital anomalies in Henan, China, has trended upward during the last decade, especially in urban regions. The incidence of NTDs has significantly decreased, which may be because of improved diagnostic techniques and folic acid supplementation. Notably, the incidence of CHD is increasing. More attention should thus be paid to the diagnosis and prevention of CHD, and measures should be implemented to decrease the incidence of CHD.

Author statements

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Ethical approval

None sought.

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Competing interests

The authors declare that they do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.12.007.

References

1. Lee K, Khoshnood B, Chen L, Wall S, Cromie W, Mittendorf RJO, et al. Infant mortality from congenital malformations in the United States, 1970-1997. *Obstetr. Gynecol.* 2001;**98**:620–7.
2. Rosano A, Botto L, Botting B, Mastroiacovo P. Infant mortality and congenital anomalies from 1950 to 1994: an international perspective. *J Epidemiol Community Health* 2000;**54**:660–6.
3. Kirby R, Mai C, Wingate M, Janevic T, Copeland G, Flood T, et al. Prevalence of selected birth defects by maternal nativity status, United States, 1999-2007. *Birth Defect. Res.* 2019;**111**:630–9.
4. Christianson AHC, Modell B. *March of dimes global report on birth defects: the hidden toll of dying and disabled children*. White Plains, New York: March of Dimes Birth Defects Foundation; 2006.
5. Ping W, Gang M, Zheng C, Qiu X. Research progress of birth defect intervention. *Matern Child Health Care China* 2016;**31**:4320–2.
6. Zhang X, Li S, Wu S, Hao X, Guo S, Suzuki K, et al. Prevalence of birth defects and risk-factor analysis from a population-based survey in Inner Mongolia, China. *BMC Pediatr* 2012;**12**:125.
7. Liu QG, Sun J, Xiao XW, Song GR. Birth defects data from surveillance hospitals in Dalian city, China, 2006-2010. *J Matern Fetal Neonatal Med* 2016;**29**:3615–21.
8. Fan L, Gong T, Cao X, Du Y. Epidemiologic characteristics of birth defects in the Hainan Province from 2000 to 2010, China. *Birth Defects Res Part A Clin Mol Teratol* 2013;**97**:750–4.
9. Nicolaou N, Renkema KY, Bongers EM, Giles RH, Knoers NV. Genetic, environmental, and epigenetic factors involved in CAKUT. *Nat Rev Nephrol* 2015;**11**:720–31.
10. Dastgiri S, Xie D, Yang T, Liu Z, Wang H. Epidemiology of birth defects based on a birth defect surveillance system from 2005 to 2014 in hunan province, China. *PLoS One* 2016;**11**.
11. Organization WHJhwwicaiio. *International classification of diseases and related health problems, 10˙ revision*. 2007.
12. Kim H, Fay M, Feuer E, Midthune DJ. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;**19**:335–51.
13. Joinpoint Regression Program. *Statistical methodology and applications branch, surveillance research Program*. Version 4.8.0.1 - April. National Cancer Institute; 2020.
14. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. *Stat Med* 2009;**28**:3670–82.
15. Liu J, Jin L, Li Z, Zhang Y, Zhang L, Wang L, et al. Prevalence and trend of isolated and complicated congenital hydrocephalus and preventive effect of folic acid in northern China, 2005-2015. *Metab Brain Dis* 2018;**33**:837–42.
16. Rozendaal AM, van Essen AJ, te Meerman GJ, Bakker MK, van der Biezen JJ, Goorhuis-Brouwer SM, et al. Periconceptional folic acid associated with an increased risk of oral clefts relative to non-folate related malformations in the Northern Netherlands: a population based case-control study. *Eur J Epidemiol* 2013;**28**:875–87.
17. Taye M, Afework M, Fantaye W, Diro E, Worku A. Factors associated with congenital anomalies in Addis Ababa and the Amhara Region, Ethiopia: a case-control study. *BMC Pediatr* 2018;**18**:142.
19. Vis JC, Duffels MG, Winter MM, Weijerman ME, Cobben JM, Huisman SA, et al. Down syndrome: a cardiovascular perspective. *J Intellect Disabil Res* 2009;**53**:419–25.
20. Mombo LE, Yangawagou-Eyeghe LM, Mickala P, Moutele J, Bah TS, Tchelougou D, et al. Patterns and risk factors of birth defects in rural areas of south-eastern Gabon. *Congenit Anom (Kyoto)* 2017;**57**:79–82.
21. Rossi AC, Prefumo F. Accuracy of ultrasonography at 11-14 weeks of gestation for detection of fetal structural anomalies: a systematic review. *Obstet Gynecol* 2013;**122**:1160–7.
22. Yang W, Zeng L, Cheng Y, Chen Z, Wang X, Li X, et al. The effects of periconceptional risk factor exposure and micronutrient supplementation on birth defects in Shaanxi Province in Western China. *PLoS One* 2012;**7**:e53429.
23. Salavati N, Strak M, Burgerhof JGM, de Walle HEK, Erwich JJHM, Bakker MK. The association of air pollution with congenital anomalies: an exploratory study in the northern Netherlands. *Int J Hyg Environ Health* 2018;**221**:1061–7.
24. Tan Y, Yang R, Zhao J, Cao Z, Chen Y, Zhang B. The associations between air pollution and adverse pregnancy outcomes in China. In: *Ambient air pollution and health impact in China*; 2017. p. 181–214.
25. Farhi A, Boyko V, Almagor J, Benenson I, Segre E, Rudich Y, et al. The possible association between exposure to air pollution and the risk for congenital malformations. *Environ Res* 2014;**135**:173–80.
26. Stothard K, Tennant P, Bell R, Rankin JJJ. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA* 2009;**301**:636–50.
27. Black AJ, Lu DYD, Yefet LS, Baird R. Sex differences in surgically correctable congenital anomalies: a systematic review. *J Pediatr Surg* 2020;**55**:811–20.
28. Deak KL, Siegel DG, George TM, Gregory S, Ashley-Koch A, Speer MC. Further evidence for a maternal genetic effect and a sex-influenced effect contributing to risk for human neural tube defects. *Birth Defects Res Part A Clin Mol Teratol* 2008;**82**:662–9.
29. Garne E. Congenital heart defects occurrence, surgery and prognosis in a Danish County. *Scand Cardiovasc J* 2004;**38**:357–62.
30. Zhang X, Chen L, Wang X, Wang X, Jia M, Ni S, et al. Changes in maternal age and prevalence of congenital anomalies during the enactment of China's universal two-child policy (2013-2017) in Zhejiang Province, China: an observational study. *PLoS Med* 2020;**17**:e1003047.

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Short Communication

Preparedness in a public health emergency: determinants of willingness and readiness to respond in the onset of the COVID-19 pandemic

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ABSTRACT

Objectives: Healthcare professionals' high risk of infection and burnout in the first months of the COVID-19 pandemic probably hindered their much-needed preparedness to respond. We aimed to inform how individual and institutional factors contributed for the preparedness to respond during the first months of a public health emergency.
Study design: Cross-sectional study.
Methods: We surveyed healthcare workers from a Local Health Unit in Portugal, which comprises primary health care centers and hospital services, including public health units and intensive care units, in the second and third months of the COVID-19 epidemic in Portugal. The 460 answers, completed by 252 participants (about 10% of the healthcare workers), were analyzed using descriptive statistics and multiple logistic regressions. We estimated adjusted odds ratios for the readiness and willingness to respond.
Results: Readiness to respond was associated with the perception of adequate infrastructures (aOR = 4.04, $P < 0.005$), lack of access to personal protective equipment (aOR = 0.26, $P < 0.05$) and organization (aOR = 0.31, $P < 0.05$). The willingness to act was associated with the perception of not being able to make a difference (aOR = 0.05, $P < 0.005$), risk of work-related burnout (aOR = 21.21, $P < 0.01$) and experiencing colleagues or patients' deaths due to COVID-19 (aOR = 0.24, $P < 0.05$).
Conclusions: Adequate organization, infrastructures, and access to personal protective equipment may be crucial for workers' preparedness in a new public health emergency, as well workers' understanding of their roles and expected impact. These factors, together with the risk of work-related burnout, shall be taken into account in the planning of the response of healthcare institutions in future public health emergencies.

Introduction

SARS-CoV-2 has spread rapidly worldwide.[1] Most infected persons present mild symptoms or none,[2] but the diagnosis of SARS-CoV-2 infection, treatment of persons with moderate or severe symptoms, and contact tracing require major efforts from resources that healthcare services may not have, especially during periods of high incidence.[1,2]

It is predictable that healthcare services may not be able to respond as promptly and with the same quality during public health emergencies — as during pandemics — as it would without this pressure. However, healthcare services are expected to prepare and promptly react to public health emergencies, and to adapt and upscale their response to face new demands.[1,2]

The capacity of response of healthcare services depends on their infrastructure, available materials, equipment, and number of human resources — and their preparedness. McCabe et al. (2010)[3] proposed three key ingredients for improving the public health emergency preparedness system: willingness – the emotional or affective dimension that depends on personal and contextual factors, readiness – the availability to respond, and the possession of

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the necessary resources in terms of staff, structure, equipment and (personal and institutional) plans for an adequate response, and ability – the aptitudes, traits, skills, and knowledge earned during education or training.

However, this pandemic has been striking healthcare workers, directly and indirectly, which can impact their preparedness. Burnout risk increased among healthcare workers,[4] and some authors have shown that having had COVID-19 symptoms or risk contacts is associated with psychological distress and lower sense of coherence.[5]

Nonetheless, little is known about how the experience of this pandemic — including burnout — contributed to the willingness and readiness to act, nor what factors drove to a higher preparedness. We hypothesize that, if little or no institutional and psychological support is given to healthcare workers, factors like the lack of formal organizational support, training or equipment, and workers' experience of the pandemic (in terms of burnout, SARS-CoV-2 infection, and transmission to others, and contact with COVID-19-related deaths) may affect their willingness and readiness to act. This study aims to understand the individual and organizational factors that have contributed to the willingness and readiness of healthcare workers to respond during the first phase of the SARS-CoV-2 pandemic.

Methods

This is an observational cross-sectional study based on a self-administered survey that explored the underlying factors that could contribute to the readiness and willingness to respond in the COVID-19 pandemic, including personal, patients- and work-related burnout.[6]

This questionnaire was sent to all workers from a Local Health Unit from an area with about 180,000 inhabitants (Matosinhos), especially affected in the first months of the pandemic. This Unit comprises a hospital, which provides infectiology, internal medicine and intensive care services, and primary health care units, including a public health unit. The questionnaire was sent between May and June 2020 (first and second fortnights of May, and in the first fortnight of June); and 460 questionnaires were completed by 252 participants (about 10% of all staff; 110 filled the questionnaire once, while 88 filled it twice and 58 three times, i.e. each fortnight). The study was approved by the ethics committee from the Matosinhos' Local Health Unit (44/20/RS).

We stratified the descriptive analysis by working or not at the frontline, as respondents' and institution's characteristics were likely to differ, and performed logistic regression analyses, mutually adjusting all models, and adjusting for sex, age, working (or not) in the frontline, education, and questionnaire wave (Table 1).

Results

In all, 60.2% of the questionnaires were answered by frontline workers; 78.0% were females, and 72.4% were younger than 44 years old. Most were ready to answer to the pandemic, and readiness was higher among those in the frontline (83.3% vs 71.7%, *P*-value<0.005); 85% were willing to answer, but 40.1% reported not having enough knowledge to answer (Table 1). A third (29.6%) of those in the frontline perceived they did not have enough training, which contrasts with 52.8% of those not working in the frontline. These results did not significantly change over time.

Regarding the potential determinants of readiness, most participants considered infrastructures, equipment, and information systems as adequate. The institution was perceived as organized for the response, and contingency plans were known by the largest majority. Most reported adequate psychological work conditions: 58.9% of respondents in the frontline and 70.6% of those not in the frontline (*P*-value<0.05).

Differences regarding the factors related to the willingness to respond were found: the perception of not being able to make any difference was higher among those not working in the frontline (11.6% vs 22.7%, *P*-value<0.005), as it was regarding the perception of their action not being effective to control the pandemic (20.0% vs 36.2%, *P*-value<0.001), and not knowing how to contribute (6.9% vs 25.3%, *P*-value<0.001). Over a quarter of responders had high or severe risk of burnout, but the proportion was higher among those not in the frontline, with statistically significant differences. Those in the frontline experienced more frequently COVID-19-related death of patients or colleagues (27.2% vs 8.2%, *P*-value<0.001).

The workers' readiness to respond to COVID-19 was strongly associated with the perception of adequate infrastructures (aOR = 4.04, *P*-value<0.005) (Table 1). The readiness to respond was reduced when workers perceived lack of access to adequate PPE (aOR = 0.26 *P*-value<0.05), as well as lack of organization in the institution (aOR = 0.31, *P*-value<0.05).

Willingness to respond was negatively associated with the perception of not being able to make a difference (aOR = 0.05, *P*-value<0.005) and positively associated with the risk of work-related burnout (aOR = 21.21, *P*-value<0.01). Having experienced the death of colleagues or patients due to COVID-19 reduced the willingness to respond (aOR = 0.24, *P*-value<0.05).

Discussion

In the first months of the response to a pandemic — caused by an unknown agent — the perception of adequate infrastructures, access to PPE, and organization of the institution determined the workers' readiness to respond. The perception of not being able to make a difference, moderate and higher risk of work-related burnout and having experienced colleagues or patients' death due to COVID-19 affected their willingness to respond.

These results are partially aligned with the framework proposed by McCabe et al. (2010):[3] physical conditions, equipment, and organization are needed to inspire readiness to act. It must be noted that in the first phase of the pandemic, there were limitations on PPE availability,[7] and hospitals faced an unprecedented need of large numbers of isolation rooms and ventilators and the need to reorganize to better answer to the pandemic. Thus, equipment and conditions were perceived as important for the readiness of healthcare workers to act, as well as organizational factors. As hypothesized,[3] the perception of not being able to make any difference diminished the willingness to respond. This finding is valuable for managers: every worker must clearly know what his/her role is and its contribution for the response. The scarcity of evidence about the disease or its treatment specificities may have lowered the importance of training and perceived knowledge on the willingness to act.

Regarding the positive association between willingness to respond and work-related burnout, a higher willingness may be associated with a higher work intensity and, indirectly, to a higher risk of burnout, especially during the first phase of the pandemic. A review showed that higher responsibility and higher working hours increased the risk of suffering from mental distress during the COVID-19 pandemic,[8] and frontline healthcare professionals showed a higher risk of insomnia, stress, and burnout.[9] Our results do not show any significant association between having experienced transmission of COVID-19 in the workplace or in the family or friends' milieu and the willingness to respond to the pandemic, except for the contact with the death of patients or colleagues due to COVID-19. The high sense of duty could have attenuated the importance of these experiences in the worker's willingness to

Table 1
Sample description and factors associated with the readiness and willingness to respond in the COVID-19 pandemic. Models are mutually adjusted and for sex, age, workplace, education, role in the pandemic response (working or not in the frontline), and waves.

	Description of the sample			Factors associated with readiness to respond		Factors associated with willingness to respond	
	In the frontline	Not in frontline	*P*-value	Adjusted odds Ratio	*P*-value	Adjusted odds Ratio	*P*-value
Ready to respond	229 (83.3%)	129 (71.7%)	0.003				
Adequate physical conditions	189 (68.2%)	132 (72.9%)	0.280	**4.04** (1.75–9.30)	0.001		
Adequate equipment and materials	200 (73.0%)	145 (79.2%)	0.130	0.73 (0.25–2.15)	0.570		
No access to adequate PPE	37 (13.4%)	13 (7.3%)	0.046	**0.26** (0.08–0.88)	0.030		
Information system was not adequate	106 (38.8%)	58 (32.2%)	0.150	0.84 (0.32–2.20)	0.710		
Information system was unable to answer	88 (32.2%)	41 (23.0%)	0.035	0.95 (0.33–2.77)	0.928		
Institution was not organized	45 (16.3%)	27 (15.0%)	0.710	**0.31** (0.12–0.81)	0.016		
Does not know contingency plan	21 (7.6%)	16 (8.8%)	0.640	0.42 (0.13–1.38)	0.153		
Adequate psychological work conditions	162 (58.9%)	127 (70.6%)	0.012	1.70 (0.73–3.97)	0.216		
Willing to respond	234 (85.4%)	153 (85.0%)	0.910				
Perception action makes no difference	32 (11.6%)	41 (22.7%)	0.002			**0.05** (0.01–0.32)	0.001
Perception that action was not effective	55 (20.0%)	64 (36.2%)	<0.001			1.60 (0.34–7.46)	0.546
Does not know to contribute	19 (6.9%)	45 (25.3%)	<0.001			2.25 (0.34–14.62)	0.397
Does not have enough knowledge	111 (40.1%)	59 (32.6%)	0.110			1.00 (0.28–3.58)	0.995
Does not have enough training	81 (29.6%)	95 (52.8%)	<0.001			0.38 (0.10–1.46)	0.161
Personal burnout - Moderate/High/Severe risk[a]	159 (57.8%)	115 (68.0%)	0.034			0.86 (0.14–5.50)	0.877
Work-related burnout - Moderate/High/Severe risk[a]	128 (48.1%)	103 (64.0%)	0.002			**21.21** (2.11–212.78)	0.009
Patient-related burnout - Moderate/High/Severe risk[a]	192 (70.6%)	115 (73.2%)	0.001			3.49 (0.65–18.87)	0.146
Was tested for SARS-CoV-2 infection	129 (47.1%)	62 (34.1%)	0.006			0.81 (0.20–3.24)	0.768
Was diagnosed for SARS-CoV-2 infection	38 (13.7%)	26 (14.5%)	0.810			0.37 (0.03–4.05)	0.413
Had contact with colleague or patient with COVID-19	237 (86.2%)	110 (61.5%)	<0.001			1.59 (0.24–10.51)	0.636
Transmitted COVID-19 to colleagues or patients	19 (6.9%)	7 (3.9%)	0.180			0.58 (0.08–4.38)	0.599
Transmitted COVID-19 to family or friends	12 (4.5%)	14 (7.7%)	0.150			0.41 (0.03–5.21)	0.490
Friends or family diagnosed with COVID-19	79 (28.7%)	58 (31.7%)	0.500			0.34 (0.09–1.32)	0.120
Experienced death of colleagues or patients due to COVID-19	74 (27.2%)	15 (8.2%)	<0.001			**0.24** (0.06–0.97)	0.045
Experienced death of family or friends due to COVID-19	9 (3.3%)	7 (3.9%)	0.740			[b]	
Had psychological care in the last 2 weeks	13 (4.7%)	3 (1.6%)	0.082			[b]	

Note: In bold the results that were statistically significant.
[a] Reference category: no/low risk.
[b] The variables "Experienced death COVID-19 of family or friends" and "Psychological care last two weeks" were omitted due to collinearity (small number of observations).

respond.[10] The small number of workers using psychological support may have also attenuated the effect of this strategy for improving their well-being and the willingness to act.

These results must be interpreted considering that, first, the sample corresponds to healthcare workers from a single center. Although, we believe these results could be observed in other centers that congregate primary care units, infectiology, internal medicine, and intensive care services located in a predominantly urban context strongly affected in the first months of the pandemic. Second, only about 10% of the whole study population agreed to participate in the survey. Support staff or older workers were underrepresented, probably due to lower digital literacy. Third, invitations to participate were repeated in time. Although responses may not be not fully independent, the existing resources and organization may have changed and, accordingly, the willingness and readiness to respond; as such, we adjusted the analysis for the wave

of questionnaires. Fourth, we cannot assume causality but only association, which can be reversely set, as we discussed regarding willingness and work-related burnout. However, it is unlikely that a higher readiness to act increased the perception of better physical conditions, organization, or accessibility to PPE.

Public health emergencies — as the COVID-19 pandemic — can put healthcare services under strain, and healthcare workers may respond differently to it. The perception of adequate infrastructures, organization, and access to PPE are crucial in creating a sense of readiness, and the knowledge that one's own actions can make a difference contributes to the willingness to act. Team manager's awareness of these factors, as well as of the risk of work-related burnout, is much needed to provide safe and healthy workplaces and an adequate response to this public health emergency, and others that may emerge in the future.

Author statements

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Ethical approval

The study was approved by the ethics committee from the Matosinhos' Local Health Unit (44/20/RS).

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Competing interests

The authors declare that there are no conflicts of interest.

References

1. Armocida B, Formenti B, Ussai S, Palestra F, Missoni E. The Italian health system and the COVID-19 challenge. *Lancet Public Heal* 2020;**5**(5):e253. https://doi.org/10.1016/S2468-2667(20)30074-8.
2. Cuadros DF, Xiao Y, Mukandavire Z, Correa-Agudelo E, Hernández A, Kim H, et al. Spatiotemporal transmission dynamics of the COVID-19 pandemic and its impact on critical healthcare capacity. *Health Place* 2020;**64**:102404. https://doi.org/10.1016/j.healthplace.2020.102404.
3. McCabe OL, Barnett DJ, Taylor HG, Links JM. Ready, willing, and able: a framework for improving the public health emergency preparedness system. *Disaster Med Public Health Prep* 2010;**4**(2):161–8. https://doi.org/10.1001/dmp-v4n2-hcn10003.
4. Gemine R, Davies GR, Tarrant S, Davies RM, James M, Lewis K. Factors associated with work-related burnout in NHS staff during COVID-19: a cross-sectional mixed methods study. *BMJ Open* 2021;**11**(1):42591. https://doi.org/10.1136/bmjopen-2020-042591.
5. Gómez-Salgado J, Domínguez-Salas S, Romero-Martín M, Ortega-Moreno M, García-Iglesias JJ, Ruiz-Frutos C. Sense of coherence and psychological distress among healthcare workers during the COVID-19 pandemic in Spain. *Sustain* 2020;**12**(17):6855. https://doi.org/10.3390/SU12176855.
6. Kristensen TS, Borritz M, Villadsen E, Christensen KB. The Copenhagen Burnout Inventory: a new tool for the assessment of burnout. *Work Stress* 2005;**19**(3):192–207. https://doi.org/10.1080/02678370500297720.
7. World Health Organization. *Shortage of personal protective equipment endangering health workers worldwide*. World Health Organization; 2020. Published, https://www.who.int/news/item/03-03-2020-shortage-of-personal-protective-equipment-endangering-health-workers-worldwide. [Accessed 30 April 2021].
8. Braquehais MD, Vargas-Cáceres S, Gómez-Durán E, Nieva G, Valero S, Casas M, et al. The impact of the COVID-19 pandemic on the mental health of healthcare professionals. *QJM An Int J Med* 2020;**113**(9):613–7. https://doi.org/10.1093/qjmed/hcaa207.
9. Stuijfzand S, Deforges C, Sandoz V, Sajin CT, Jaques C, Elmers J, et al. Psychological impact of an epidemic/pandemic on the mental health of healthcare professionals: a rapid review. *BMC Publ Health* 2020;**20**(1):1230. https://doi.org/10.1186/s12889-020-09322-z.
10. Damery S, Draper H, Wilson S, Greenfield S, Ives J, Parry J, et al. Healthcare workers' perceptions of the duty to work during an influenza pandemic. *J Med Ethics* 2010;**36**(1):12–8. https://doi.org/10.1136/jme.2009.032821.

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Review Paper

Prevalence of HIV, hepatitis B virus, and hepatitis C virus among incarcerated people in Iran: a systematic review and meta-analysis

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ABSTRACT

Objectives: Incarcerated people are at higher risk for HIV, Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) infections. This review systematically summarized the evidence on the prevalence of these infections among incarcerated people in Iran.
Study design: A systematic review and meta-analysis.
Methods: We searched Embase, PubMed, Web of Science, Scopus, PsychInfo, Iranian databases, including IranMedex, Magiran, Scientific Information Database (SID), and IranDoc. A grey literature review was conducted to find unpublished reports from the Ministry of Health and experts throughout the country. Included studies reported data on the prevalence of HIV, HBV, or HCV infections. A random-effects meta-analysis was performed to estimate the pooled prevalence. A meta-regression analysis was also conducted.
Results: Of 1461 screened records, 23 records were eligible (total participants = 199,855). The pooled prevalence of HIV (17 studies), HBV (6 studies), and HCV (10 studies) was 2.77% (95% CI: 1.96, 3.70), 2.89% (95% CI: 2.28, 3.56), and 21.57% (95% CI: 13.62, 30.76), respectively. Meta-regression analyses showed that HIV (*P*-value = 0.05) and HCV (*P*-value = 0.02) were reduced over time using survey year as the interested variable in the model. Also, lifetime history of drug injection had a significant association with the HIV infection (*P*-value = 0.03).
Conclusion: The findings suggest that the prevalences of these infections are relatively considerable among Iranian incarcerated people. These findings support developing interventions to reduce the risk of the acquisition and circulation of these infections among incarcerated people, and continued harm reduction programs among most at-risk incarcerated people, as well as HCV treatment.

Introduction

Globally, HIV, hepatitis B virus (HBV), and hepatitis C (HCV) virus are major public health concerns. About 38 million people were living with HIV worldwide in 2019.[1] In 2015, the World Health Organization (WHO) estimated that 257 million and 71 million people were living with HBV and HCV, respectively.[2] Previous studies suggested a direct association between high-risk behaviors such as drug use and needle sharing and the transmission risk of blood-borne infections such as HIV, HBV, and HCV.[2,3]

Incarcerated people are at greater risk for some of the blood-born infections such as HIV, HBV, and HCV[4] than non-incarcerated people. These infections are particularly higher among incarcerated people with a history of risky practices, such as those who inject drugs or have a history of drug injection. The prevalence of these infections has been reported high among incarcerated people in Iran. During the 1990s, several HIV outbreaks were reported among incarcerated people in Iran.[5] The outbreaks led to elevated concerns for incarcerated people's health and their networks. While the HIV prevalence among incarcerated

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people in Iran was estimated at 0.0%–0.4% before 1998, the prevalence rose to 4.5% after 1998.[6]

While people who inject drugs (PWID) contribute to a substantial portion of incarcerated people with HIV in Iran,[7] they are also at greater likelihood of being incarcerated; for example, 65.5% of PWID in Iran reported lifetime experience of incarceration.[8] As such, risky behaviors such as drug use and drug injection is prevalent among incarcerated people; for example, a study in 2015 showed that approximately 20% of incarcerated people in Iran had a history of drug injection inside prison.[9] A report published in 2006 also demonstrated that the prevalence of sharing injection equipment was 82% among PWID who had a lifetime history of drug injection inside prison; of them, 36% were HIV seropositive.[10] Internationally, estimates suggest that incarcerated people are approximately 15 times more likely to be living with HIV compared to people who are not incarcerated.[11,12] A 2018 systematic review and meta-analysis showed that *recent* incarceration increases the risk of HIV acquisition by 81% (i.e. relative risk = 1.81; 95% CI: 1.40, 2.34) and the risk of HCV acquisition by 62% (i.e. relative risk = 1.62; 95% CI: 1.28, 2.05). Additionally, *past* history of incarceration was associated with a 25% increase in HIV and a 21% increase in HCV acquisition risk.[15] To improve our understanding concerning the burden of HIV, HBV, and HCV infections among incarcerated people in Iran, as one of the HIV key affected subpopulations, we performed a systematic review and meta-analysis in order to quantitively summarize the existing body of evidence on the prevalence of these three infections.

Methods

The present review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[16]

Search strategy

We searched the articles and grey literature that reported the prevalence of HIV, HBV, or HCV infection from inception to February 10, 2021. The following electronic databases were searched: PubMed, Embase, Web of Science, Scopus, and PsycINFO for the English language articles. We also searched IranMedex, Magiran, Scientific Information Database (SID), and IranDoc as commonly used Iranian databases. The search strategy consisted of

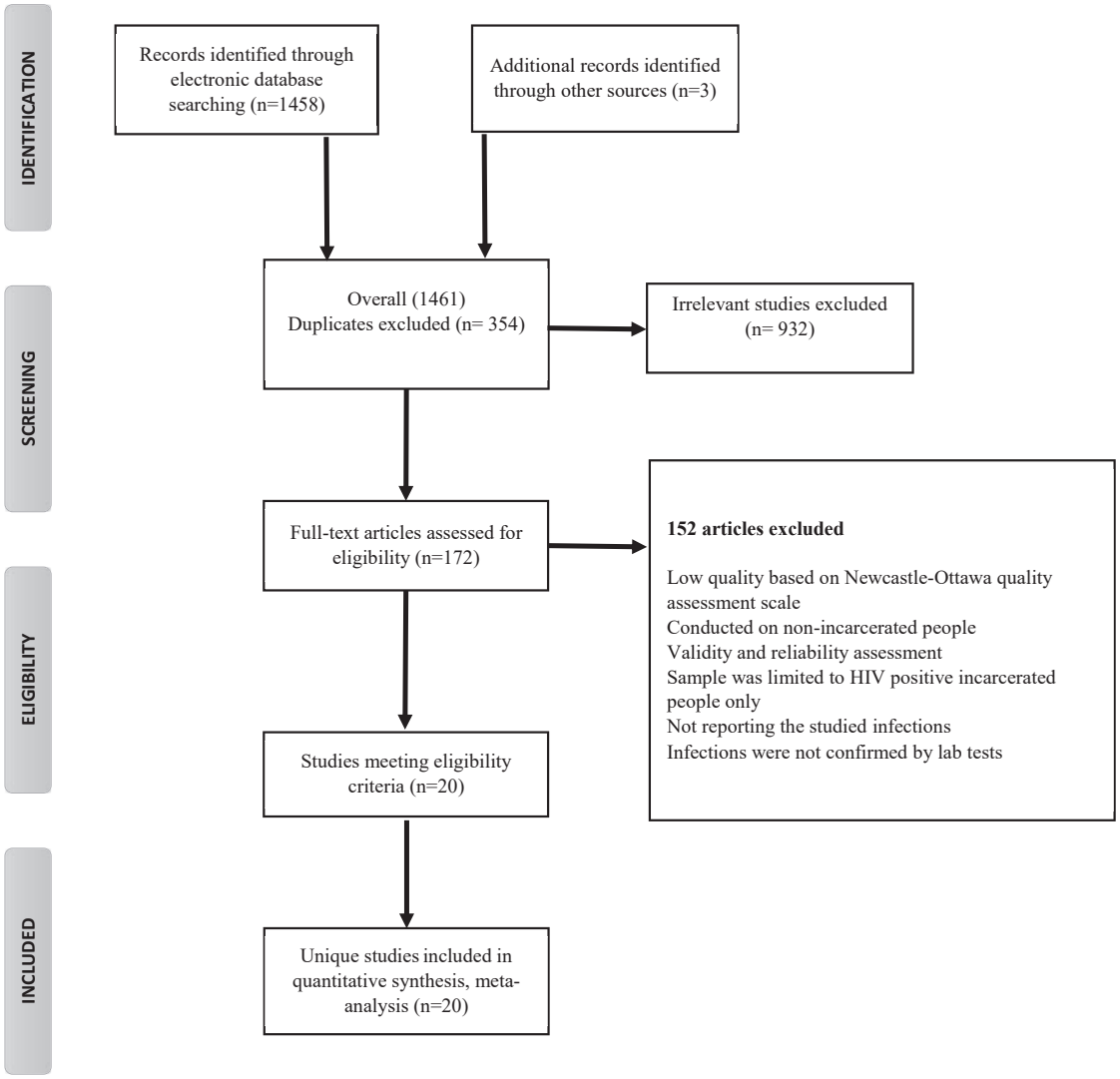

Fig. 1. PRISMA diagram for study selection of HIV, HBV, and HCV among incarcerated people, Iran.

the terms for incarcerated people (e.g. prisons, criminals, incarcerate, jail, correctional facility, correctional institute, detain, offender) and Iran (details are shown in Appendix A). Additionally, we conducted a grey literature review to identify unpublished documents. To do this, we reached out to institutions, research centers, and well-known experts who were well-known in the areas of HIV, HBV, and HCV and asked for providing and sharing unpublished records.

Eligibility criteria and quality assessment

We included original studies that reported HIV, HBV, and HCV infections among incarcerated people in Iran. The inclusion criteria consisted of (a) quantitative studies, (b) studies conducted in Iran, (c) studies published in Persian or English, and (d) measured HIV (HIV Ab) or HBV (HBs Ag) or HCV (HCV Ab) infection by serologic test, and reported the prevalence of these infections separately with a confirmatory test. The exclusion criteria included (a) unclear type of serological test, (b) lack of a serological test for the studied infections, and (c) no quantitative estimate of these infections.

Data extraction

After eliminating duplicates, two co-authors (S.M. and G.M.) screened titles and abstracts independently and removed irrelevant studies. Disagreements between the two reviewers were resolved by discussion with the senior author (H.S.). Data were extracted by two co-authors (S.M. and G.M.) and double-checked for the following items: (a) study design, (b) sample size, (c) study location and coverage, and (d) the prevalence of HIV, HBV, and HCV.

Quality assessment

The Newcastle–Ottawa scale (NOS) was used to examine the quality of the included studies. The NOS assesses the extent to which a study addressed the potential biases during the different levels of the study. The studies were classified into three categories, including unsatisfactory (score range: 0–4), satisfactory (score range: 5–6), good (score range: 7–8), and very good (score range: 9–10).[17] The details of the quality assessment of the included studies are provided in Appendix B.

Analytic approach

The pooled prevalence and 95% confidence intervals (CI) were reported for the three studied infections. The Freeman-Tukey double arcsine transformation was used to estimate the pooled prevalence for each outcome.[18] A random-effects meta-analysis model through the DerSimonian and Laird method was applied to pool the data.[19] To evaluate the possibility of heterogeneity between studies, the I^2 value was examined. We used meta-

Table 1
Included studies for a systematic review of HIV, HBV, and HCV prevalence among incarcerated people in Iran.

Author, published year	Geographical coverage	Sample size	Age	Sampling method	Test type	Reported infection	Study type
Khani et al. 2003[41]	Zanjan (city)	346	Mean: 33.7	Random	ELISA/western blot	HIV	Cross-sectional
Rowhani-Rahbar et al. 2004[42]	Mashhad (city)	101	Mean: 32.8	Random	ELISA/western blot	HIV	Cross-sectional
Alizade et al. 2005[43]	Hamedan (city)	427	Mean: 37.9	Random	ELISA/RIBA	HCV	Cross-sectional
Javadi et al. 2006[44]	Isfahan and Lorestan and Chaharmahal va Bakhtiari (province)	1431	Not reported	Random	Double ELISA	HBV; HCV	Cross-sectional
Amiri et al. 2007[45]	Gilan (province)	541	Mean: 34.7	Census	Double ELISA	HCV	Cross-sectional
Pourahmad et al. 2007[46]	Isfahan, Lorestan and Chaharmahal va Bakhtiari (province)	1431	Age range: 25- 60	Random	Double ELISA	HIV; HBV; HCV	Cross-sectional
Khodabakhshi et al. 2007[23]	Gorgan (city)	121	Not reported	Random	ELISA/western blot	HIV; HBV	Cross-sectional
Davoodian et al. 2009[27]	Hormozgan (province)	249	Mean: 35.4	Random	ELISA/western blot	HIV	Cross-sectional
BBSS (2009)[47]	National	4543	Mean: 32.2	Random	Double ELISA	HIV	Cross-sectional
Afsar Kazerooni et al. 2010[48]	Shiraz (city)	363	Mean: 33.2	Random	Double ELISA	HIV	Cross-sectional
Moradi et al. 2012[49]	Hamedan (city)	118	Mean: 32.0	Census	ELISA/western blot	HIV	Cross-sectional
Nokhodian et al. 2012[26]	Isfahan (city)	163	Mean: 34.5	Census	ELISA/western blot	HIV; HCV	Cross-sectional
Ataie et al. 2013[50]	Isfahan (city)	160	Mean: 16.6	Census	ELISA/western blot	HIV	Cross-sectional
Dibaj et al. 2013[51]	Isfahan (province)	970	Mean: 32.9	Census	ELISA/western blot	HIV	Cross-sectional
Haghdoost et al. 2013[24]	National	155,771	Not reported	Random	Double ELISA	HIV	Cross-sectional
BBSS (2013)[52]	National	5390	Mean: 35.1	Random	Double ELISA	HIV	Cross-sectional
Ziaee et al. 2014[53]	South Khorasan (province)	881	Mean: 34.7	Random	ELISA/western blot	HIV; HCV	Cross-sectional
Khajedalouee et al. 2016[29]	Mashhad (city)	1114	Not reported	random	ELISA/PCR	HCV	Cross-sectional
BBSS (2017)[54]	National	5775	Mean: 35.8	Random	Double ELISA	HIV	Cross-sectional
SeyedAlinaghi et al. 2017[55]	Tehran (province)	6900	Mean: 30.7	Census	Unigold/ELISA/ western blot	HIV	Cross-sectional
Moradi et al. 2018[9]	National	5508	Mean: 39.5	Multi- stage	Double ELISA	HBV, HCV	Cross-sectional
Moradi et al. 2019[25]	National	6481	Mean: 36.3	Multi- stage	Double ELISA	HBV; HCV	Cross-sectional
Khademi et al. 2019[28]	Kermanshah (province)	1034	Mean: 35.5	census	Rapid test/double ELISA	HIV; HBV, HCV	Cross-sectional

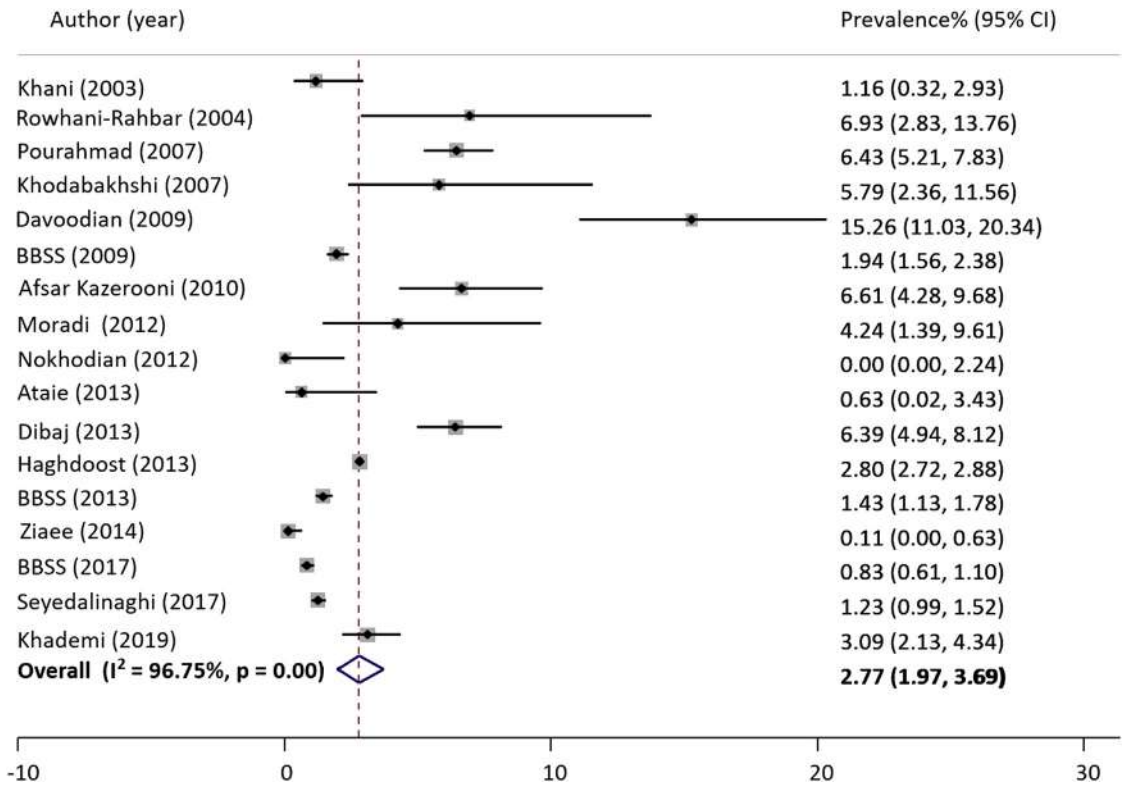

Fig. 2. The overall prevalence of HIV among incarcerated people in Iran based on the random-effects model.

regression by Knapp-Hartung modification to investigate the source of heterogeneity between studies.[20] Meta-regression models were used to assess the role of the survey year by assuming that the prevalence of these infections reduces over time and the role of a lifetime history of drug injection by assuming that ever drug injection increases the prevalence of these infections. Given the lack of enough records in the meta-analysis stage when analyzing HBV ($n = 6$), meta-regression analyses were limited to only HIV and HCV.[21] The Stata's *metaprop* package was used for analyses.[22] Stata version 14.2 was used for conducting meta-analyses.

Results

Participants and study characteristics

We screened 1458 records in electronic databases and three additional unpublished reports through other sources, including national HIV bio-behavioral surveillance surveys (BBSS) among incarcerated people, conducted in 2009, 2013, and 2017. After removing duplicates (354 records) and irrelevant papers (932 records) based on titles and abstracts, 172 articles and three reports received the full-text review. In the full-text review phase, 152 articles were removed, mainly due to being non-original articles, conducted among incarcerated people living with HIV, did not measure the study outcomes of interest, used self-report tests instead of serologic tests, did not use confirmation tests for the studied infections (Fig. 1). In the final step, data from 20 published articles and three national BBSS reports, yielding a total of 199,855 participants, were extracted. The mean age of participants in included studies was ranged between 16.6 and 37.9 years old. The smallest sample size ($n = 121$) was for a study conducted in Gorgan, a northern city in Iran,[23] while the maximum sample size ($n = 155,771$) was for a national study that used aggregated data from HIV sentinel serosurveys from 1991 to 2007.[24] The majority of studies used simple random sampling and census for recruiting participants, with two studies using a multistage cluster sampling method[9,25] (Table 1). Seventeen studies reported eligible information for pooling HIV infection data, ten studies for HCV, and six studies for HBV.

HIV prevalence

The pooled prevalence of HIV infection based on the confirmed HIV Ab test was estimated as 2.77% (95% CI: 1.97, 3.69). The lowest prevalence estimation was 0.00% (95% CI: 0.00, 2.24) in a 2002 study conducted in Isfahan, a central city in Iran.[26] The highest prevalence estimation was 15.26% (95% CI: 11.03, 20.34) in a 2002 study conducted in Bandar-Abbas, a southern city in Iran[27] (Fig. 2). Results of the univariate meta-regression analyses showed that a history of lifetime drug injection increased the likelihood of HIV prevalence among incarcerated people (*P*-value: 0.03). The survey year was, however, negatively associated with the HIV prevalence (*P*-value: 0.05) (Table 2).

Table 2
Meta-regression results.

Prevalence	Coefficient	95% Confidence Intervals	*P*-value
HIV prevalence			
Survey year	−0.001	−0.002; 0.000	0.05
Lifetime drug injection	0.001	0.000; 0.001	0.03
HCV prevalence			
Conducted Date	−0.020	−0.032; −0.004	0.02
Lifetime drug injection	0.005	−0.005; 0.015	0.30

HBV prevalence

The pooled prevalence of HBV was 2.89% (95% CI: 2.28, 3.56). The lowest estimate was for a 2017 study in Kermanshah, located in the western part of Iran, which was 1.26% (95% CI: 0.67, 2.14).[28] The study in Khorasan Razavi prison in 2008, a northeastern city in Iran, reported the highest prevalence of HBV as 4.22% (95% CI: 3.12, 5.57)[29] (Fig. 3). Meta-regression analyses were not done for HBV due to the low number of records in the final stage.

HCV prevalence

The pooled prevalence of HCV infection among incarcerated people in Iran was 21.57% (95% CI: 13.62, 30.76). Nokhodian et al. (2009) reported the lowest HCV prevalence as 7.36% (95% CI: 3.86, 12.51) in Isfahan prison.[26] Amiri et al. (2009), in a national survey reported the highest HCV estimation at 51.94% (95%CI: 47.64, 56.22)[30] (Fig. 4). The meta-regression analyses showed that the survey year was negatively associated with the HCV prevalence (*P*-value: 0.02) (Table 2).

Discussion

The findings of this systematic review and meta-analysis showed that the pooled estimate of HIV among incarcerated people in Iran was 2.77%, with 21.57% as the pooled estimate of HCV and 2.89% as the pooled estimate of HBV. The prevalence of HIV and HCV was shown to be reduced over time. Lifetime drug injection increased the likelihood of HIV prevalence.

The pooled HIV prevalence for our study was 2.77%. These results are approximately in line with previous reviews in Iran. For example, a 2012 systematic review and meta-analysis conducted by Bagheri Amiri et al. estimated HIV prevalence among incarcerated people at 3.42%.[31] The relatively lower estimation in our study may suggest that HIV prevalence among incarcerated people has a decreasing trend with a low slope. According to the meta-regression results, the prevalence of HIV among incarcerated people decreases 0.1% per year, which supports the decreasing trend. The observed decrease might be due to harm reduction programs such as opioid substitution treatment (OST) and needle and syringe program (NSP) inside and outside of the prisons in Iran. However, the reducing trend is very low, and additional interventions concentrating on the sexual transmission way of HIV are needed. Improving the interventions such as distributing free condoms, sexual health counseling, providing pre-exposure prophylaxis, and periodic HIV testing inside the prisons could be effective to accelerate the HIV reduction among incarcerated people in Iran. However, free condoms are available in conjugal visits. It is not available for sexual acts among the incarcerated people inside the prisons. With regard to other populations at risk for HIV, the pooled prevalence of HIV among men who have sex with men in Iran was 7.0%,[32] which is substantially higher than our estimation. However, our estimation was similar with the pooled prevalence of HIV among female sex workers has been estimated as 2.2%.[33]

Based on our estimations, the pooled prevalence of HBV among incarcerated people was 2.89%. A review conducted by Dolan et al. estimated that the prevalence of HBV among incarcerated people in east and central Africa was 23.5%, which was the highest among all regions in the world. In addition, the HBV prevalence among incarcerated people in eastern Europe and central Asia was 10.4%.[34] The diversity of prevalence in this study was because of the extended geographical coverage of different countries. Overall, the estimated prevalence of HBV among incarcerated people in Iran was considerably lower than HBV prevalence among incarcerated people worldwide. However, the estimated prevalence of HBV among incarcerated people in our study was about 30% higher than HBV prevalence in the general population of Iran.[35] The observed difference could be noticeable from the public health viewpoint because incarcerated people could be a potential source of infection for the general population when released from prison. Overall, it seems that HBV control policies resulted in effective outcomes. Part of this might be due to the national HBV vaccination in Iran having been started in 1992.[36] Considering other populations in Iran, the pooled prevalence of HBV among incarcerated people was substantially lower than the pooled prevalence of HBV among PWID (4.8%).[37]

The findings suggested that HCV was recognized as the most common blood-borne infection among incarcerated people in Iran. We estimated that 21.57% of incarcerated people in Iran were HCV

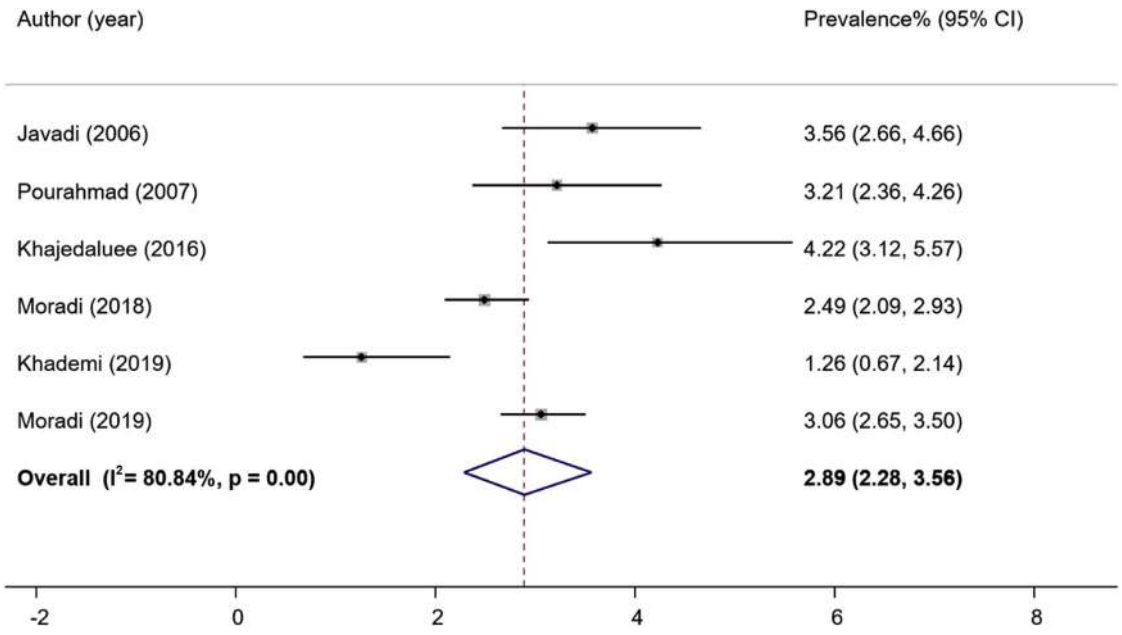

Fig. 3. The overall prevalence of HBV among incarcerated people in Iran based on the random-effects model.

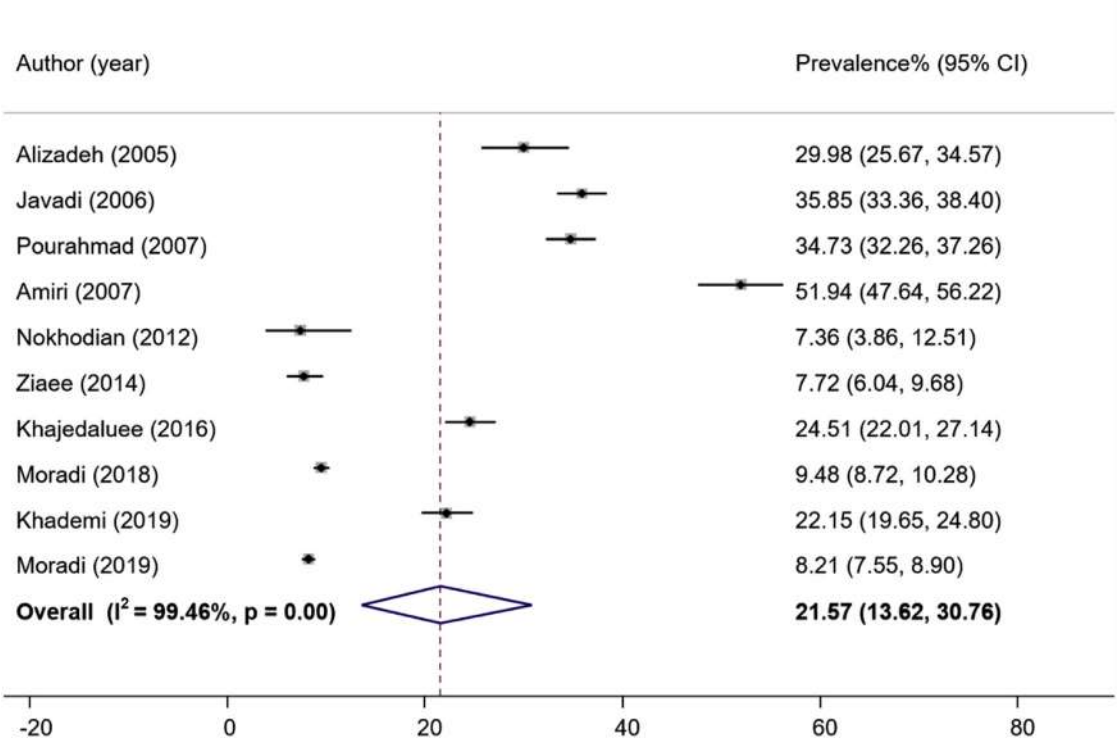

Fig. 4. the overall prevalence of HCV among incarcerated people in Iran based on the random-effects model.

seropositive. The pooled prevalence of HCV among incarcerated people worldwide was estimated at 13.22%, which was about half of our estimations.[38] The plausible reason for this difference could be explained by the lack of an active national program for diagnosing HCV infection and treatment in Iran. The high prevalence of HCV among incarcerated people in Iran highlights the need for HCV prevention and treatment programs. A systematic review and meta-analysis estimated the prevalence of HCV among Iran's general population as 0.6%, which was significantly lower than our estimation.[39] This underscores that incarcerated people should be considered as a priority population of HCV prevention and treatment programs. The mismanagement of HCV in incarcerated people could lead to the spread of the virus inside and outside of the prisons and have a significant effect on public health in Iran. Consequently, controlling HCV among incarcerated people should be a priority for health policymakers in Iran. The results of the meta-regression suggested that the HCV prevalence among incarcerated people in Iran reduced 2.0% each year, which is low according to the high prevalence of this infection. Consequently, prevention and treatment programs are needed to decrease HCV prevalence among incarcerated people in Iran. Previous studies have estimated the pooled prevalence of HCV among the PWID at 41.3%,[40] which was about twice the HCV prevalence among incarcerated people.

Our review has some limitations that should be noted. First, because of a limited number of studies, determining heterogeneity for more variables was impossible. Second, some studies did not report the mean age of participants, and most participants were male. Consequently, we were not able to do more subgroup analysis or meta-regression analysis.

Conclusion

This systematic review and meta-analysis documented the burden of HIV, HBV, and HCV among incarcerated people in Iran. Results showed that the prevalence of these infections among this key affected population is considerably high, in particular, HCV. Such high prevalences among incarcerated people could be partially driven by people who inject drugs either inside prisons or those who inject drugs outside the prisons while they have a higher risk of being arrested.

The trend of these prevalences was shown to be negative, which can be mainly due to the results of the continued attempts in scaling up and distributing harm reductions programs and services inside and outside prisons for people with high-risk practices. A history of drug injection was associated with a higher prevalence of HIV and HCV, which is not a surprising result given the key role of drug injection in the epidemic of these infections among the key affected populations. Evidence-informed prevention programs should be developed to reduce the risk of these infections among these socially and structurally marginalized populations. Harm reduction services should be continued inside prisons, with a particular focus on those who inject drugs.

Author statements

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Ethical approval

None sought.

Funding

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Competing interests

Authors have no competing interest to declare and state.

Authors' contributions

GM searched the online database for the study. SM and GM performed the title/abstract and full texts screening, data extraction. FT and FM contributed to data analysis. SM drafted the primary manuscript. SM, MS, HS, MK, and KD contributed to the study design and revision of the manuscript. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.11.020.

References

1. *Global HIV & AIDS statistics — 2020 fact sheet*. UNAIDS; 2020. Available from: https://www.unaids.org/en/resources/fact-sheet.
2. Chan M. *Global hepatitis report, 2017*. WHO; 2017. Available from: http://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf;jsessionid=79E68B39ECFDAD8B9E5972D3A55E4CE8?sequence=1.
3. Ghasemian R, Najafi N, Amirkhanloo K. The study of infections due to injection drug abuse in the injecting drug users hospitalized at imam khomeini hospital in Sari and Razi Hospital in Ghaemshahr in 2007-2009. *J Mazandaran Univ Med Sci* 2011;**21**(83):9–15.
4. Dolan K, Kite B, Black E, Aceijas C, Stimson GV. HIV in prison in low-income and middle-income countries. *Lancet Infect Dis* 2007;**7**(1):32–41.
5. Farnia M, Ebrahimi B, Shams A, Zamani S. Scaling up methadone maintenance treatment for opioid-dependent prisoners in Iran. *Int J Drug Pol* 2010;**21**(5):422–4.
6. Haghdoost A-A, Mirzazadeh A, Shokoohi M, Sedaghat A, Gouya MM. HIV trend among Iranian prisoners in 1990s and 2000s; analysis of aggregated data from HIV sentinel sero-surveys. *Harm Reduct J* 2013;**10**(1):1–5.
7. Rich JD, Chin-Hong PV, Busi KA, Mayer KH, Flanigan TP. Hepatitis C and HIV in male prisoners. *JAIDS J Acquir Immune Defici Syndr* 1997;**16**(5):408–9.
8. Khezri M, Karamouzian M, Sharifi H, Ghalekhani N, Tavakoli F, Mehmandoost S, et al. Willingness to utilize supervised injection facilities among people who inject drugs in Iran: findings from 2020 national HIV bio-behavioral surveillance survey. *Int J Drug Pol* 2021;**97**:103355.
9. Moradi G, Gouya MM, Azimizan Zavareh F, Mohamadi Bolbanabad A, Darvishi S, Aghasadeghi MR, et al. Prevalence and risk factors for HBV and HCV in prisoners in Iran: a national bio-behavioural surveillance survey in 2015. *Trop Med Int Health* 2018;**23**(6):641–9.
10. Zamani S, Kihara M, Gouya MM, Vazirian M, Nassirimanesh B, Ono-Kihara M, et al. High prevalence of HIV infection associated with incarceration among community-based injecting drug users in Tehran, Iran. *JAIDS J Acquir Immune Defic Syndr* 2006;**42**(3):342–6.
11. Beg M. *Update on HIV in prisons and other closed settings*. United Nations Office on Drugs and Crime; 2017. 13 December.
12. Organization WH. *People in prisons and other closed settings*. World Health Organization; 2019 [updated May 2019. Available from: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/populations/people-in-prisons.
15. Stone J, Fraser H, Lim AG, Walker JG, Ward Z, MacGregor L, et al. Incarceration history and risk of HIV and hepatitis C virus acquisition among people who inject drugs: a systematic review and meta-analysis. *Lancet Infect Dis* 2018;**18**(12):1397–409.
16. McInnes MD, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *Jama* 2018;**319**(4):388–96.
17. Wells GA, Shea B, O'Connell Da, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. 2000. Oxford.
18. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Stat* 1950:607–11.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials* 1986;**7**(3):177–88.
20. Röver C, Knapp G, Friede T. Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. *BMC Med Res Methodol* 2015;**15**(1):1–7.
21. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, et al. Development of the instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ* 2020;**192**(32):E901–6.
22. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Publ Health* 2014;**72**(1):1–10.
23. Behnaz K, Abdollah A, Fateme F, Mohammadreza R. Prevalence and risk factors of HIV, hepatitis B virus and hepatitis C virus infections in drug addicts among Gorgan prisoners. *J Med Sci* 2007;**7**(2):252–4.
24. Haghdoost A-A, Mirzazadeh A, Shokoohi M, Sedaghat A, Gouya MM. HIV trend among Iranian prisoners in 1990s and 2000s; analysis of aggregated data from HIV sentinel sero-surveys. *Harm Reduct J* 2013;**10**:32.
25. Moradi G, Jafari S, Zarei B, Mahboobi M, Zavareh FA, Molaeipoor L, et al. Prevalence and risk factors for hepatitis B and hepatitis C exposure in Iranian prisoners: a national study in 2016. *Hepat Mon* 2019;**19**(7):10.
26. Nokhodian Z, Yazdani MR, Yaran M, Shoaei P, Mirian M, Ataei B, et al. Prevalence and risk factors of HIV, syphilis, hepatitis B and C among female prisoners in Isfahan, Iran. *Hepat Mon* 2012;**12**(7):442–7.
27. Davoodian P, Dadvand H, Mahoori K, Amoozandeh A, Salavati A. Prevalence of selected sexually and blood-borne infections in Injecting drug abuser inmates of bandar abbas and roodan correction facilities, Iran, 2002. *Braz J Infect Dis* 2009;**13**(5):356–8.
28. Khademi N, Skakiba E, Khodadoust M, Khoramdad M. Seroprevalence and related risk behaviors of hepatitis C, hepatitis B and HIV infections among male prisoners in Kermanshah. *Iran* 2019;**22**(10):588–91.
29. Khajedaluee M, Babaei A, Vakili R, Valizade N, Shandiz FH, Alavian SM, et al. Sero-prevalence of bloodborne tumor viruses (HCV, HBV, HTLV-I and KSHV infections) and related risk factors among prisoners in Razavi Khorasan province, Iran, in 2008. *Hepat Mon* 2016;**16**(12).
30. Amiri M, Dejman M, Dastoury M, Roushanfekr P. The relationship between addiction and socio-demographic characteristics of Iranian newcomer prisoners. *Global J Health Sci* 2013;**6**(2):168–74.
31. Bagheri Amiri F, Mostafavi E, Mirzazadeh A. HIV, HBV and HCV coinfection prevalence in Iran-a systematic review and meta-analysis. *PLoS One* 2016;**11**(3):e0151946.
32. Ghalichi L, Naserbakht M, Eftekhar Ardebili M, Janani L, Pournik O, Tavakoli F, et al. HIV prevalence among men who have sex with men in Iran: a systematic review and meta-analysis. *Med J Islam Repub Iran* 2021;**35**(1):919–26.
33. Karamouzian M, Nasirian M, Hoseini SG, Mirzazadeh A. HIV and other sexually transmitted infections among female sex workers in Iran: a systematic review and meta-analysis. *Arch Sex Behav* 2020;**49**(6):1923–37.
34. Dolan K, Wirtz AL, Moazen B, Ndeffo-Mbah M, Galvani A, Kinner SA, et al. Global burden of HIV, viral hepatitis, and tuberculosis in prisoners and detainees. *Lancet* 2016;**388**(10049):1089–102.
35. Amini N, Alavian SM, Kabir A, Hosseini SYS, Andabili SHA. Clinical features and Seroepidemiology of Anti-HDV Antibody in patients with chronic hepatitis B virus infection in Iran: a meta-analysis. *Hepat Mon* 2011;**11**(12):960.
36. Merat S, Malekzadeh R, Rezvan H, Khatibian M. *Hepatitis B in Iran*. 2000.
37. Rostam-Abadi Y, Rafiemanesh H, Gholami J, Shadloo B, Amin-Esmaeili M, Rahimi-Movaghar A. Hepatitis B virus infection among people who use drugs in Iran: a systematic review, meta-analysis, and trend analysis. *Harm Reduct J* 2020;**17**(1):1–19.
38. Moradi G, Goodarzi E, Khazaei Z. Prevalence of Hepatitis B and C in prisons worldwide: a meta-analysis during the years 2005-2015. *Biomed Res Ther* 2018;**5**(4):2235–51.
39. Mirminachi B, Mohammadi Z, Merat S, Neishabouri A, Sharifi AH, Alavian SH, et al. Update on the prevalence of hepatitis c virus infection among iranian general population: a systematic review and meta-analysis. *Hepat Mon* 2017;**17**(2).
40. Nematollahi S, Ayubi E, Almasi-Hashiani A, Mansori K, Moradi Y, Veisani Y, et al. Prevalence of hepatitis C virus infection among high-risk groups in Iran: a systematic review and meta-analysis. *Publ Health* 2018;**161**:90–8.
41. Khani M, Vakili MM. Prevalence and risk factors of HIV, hepatitis B virus and hepatitis C virus infections in drug addicts among Zanjan prisoners. *Arch Iran Med* 2003;**6**(1):1–4.
42. Rowhani-Rahbar A, Tabatabee-Yazdi A, Panahi M. Prevalence of common blood-borne infections among imprisoned injection drug users in Mashhad, North-East of Iran. *Arch Iran Med* 2004;**7**(3):190–4.
43. Alizadeh AHM, Alavian SM, Jafari K, Yazdi N. Prevalence of hepatitis C virus infection and its related risk factors in drug abuser prisoners in Hamedan - Iran. *World J Gastroenterol* 2005;**11**(26):4085–9.
44. Javadi AA, Avijgan M, Hafizi M. Prevalence of HBV and HCV infections and associated risk factors in addict prisoners. *Iran J Public Health* 2006;**35**(4):33–6.
45. Mohtasham Amiri Z, Rezvani M, Jafari Shakib R, Jafari Shakib A. Prevalence of hepatitis C virus infection and risk factors of drug using prisoners in Guilan province. *East Mediterr Health J* 2007;**13**(2):250–6.
46. Pourahmad M, Javady A, Karimi I, Ataei B, Kassaeian N. Seroprevalence of and risk factors associated with hepatitis B, hepatitis C, and human immunodeficiency virus among prisoners in Iran. *Infect Dis Clin Pract* 2007;**15**(6):368–72.
47. Navadeh S, Mirzazadeh A, Gouya MM, Farnia M, Alasvand R, Haghdoost A-A. HIV prevalence and related risk behaviours among prisoners in Iran: results of the national biobehavioural survey, 2009. *Sex Transm Infect* 2013;**89**(Suppl 3):iii33–66.
48. Kazerooni PA, Lari MA, Joolaei H, Parsa N. Knowledge and attitude of male intravenous drug users on HIV/AIDS associated high risk behaviors in Shiraz Pir-Banon jail, Fars Province, Southern Iran. *Iran Red Crescent Med J* 2010;**12**(3):334–6.
49. Moradi AR, Emdadi A, Soori B, Mostafavi E. Prevalence of human immunodeficiency virus infection among injection drug users released from jail. *Addict Health* 2012;**4**(3–4):151–5.

50. Ataie M, Nokhodian Z, Ataei B, Kassaian N, Yaran M, Hassannejad R. Seroprevalence of hepatitis B virus and human immunodeficiency virus among young prisoners. *J Res Med Sci* 2013;**18**(1):70–2.
51. Dibaj R, Ataei B, Yaran M, Nokhodian Z, Tayeri K, Ali Z. Prevalence of HIV infection in inmates with history of injection drug use and evaluation of risk factors, in Isfahan, Iran. *Pakistan J Med Sci* 2013;**29**(1 SUPPL):399–402.
52. Haghdoost AA, Danesh A, Khajekazemi R, Sharifi H, Shokoohi M, Sedaghat A, et al. *Third National Bio-Behavioural Surveillance Survey in Prisoners in Iran, 2012-2013*. Iran: HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance; 2012-2013. Unpublished report.
53. Ziaee M, Sharifzadeh G, Namaee MH, Fereidouni M. Prevalence of HIV and hepatitis B, C, D infections and their associated risk factors among prisoners in southern Khorasan province, Iran. *Iran J Public Health* 2014;**43**(2):229–34.
54. Sharifi H, Hosseini-Hooshyar S, Khajekazemi R, Mousavian Gh, Tavakoli F, Najafi E, et al. *National HIV Bio-Behavioural Surveillance Survey (BBSS) in Prisoners, 4th Round – Iran 2017*. Iran: HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance; 2017. Unpublished report.
55. Seyedalinaghi SA, Farhoudi B, Mohraz M, Golsoorat Pahlaviani F, Hosseini M, Farnia M, et al. Prevalence and associated factors of HIV infection among male prisoners in Tehran, Iran. *Arch Iran Med* 2017;**20**(6):356–60.

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Original Research

Return to work after COVID-19 infection – A Danish nationwide registry study

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ABSTRACT

Objectives: This study aimed to explore return to work after COVID-19 and how disease severity affects this.
Study design: This is a Nationwide Danish registry–based cohort study using a retrospective follow-up design.
Methods: Patients with a first-time positive SARS-CoV-2 polymerase chain reaction test between 1 January 2020 and 30 May 2020, including 18–64 years old, 30-day survivors, and available to the workforce at the time of the first positive test were included. Admission types (i.e. no admission, admission to non–intensive care unit [ICU] department and admission to ICU) and return to work was investigated using Cox regression standardised to the age, sex, comorbidity and education-level distribution of all included subjects with estimates at 3 months from positive test displayed.
Results: Among the 7466 patients included in the study, 81.9% (6119/7466) and 98.4% (7344/7466) returned to work within 4 weeks and 6 months, respectively, with 1.5% (109/7466) not returning. Of the patients admitted, 72.1% (627/870) and 92.6% (805/870) returned 1 month and 6 months after admission to the hospital, with 6.6% (58/870) not returning within 6 months. Of patients admitted to the ICU, 36% (9/25) did not return within 6 months. Patients with an admission had a lower chance of return to work 3 months from positive test (relative risk [RR] 0.95, 95% confidence interval [CI] 0.94–0.96), with the lowest chance in patients admitted to an ICU department (RR 0.54, 95% CI 0.35–0.72). Female sex, older age, and comorbidity were associated with a lower chance of returning to work.
Conclusion: Hospitalised patients with COVID-19 infection have a lower chance of returning to work with potential implications for postinfection follow-up and rehabilitation.

Introduction

COVID-19 is a global challenge for both public health and the societal economy, which may influence daily living in years to come. Studies are emerging on the long-term effects of COVID-19 where development of neurological disorders, fatigue, respiratory symptoms, muscle weakness, sleep difficulties and anxiety or depression symptoms have been identified as long-term effects of COVID-19.[1–3]

COVID-19 has, on an individual level, both direct costs associated with the treatment of the disease and indirect costs with sick leave. The indirect costs have been estimated to be about 10 times higher than the direct costs of influenza.[4] With COVID-19 outmatching influenza in transmission and disease severity, it is highly likely that the indirect consequences related to sick leave are much higher for COVID-19.[5]

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Sick leave and long-term sick leave in patients who were part of the workforce before COVID-19 infection may likely reflect the long-term adverse effects of COVID-19 infection. As such, long-term sick leave after COVID-19 infection represents the proportion of patients who are likely to suffer from disabling sequelae after the infection. In contrast, return to work represents the ability to return to a societal function as before the infection. Few studies have explored return to work and sick leave after COVID-19 infection. Older age, hospitalisation, and female sex have been identified as risk factors of longer sick leave after COVID-19 infection.[6,7] More studies are needed to confirm these previous findings and identify new risk factors of sick leave and delayed return to work.

The primary aim of this study was to explore sick leave and return to work using nationwide register-based data on weekly updated employment status in COVID-19 patients aged between 18 and 64 years. Return to work serves as a proxy for functional recovery, whereas prolonged sick leave indicates long-term impairment. Patients with a positive COVID-19 test not admitted to the hospital are compared with patients admitted to the hospital and patients admitted to an intensive care unit (ICU) as an indicator of disease severity.

The secondary aim was to compare COVID-19 patients admitted to hospital to patients admitted with influenza to explore employment status post-COVID-19 relative to a well-known infectious disease.

The first case of COVID-19 in Denmark was detected in February 2020, with the first lockdown measures starting 13 March, with measures such as social distancing including working from home for non-critical employees, during the first wave. A gradual reopening started on 15 April.

Methods

Study design

This is a Nationwide Danish registry–based cohort study using a retrospective follow-up design.

Data sources and setting

All 5.8 million Danish citizens have a unique civil personal registration (CPR) number. In this study, the CPR number was used to identify individuals across the different national Danish registries.[8] Using these nationwide registries, we accessed all positive SARS-CoV-2 polymerase chain reaction (PCR) tests in Denmark. During the study period (1 January 2020 to 30 May 2020), PCR test has been the primary diagnostic tool in Denmark for diagnosing COVID-19. The following registries were used to gather information: (1) the Danish National Patient Registry on admission and comorbidities; (2) The Danish Prescription Registry for prescription medication and to define certain comorbid conditions;[9,10] (3) the Danish Cause of Death Registry[11] for date of death; (4) The Statistics of Denmark for age, sex and educational level;[8,12] and (5) the Danish Labour Market Registry (the DREAM database) for workforce connection.[13] As part of the Danish taxpaying system, all Danish citizens have access to free health care, education, and financial support if citizens are unable to support themselves. Financial support includes, among others, sick leave benefit (available after 4 weeks of sick leave to citizens who are working or available to the workforce), unemployment benefit (for persons who are available to the workforce) and early retirement benefit.

Approval to conduct the study and process the data was granted by The Capital Region of Denmark (approval nr. P-2019-191). Retrospective registry research does not require ethical approval by Danish law.

Population

For the primary analysis, all COVID-19 PCR-positive patients between 1 January 2020 and 30 May 2020 were included at the time of the first positive COVID-19 PCR test. Patients aged <18 or >64 years were excluded from the study together with patients not available to the workforce (e.g. patients receiving early retirement [see table S1]). Patients dying or emigrating within 30 days of inclusion time were excluded.

Influenza patients admitted between 1 February 2019 and 30 May 2020 were included for the purpose of a comparative analysis. The period here differed from the COVID-19 population to ensure enough patients included.

Exposure

Study variables

Admission to the hospital with COVID-19 was defined by a discharge diagnosis of COVID-19 (International Classification of Disease, 10th revision [ICD-10]: DB342 or DB972) after their positive PCR test and an admission less than 30 days from the positive test. Influenza admission was defined as a discharge diagnosis of influenza (ICD-10: DJ09 or DJ10).

Admission to the ICU was defined as admission with a procedure code of either intensive care observation or intensive care treatment (NABE or NABB), which previously has been validated with a positive predictive value of 87.2%.[14]

Adjustment for age, sex, comorbidities (using Charlson comorbidity index) and education level was performed in all analyses as relevant confounders of return to work. Age was treated as a categorical variable using 18–25, 26–35, 36–45, 46–55, and 56–64 age intervals. Charlson comorbidity index was treated as a categorical variable with a score above or equal to 4 gathered into one group.[15] Education was according to the International Standard of Education (ISCED) level divided into short (0–2), medium (3), short higher (5–6), and long higher education (7–8).[16] ISCED level 4 is not a part of the Danish education system.

Outcomes

The primary outcome was return to work. The secondary outcome was sick leave. Public sick leave benefits start after 1 month of sick leave and are recorded in the DREAM registry from this timepoint. Because of this delay in recording, follow-up started after 1 month. In the study, we will refer to time from positive test, not start of follow-up. The risk of sick leave is defined as sick leave (yes/no) 1 month after positive test.

Patients who returned to work or who were available to the work force within 1 month of inclusion were classified as ‘early returners’, patients returning to work after 1 month up to a maximum follow-up of 6 months were classified as ‘late returners’, and patients not returning within the 6 months, as ‘non-returners’.

Statistical analysis

Continuous variables are presented using mean and standard deviation when normally distributed and otherwise using median and 25–75 percentiles. Categorical data are presented using counts and percentages. Cumulative incidence plots of return to work are presented for both the primary and the subgroup analyses.

Incidence with confidence intervals at 1, 3, and 6 months of patients not returning to work are shown according to admission, sex, and age.

Multivariable Cox regression analysis was used to explore differences in return to work in patient not admitted, admitted, or

admitted to ICU as the primary analysis and between patients admitted with COVID-19 or influenza as part of the subgroup analysis. Cox regression was standardised to the age, sex, comorbidity and educational level status of all included subjects with relative risks and absolute risk at 3 months reported.

Logistic regression analysis was used to explore differences in sick leave 1 month after positive test at the start of follow-up between patient not admitted, admitted, or admitted to ICU as the primary analysis and between patients admitted with COVID-19 or influenza as part of the subgroup analysis. Logistic regression was standardised to the age, sex, comorbidity and educational level status of all included subjects with relative risks and absolute risks reported.

Results

Patients

During the study period, 7640 patients between aged 18 and 64 years who were available to the workforce had a positive COVID-19 test and after exclusion of patients emigrating (N = 32) or dying within 1 month (N = 13) or had missing data (N = 139), 7466 patients were included in the study.

Baseline characteristics are shown in Table 1.

Return to work

Of the 7466 patients, 82.0% (6119/7466) had returned to work within 4 weeks of their first positive COVID-19 test, an additional of 16.4% (1225/7466) returned within 6 months and 1.5% (109/7466) did not return to work and were receiving sick leave benefit after 6 months. During follow-up, eight patients died without returning to work, and five patients either emigrated or left the workforce permanently without returning to work.

Among 30-day survivors of COVID-19 who were admitted to the hospital and discharged with a primary diagnosis of COVID-19, 72.1% (627/870) had returned to work within 4 weeks, an additional 20.5% (178/870) returned within 6 months, and 6.6% (58/870) did not return within 6 months. Of these 870 patients, 25 were admitted to the ICU, of whom 36% (9/25) did not return within 6 months.

In patients admitted with influenza, 91.6% (377/466) had returned to work within the first 4 weeks from their admission to the hospital, 96.6% (402/416) returned within the 6-months follow-up, and 2.6% (11/416) did not return to work.

The cumulative incidence plot for return to work between different admission types is shown in Fig. 1. Patients not admitted are seen with the highest rate of return, patients admitted with a lower rate, and patients admitted to an ICU department with the lowest return rates during follow-up.

The cumulative incidence plot of return to work between patients admitted with COVID-19 and patients admitted with influenza is shown in Fig. 2. This figure show patients with COVID-19 have a reduced chance of return to work compared with patients admitted with influenza.

The cumulative incidences of no return to work within 1-, 3-, and 6-month follow-up from positive COVID-19 test in subgroups of admission status, sex, and age are shown in Fig. 3. Very few patients in all subgroups of no admission did not return to work after 3 months. More female than male patients did not return to work after 1 month in patients not admitted to the hospital. In admitted patients, longer sick leave was overserved at all time-points compared with patients not admitted, especially men aged 56–64 years experienced long sick leaves.

The relative chance of return to work 12 weeks after the first positive test between admission types and between influenza and COVID-19 is shown in Fig. 4, and the average standardised chance in Table 2, with the Cox regression used for g-modelling, is shown in figure S1 and S2. These figures show that patients admitted to the ICU are least likely to return to work, followed by patients admitted to a non-ICU department. Furthermore, the Cox model revealed increasing age, female sex, and comorbidity as risk factors for reduced chance of return to work (figure S1).

Sick leave

The relative risk of sick leave above 4 weeks between patients not admitted vs admitted to non-ICU department vs admitted to ICU department and between influenza and COVID-19 is shown in Fig. 5, and average standardised risk in Table 3 with the logistic regression model shown in figure S3 and S4. Admission to non-ICU, admission to ICU, and COVID-19 admissions compared with influenza admissions reveal a higher risk of sick leave above 4 weeks, with the highest relative risk in patients not admitted compared with patients admitted to the ICU. Furthermore, the logistic regression model revealed an increased likelihood of sick leave with increasing age, female sex, and in patients with comorbidity.

Discussion

The study finds that most patients return to work after positive COVID-19 test within 4 weeks and that only very few patients had not returned to work within 6 months of follow-up. Tardive return to work was seen in patients admitted to the hospital and especially patients admitted to the ICU. The chance of returning to work is significantly lower for hospitalised patients compared with patients who were not hospitalised. Return to work after admission to the hospital is less often seen in COVID-19 patients compared with patients admitted with influenza.

Overall, in our study, less than 2% of patients did not return to work within 6 months. With COVID-19 affecting millions of people worldwide, the relatively few patients not returning may still amount to many patients affected as well as a considerable cost for society. Large surges in sick leave have been observed previously in relation to the first wave of COVID-19.[17] In our study, we find that 6.6% of patients admitted to the hospital did not return to work. Huang et al. previously explored 6-month consequences of COVID-19 and found that 7% of hospital admitted experienced problems walking around and 2% problems preforming usual activity.[1] Disabilities as these may impair patients' ability to work and the result in our study may therefore reflect the lack of recovery seen in some patients. Not surprisingly, the patients admitted to ICU experience a tardive return to work with almost half the relative chance of returning to work compared with patients not admitted to the hospital. Nonetheless, the absolute chance of returning to work within 3 months from positive test was 94% for patients admitted to a non-ICU department and 53% in patients admitted to an ICU department versus 99% in patients not admitted to hospital. Return to work has been explored in a COVID-19 ICU cohort, which found that 73% returned after 6 months.[18] In our study, 60% returned to work, which is comparable taking the relatively few ICU admissions into account. In continuation, the difference in return to work seen between non-admitted and admitted patients indicates that the initial disease severity is a good indicator of patients' risk of prolonged return to work.

Poor health has previously been linked with a higher likelihood of unemployment.[19] It is likely, with 1.5% still receiving sick leave benefit after 6 months, that some patients may have long-lasting health issues following COVID-19 infection that may make them

Table 1
Baseline characteristics at positive COVID-19 test in Denmark 2020 between 1 January 2020 to 30 May 2020.

Variable	Level	Not admitted ($n = 6590$)	Admitted ($n = 876$)
Admitted to ICU			24 (2.7)
Sex	Female	4128 (62.6)	389 (44.4)
	Male	2462 (37.4)	487 (55.6)
Age, mean (SD)		41.6 (12.7)	46.2 (11.9)
Age group (years)	18–25	844 (12.8)	65 (7.4)
	26–35	1503 (22.8)	180 (20.5)
	36–45	1515 (23.0)	121 (13.8)
	46–55	1583 (24.0)	286 (32.6)
	56–64	1145 (17.4)	224 (25.6)
Education level	Short	903 (13.7)	128 (14.6)
	Medium	2573 (39.0)	352 (40.2)
	Long	2204 (33.4)	252 (28.8)
	Very long	910 (13.8)	144 (16.4)
Workforce connection	Working	5658 (85.9)	756 (86.3)
	Benefits classified as work	693 (10.5)	68 (7.8)
	Available to work	239 (3.6)	52 (5.9)
Charlson comorbidity score	0	6135 (93.1)	768 (87.7)
	1	307 (4.7)	61 (7.0)
	2	120 (1.8)	29 (3.3)
	3	8 (0.1)	11 (1.3)
	4+	20 (0.3)	7 (0.8)
Return to work	Did not return to work	51 (0.8)	58 (6.6)
	Returned	6535 (99.2)	809 (92.4)
	Died, emigrated or early retirement	4 (0.1)	9 (1.0)
Admission days, median (IQR)			3 (1, 7)
Peripheral vascular disease		18 (0.3)	7 (0.8)
Coronary artery disease		14 (0.2)	4 (0.5)
Chronic heart failure		13 (0.2)	4 (0.5)
Cerebrovascular disease		26 (0.4)	7 (0.8)
Dementia		≤3	≤3
Chronic pulmonary disease		133 (2.0)	32 (3.7)
Rheumatic disease		51 (0.8)	10 (1.1)
Peptic ulcus		14 (0.2)	≤3
Mild liver disease		27 (0.4)	8 (0.9)
Diabetes		62 (0.9)	14 (1.6)
Diabetes with complications		24 (0.4)	11 (1.3)
Hemiplegia		≤3	≤3
Chronic renal failure		8 (0.1)	6 (0.7)
Cancer		78 (1.2)	15 (1.7)
Severe liver disease		≤3	4 (0.5)
Cancer with metastases		≤3	≤3
HIV/AIDS		14 (0.2)	≤3

ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

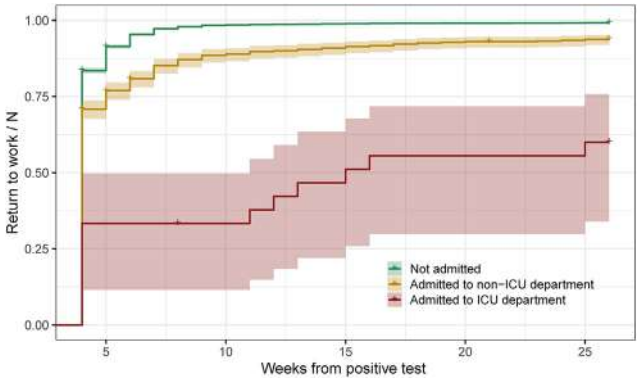

Fig. 1. Cumulative incidence plot of all PCR-positive COVID-19 patients with follow-up starting 4 weeks after positive test.

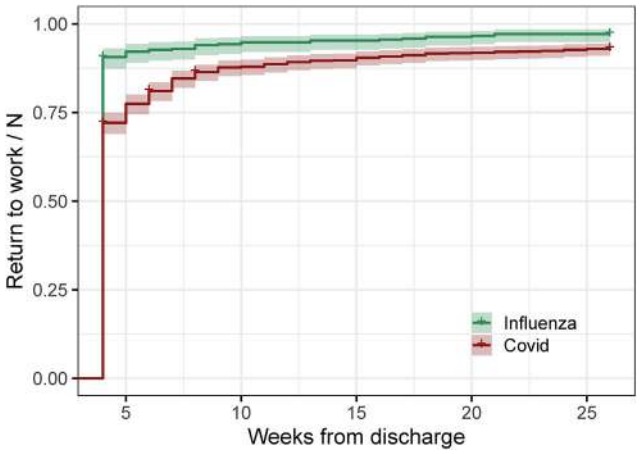

Fig. 2. Cumulative incidence plot of return to the workforce in patients admitted to the hospital with either COVID-19 or influenza. Follow-up starts 4 weeks after admission.

more vulnerable to unemployment and maybe early retirement. These endpoints were however not explored due to the bias of lockdown measures on unemployment and the relatively limited follow-up time regarding the access to early retirement.

In this study, we found that women and older males had prolonged return to work. In the literature, it is described that males have more severe disease manifestations of COVID-19,[20] which support our findings in the male group; however, it is contradictive that females should have longer sick leaves. Nonetheless, it is consistent with the findings in the preliminary results by Skyrud et al.[7] Westerlind et al. found that admitted females had shorter

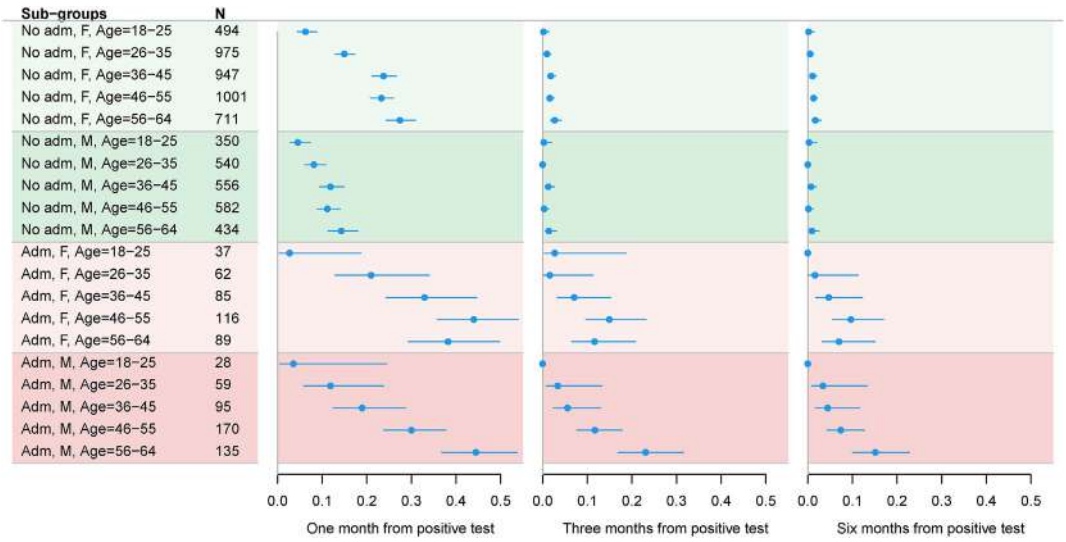

Fig. 3. Patients not returning to work in % after first admission to the hospital in subgroups. Estimates and confidence intervals extracted from cumulative incidence. Abreviations: Adm = Admission, M = Male, F = Female.

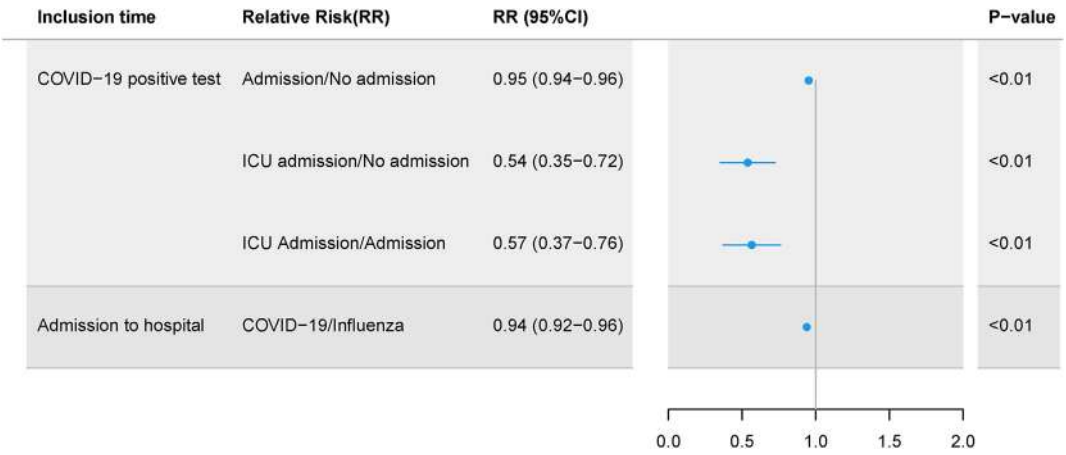

Fig. 4. Relative chance of return to work within 3 months calculated from cox regression model. CI, confidence interval.

Table 2
Mean chance of return to work.

Inclusion time	Mean risk	Mean risk (95% CI)
COVID-19 positive test	No admission	0.99 (0.98–0.99)
	Admission	0.94 (0.93–0.95)
	ICU admission	0.53 (0.35–0.71)
Admission to hospital	Influenza	0.96 (0.94–0.97)
	COVID-19	0.90 (0.88–0.92)

CI, confidence interval.

sick leaves compared with admitted males, whereas non-admitted females had longer sick leaves compared with males.[6] Similar tendencies are seen in this study with the overall effect indicating a reduced chance of return to work in women, which is somewhat surprising; however, nonetheless supported by the other studies.[6,7]

For hospitalised patients, we were able to compare return to work and sick leave in patients hospitalised due to COVID-19 with patients hospitalised due to influenza. We found that 2.6% of patients hospitalised with influenza did not return to work versus 6.6% in patients with COVID-19. The differences seen between influenza and COVID-19 are in line with what other studies have shown in that COVID-19 patients have worse outcomes compared with influenza patients.[5,21]

Long-term physical impairment is a likely underlying cause of the delayed or lack of return to work seen in our study. Others have found that COVID-19 patients admitted to hospital have low physical performance and impaired activities of daily living after hospitalisation.[22] Non-admitted patients at a working age have also been found to have symptoms and impairment after the acute phase of COVID-19 infection.[23] It is furthermore expected that COVID-19 may come with a risk of continuing to work while unwell, which may create delayed recovery and increased risk of future sick leave.[24]

Our study indicates that patients admitted to the hospital and patients of higher age are more vulnerable to having longer return to work similar to the findings in Westerlind et al. study.[6] These and our other findings may have implications for post-COVID-19 infection control and rehabilitation. Rehabilitation has been shown to improve lung function and quality of life after COVID-19 infection.[25] Future studies should explore rehabilitation after COVID-19 infection in patients' part of the workforce, considering the cost-effectiveness. If rehabilitation can improve patients' return to work and recovery, then it is likely that the decreased expenses

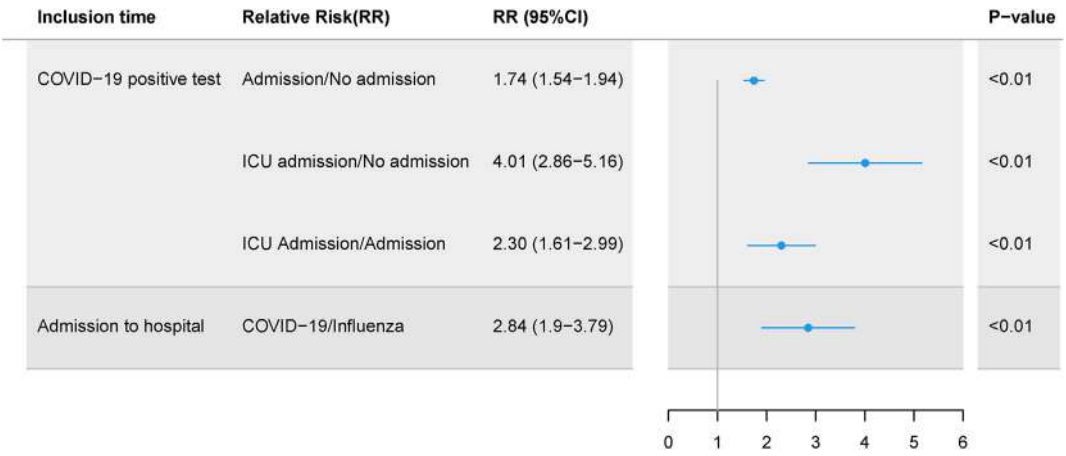

Fig. 5. Relative risk of sick leave above 4 weeks calculated from logistic regression model. CI, confidence interval.

Table 3
Mean chance of sick leave above 4 weeks.

Inclusion time	Mean risk	Mean risk (95% CI)
COVID-19 positive test	No admission	0.16 (0.16–0.17)
	Admission	0.29 (0.26–0.32)
	ICU admission	0.66 (0.47–0.84)
Admission to hospital	Influenza	0.09 (0.06–0.12)
	COVID-19	0.26 (0.23–0.29)

CI, confidence interval.

in sickness benefit and the increased tax revenue is able to finance an increased focus of rehabilitation for this group of patients.

It is expected that the external validity of our results is good with similar findings regarding the effect of age, disease severity, and being female as discussed, with however relatively few studies on return to work after COVID-19 infection available.

Most COVID-19 patients return to the workforce quickly making universal interventions towards COVID-19 patients redundant. Efforts towards improving patients experiencing prolonged recovery from COVID-19 infections are already implemented in many countries with post-COVID-19 clinics. With a public financial incentive for patients to return to work as quickly as possible, efforts such as rehabilitation should be implemented as quickly as possible. These efforts should be aimed at the patients' part of the workforce who do not return to work following the contagious phase. This is not only in the patient's interest but is also likely a cost-effective strategy on a societal level. In the Danish setting, this could be that when public sick leave compensation starts, patients must be seen in a post-COVID-19 clinic to evaluate rehabilitation needs.

Strengths and limitations

Our study uses nationwide data on patients with a positive SARS-COV-2 PCR test, which in the period explored was the primary diagnostic tool for COVID-19 in Denmark. This means that our study includes most patients in the first wave of COVID-19 patients with a confirmed diagnosis, from patients who have mild disease to patients in need of hospital care hereby indicating how COVID-19 impacts longer sick leave periods in Denmark.

Due to the epidemiologic design, there are, however, limitations. The comparison of COVID-19 and influenza patients may be affected by restrictions implemented during the COVID-19 lockdown. Patients dying, emigrating or leaving the workforce due to early retirement were censored in the analyses. However, this was only the case for 13 patients. Patients' work capability at the time of return to work was unfortunately not available. Patients may be returning to part-time work instead of full-time work hereby impacting the workforce further.

Conclusions

The vast majority of patients returned to work after COVID-19 infection, with patients experiencing severe COVID-19 having prolonged time to return to work. Furthermore, COVID-19 patients experience longer time to return to work than what was observed in influenza patients. Future studies should explore if increasing rehabilitation treatment of severe COVID-19 patients can improve return to work and the cost-efficiency of the intervention.

Author statements

Ethical approval

Danish registry studies using encrypted data do not require ethical approval.

Funding

No funding was obtained for this study.

Competing interests

CTP has received grants for studies from Bayer and Novo Nordisk. KK has received research grants from The Laerdal Foundation and speaker's honoraria from Novartis. JB reports advisory board honorary from Bayer. No grants were obtained for the present study. The remaining authors do not have any conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.12.012.

References

1. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021;**397**(10270):220–32.

2. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236379survivors of COVID -19:a retrospective cohort study using electronic health records. *Lancet Psychiatr* 2021;**8**(5):416–27.
3. Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin Microbiol Infect – Off Publ European Soc Clin Microbiol Infect Dis* 2021;**27**(1):89–95.
4. Xue Y, Kristiansen IS, de Blasio BF. Modeling the cost of influenza: the impact of missing costs of unreported complications and sick leave. *BMC Publ Health* 2010;**10**:724.
5. Ludwig M, Jacob J, Basedow F, Andersohn F, Walker J. Clinical outcomes and characteristics of patients hospitalized for Influenza or COVID-19 in Germany. *Int J Infect Dis* 2021;**103**:316–22.
6. Westerlind E, Palstam A, Sunnerhagen KS, Persson HC. Patterns and predictors of sick leave after Covid-19 and long Covid in a national Swedish cohort. *BMC Publ Health* 2021;**21**(1):1023.
7. Skyrud K, Telle K, Hernæs K, Magnusson K. *Impacts of COVID-19 on sick leave*. 2021. Pre Print available from: https://www.medrxiv.org. [Accessed 2 July 2021].
8. Schmidt M, Pedersen L, Sorensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol* 2014;**29**(8):541–9.
9. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–90.
10. Kildemoes HW, Sorensen HT, Hallas J. The Danish national prescription registry. *Scand J Publ Health* 2011;**39**(7 Suppl):38–41.
11. Helweg-Larsen K. The Danish register of causes of death. *Scand J Publ Health* 2011;**39**(7 Suppl):26–9.
12. Jensen VM, Rasmussen AW. Danish education registers. *Scand J Publ Health* 2011;**39**(7 Suppl):91–4.
13. Hjollund NH, Larsen FB, Andersen JH. Register-based follow-up of social benefits and other transfer payments: accuracy and degree of completeness in a Danish interdepartmental administrative database compared with a population-based survey. *Scand J Publ Health* 2007;**35**(5):497–502.
14. Blichert-Hansen L, Nielsson MS, Nielsen RB, Christiansen CF, Norgaard M. Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the Danish National Patient Registry: a short report. *Clin Epidemiol* 2013;**5**:9–12.
15. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic Co-morbidity in longitudinal-studies - development and validation. *J Chron Dis* 1987;**40**(5):373–83.
16. UNESCO Institute for Statistics. *International standard classification of education ISCED 2011*. Montréal; 2012.
17. Calvo-Bonacho E, Catalina-Romero C, Fernandez-Labandera C, Fernandez-Meseguer A, Gonzalez-Quintela A, Martinez-Munoz P, et al. COVID-19 and sick leave: an analysis of the ibermutua cohort of over 1,651,305 Spanish workers in the first trimester of 2020. *Front Public Health* 2020;**8**:580546.
18. Carenzo L, Dalla Corte F, Haines RW, Palandri C, Milani A, Aghemo A, et al. Return to work after coronavirus disease 2019 acute respiratory distress syndrome and intensive care admission: prospective, case series at 6 Months from hospital discharge. *Crit Care Med* 2021;**49**(11):e1157–62.
19. Bockerman P, Ilmakunnas P. Unemployment and self-assessed health: evidence from panel data. *Health Econ* 2009;**18**(2):161–79.
20. Kragholm K, Andersen MP, Gerds TA, Butt JH, Ostergaard L, Polcwiartek C, et al. Association between male sex and outcomes of Coronavirus Disease 2019 (Covid-19) - a Danish nationwide, register-based study. *Clin Infect Dis* 2021;**73**(11):e4025–30.
21. Piroth L, Cottenet J, Mariet A-S, Bonniaud P, Blot M, Tubert-Bitter P, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med* 2021;**9**(3):251–9.
22. Belli S, Balbi B, Prince I, Cattaneo D, Masocco F, Zaccaria S, et al. Low physical functioning and impaired performance of activities of daily life in COVID-19 patients who survived hospitalisation. *Eur Respir J* 2020;**56**(4).
23. Meys R, Delbressine JM, Goertz YMJ, Vaes AW, Machado FVC, Van Herck M, et al. Generic and respiratory-specific quality of life in non-hospitalized patients with COVID-19. *J Clin Med* 2020;**9**(12).
24. Kinman G, Grant C. Presenteeism during the COVID-19 pandemic: risks and solutions. *Occup Med (Lond)* 2021;**71**(6-7):243–4. https://doi.org/10.1093/occmed/kqaa193.
25. Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: a randomized controlled study. *Compl Ther Clin Pract* 2020;**39**:101166.

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Short Communication

SARS-CoV-2 serosurvey among adults involved in healthcare and health research in Guinea-Bissau, West Africa

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ABSTRACT

Objectives: Many African countries have reported fewer COVID-19 cases than countries elsewhere. By the end of 2020, Guinea-Bissau, West Africa, had <2500 PCR-confirmed cases corresponding to 0.1% of the ~1.8 million national population. We assessed the prevalence of SARS-CoV-2 antibodies in urban Guinea-Bissau to help guide the pandemic response in Guinea-Bissau.

Study design: Cross-sectional assessment of SARS-CoV-2 antibody in a cohort of staff at the Bandim Health Project.

Methods: We measured IgG antibodies using point-of-care rapid tests among 140 staff and associates at a biometric research field station in Bissau, the capital of Guinea-Bissau, during November 2020.

Results: Of 140 participants, 25 (18%) were IgG-positive. Among IgG-positives, 12 (48%) reported an episode of illness since the onset of the pandemic. Twenty-five (18%) participants had been PCR-tested between May and September; 7 (28%) had been PCR-positive. Four of these seven tested IgG-negative in the present study. Five participants reported that somebody had died in their house, corresponding crudely to an annual death rate of 4.5/1000 people; no death was attributed to COVID-19. Outdoor workers had a lower prevalence of IgG-positivity.

Conclusions: In spite of the low official number of COVID-19 cases, our serosurvey found a high prevalence of IgG-positivity. Most IgG-positives had not been ill. The official number of PCR-confirmed COVID-19 cases has thus grossly underestimated the prevalence of COVID-19 during the pandemic. The observed overall mortality rate in households of Bandim Health Project employees was not higher than the official Guinean mortality rate of 9.6/1000 people.

Background

In Guinea-Bissau, a low-income country with a population of 1.9 million inhabitants, the first case of COVID-19 was registered on March 25, 2020, and quickly followed by a lockdown that lasted several months. Per December 20, of 35,644 people tested by PCR, 2447 (6.9%) tested positive for SARS-CoV-2 (0.1% of the national population) with 45 deaths (1.8% of positive cases) (Supplementary Fig. 1).

The Bandim Health Project (BHP, www.bandim.org) employs ~180 staff members in a Health and Demographic Surveillance System that covers the urban suburbs of Bandim, Belém, Mindará and Cuntum in Guinea-Bissau's capital, Bissau. Most staff and associates had been working throughout the epidemic, and we aimed to study the prevalence of SARS-CoV-2 antibodies by conducting a serosurvey among our local staff and associates.

Methods

We performed a serosurvey among field assistants who conducted house visits to collect demographic and health information, office staff members, and staff placed at three health centers in the study area and the nearby national hospital. From November 9 to

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November 24, 2020, after informed oral and written consent, we interviewed participants about background factors and about illness and mortality in their homes since March 25, 2020. For assessing SARS-CoV-2 antibody among participants, two drops of blood obtained by finger prick were applied to a point-of-care antibody test (OnSite COVID-19 IgG/IgM Rapid Test, CTK Biotech).

The study was approved by the Guinean National Ethics Committee (Ref 116/CNES/INASA/2020).

Results

A total of 146 staff and associates were present to be tested during the survey. Of these, 6 declined participation. Of 140 tested, 25 (18%) were IgG-positive. One participant who was IgM-positive and had a slight fever was referred for PCR testing, which was negative; all symptoms waned after a day.

The average age of IgG-positives tended to be higher than among IgG-negatives (mean 46 years (range 26–70) vs 41 years (range 19–63), $P = 0.05$). There tended to be more infected females than males (24% vs 13%, $P = 0.10$) (Table 1). The ethnicities that traditionally populated the study area had a higher risk of being IgG-positive than other ethnicities. All participants reported using masks.

The highest proportion of IgG-positives (42%) was found among laboratory staff, followed by frontline healthcare workers (HCWs) (doctors, nurses, or midwives) (24%) and office personnel (17%). In the combined group of frontline HCWs and laboratory technicians, 28% tested positive (P for the same risk as others = 0.01). The lowest proportions were among field assistants (8%) and other staff (mechanics, guards, cleaners) (9%).

The area of residence was associated with the risk of being IgG-positive, the proportion varying from 9% to 37% ($P = 0.02$ for the same risk across areas), the proportion being highest for those coming from outside the study area.

In a multivariable analysis retaining age and sex and the three variables (ethnicity, type of work, and area of residence) that were significant in univariate analysis, all three variables remained independently associated with the risk of being IgG-positive.

In urban Guinea-Bissau, most people live in multifamily houses. There was no association between being IgG-positive and the number of household inhabitants or the total number of people in the multifamily house (Table 1). Five people reported that somebody in their house had died during the past 8 months of the pandemic. With a mean of 12 people per house, this translates to a crude yearly mortality rate of 4.5/1000 people (5 deaths in 140 BHP staff houses * 12 persons/house * (8/12) years of observation). No death was attributed to COVID-19.

Table 1
Characteristics of individuals testing IgG positive or IgG negative for SARS-CoV2 in Guinea-Bissau, Nov 2020.

		IgG positive (% of group) N = 25	IgG negative $N = 115$	Relative risk (95% CI)	P-value*	Multivariable model[c]
Mean age in years (range)		46 (26–70)	41 (19–63)	1.03 (1.00–1.07)	0.05	1.02 (0.98–1.05)
Sex	Male	10 (13%)	67	Ref	0.10	Ref
	Female	15 (24%)	48	1.83 (0.88–3.81)		1.21 (0.57–2.60)
Ethnicity[a]	Pepel/Manjaco/Mancanha	20 (27%)	54	3.57 (1.41–9.00)	0.003	3.19 (1.23–8.27)
	Other	5 (8%)	61	Ref		Ref
Type of work	Field assistants	2 (8%)	24	Ref	0.05	
	Office staff	6 (17%)	30	2.17 (0.47–9.95)		
	Doctors/nurses/midwifes	10 (24%)	31	3.17 (0.75–13.4)		
	Lab technicians	5 (42%)	7	5.41 (1.21–24)		
	Other staff	2 (8%)	23	1.04 (0.16–6.87)		
Healthcare worker	Yes	15 (28%)	38	2.46 (1.19–5.09)	0.01	2.22 (1.06–4.67)
	No	10 (11%)	77	Ref		Ref
Area of residence[b]	Bandim/Belém/Mindera/Cuntum	5 (9%)	50	Ref	0.02	Ref
	Praça/Antula	4 (15%)	23	1.62 (0.47–5.61)		1.63 (0.50–5.66)
	Missira/Militar/Aeroporto	5 (18%)	23	1.96 (0.62–6.25)		2.23 (0.80–6.19)
	Bor/Quelélé/Enterramento	11 (37%)	19	4.03 (1.54–10.6)		3.17 (1.22–8.22)
Median number of people in household		5 (1–9)	5 (1–21)		0.77	
Median number of people in house		10 (3–26)	12 (1–30)		0.43	
Ill during the pandemic	Yes	12 (21%)	45	1.34 (0.66–2.74)	0.42	
	No	13 (16%)	70	Ref		
Among the ill		$N = 12$	$N = 45$			
Loss of taste/smell	Yes	7 (28%)	18	1.79 (0.64–5.02)	0.27	
	No	5 (16%)	27	Ref		
Fever	Yes	8 (23%)	27	1.26 (0.42–3.72)	0.68	
	No	4 (18%)	18	Ref		
Cough	Yes	3 (16%)	16	0.67 (0.20–2.20)	0.61	
	No	9 (24%)	29	Ref		
Runny nose	Yes	8 (17%)	40	0.38 (0.14–0.99)	0.05	
	No	4 (44%)	5	Ref		
Difficulties breathing	Yes	2 (33%)	4	1.70 (0.48–6.06)	0.41	
	No	10 (20%)	41	Ref		
Fatigue	Yes	4 (29%)	16	0.90 (0.31–2.65)	0.85	
	No	8 (20%)	29	Ref		

*By rank-sum test (number of people in household/house) or Poisson test with robust variance estimation (rest).
[a] Grouped into traditional ethnicities in the study area, with related languages and social structures vs others.
[b] Grouped by geographical vicinity: the Bandim Health Project study area (Bandim/Belém/Cuntum); areas closer to city (Praça/Antula); areas further from the city on the northern side (Missira/Militar/Aeroporto); areas further out of the city on the southern side (Bor/Quelélé/Enterramento).
[c] Retaining age, sex, and variables that were significant in univariate analysis.

The risk of being IgG-positive did not correlate with self-reported illness (Table 1). Among the IgG-positives, 12 (48%) reported having been ill since the onset of the pandemic, vs. 45 (40%) of IgG negative ($P = 0.41$). Of the 57 persons reporting being ill, 25 reported loss of smell or taste: 7 of these were IgG-positive (58% of IgG-positives), while 18 were IgG-negative (40% of IgG-negatives) ($P = 0.27$). One person was hospitalized during the pandemic; this person was not PCR-positive and tested IgG negative here.

Interestingly, 25 (18%) participants had been PCR-tested between March and September; 7 reported having been previously tested positive. Among these 7, 6 reported being ill during the pandemic, all reported loss of taste/smell and runny nose, approximately half reported fever and/or cough; only one reported difficulty breathing and one reported fatigue. Four of the 7 PCR-positives tested IgG-negative.

Discussion

COVID-19 infections appeared to have been widely transmitted in Bissau in November 2020, with the apparent decline of the first wave coinciding with the start of the rainy season in June 2020. In this serosurvey from November 2020, 18% (25/140) had IgG antibodies.

Only 3 of 7 past PCR-positive also tested IgG-positive. Given that the first pandemic wave might have peaked in weeks 17–23 (Supplementary Fig. 1), most may have been infected more than 5 months before our survey. It has previously been shown that negative SARS-CoV-2 serology does not exclude previous infection.[1] Point-of-care rapid tests are not as precise or sensitive as laboratory antibody tests. The CTK test used for the present study was, however, among the best in a comparison of nine SARS-CoV-2 immunoassays, with a sensitivity of 90% and a specificity of 100%.[2]

The point-of-care test is not a quantitative test, but we noted that many positives exhibited a quite weak, lighter colored IgG band than we have seen for people recently infected in Denmark. Only 12 of the 25 IgG-positive individuals reported being ill during the pandemic. Loss of smell/taste is a common symptom of COVID-19 and was reported by all who had been ill *and* had a positive PCR test but was also reported by many IgG-negative individuals. Hence, the true prevalence of past infection might be underestimated by IgG-positivity. On the other hand, HCWs were overrepresented in our study population, which could overestimate the seroprevalence compared to the general population.

A meta-analysis of serosurveys conducted in Africa identified 23 studies (including the present study) conducted between April 2020 and April 2021 and reported an overall seroprevalence of 22% (95% Confidence Interval: 14%–31%); the estimate for West Africa was 25% (13%–39%).[3] In a systematic review and meta-analysis of the global seroprevalence in 2020 involving 968 seroprevalence studies and 9.3 million participants from 74 countries, the median global seroprevalence was 4.5% (Interquartile Range (IQR), 2.4%–8.4%), but in Sub-Saharan Africa, the seroprevalence was 5.01 (2.89–8.69) times higher than in high-income countries, being 19.5% (IQR, 9.0%–26.0%).[4]

We did not find indications of a higher than anticipated overall mortality, but the households of Bandim Health Project employees, although diverse, might not be representative for the background population due to differences in educational level, household income, and access to healthcare. However, official figures also suggest that the mortality rate of COVID-19 per million in Africa is lower than in other regions.[5] It has been speculated that this could be due to swift and effective government response to the COVID-19 threat and high adherence to preventative strategies.[5] However, the seroprevalence rates[3,4] suggest that the continent has had a high burden of COVID-19 infections. Our study indicates that many of them could have gone unnoticed, which could indicate that the low mortality is due to lower disease severity. It has been hypothesized that this could involve factors such as demographics and cross-protection from other pathogens.[5] Another explanation for the low observed mortality rate of COVID-19 is the under-registration of infections and deaths. Future studies, unfortunately, are unlikely to throw much light on this, since the low testing rates makes it difficult to disentangle deaths from COVID-19 from deaths caused by lockdowns and other pandemic-related causes.

Our numbers were small, but laboratory workers had the highest risk of all and may be a subgroup that deserves special attention as they collect and process patient samples, but perhaps without the same level of protection as frontline HCWs. Our data suggest that persons working outside may have a lower risk.

The highest risk was noted for participants residing outside the BHP's study area. This may suggest that infection was more present in some areas and that people were infected, to a large extent, at home. However, there was no association with the number of people in the household or the house, as would be anticipated if infection at home was prevalent. Alternatively, since the prevalence was highest in the most distant suburbs, shared transport, which often consists of crowded minibuses, could be a risk factor.

In conclusion, our survey found a high prevalence of IgG-positive individuals in an urban African setting. COVID-19 was certainly here. The official numbers grossly underestimate the true number of COVID-19 cases. More than half of the IgG-positives had not been ill. Studies are ongoing to assess the overall mortality impact of the pandemic. Despite low official numbers, the toll might have been high and undetected among the elderly.

What is already known on this subject

- Many African countries have experienced far fewer COVID-19 cases than countries in Europe, Asia, or the Americas.
- By the end of 2020, Guinea-Bissau had <2500 PCR-confirmed cases corresponding to 0.1% of the national population.

What this study adds

- Among 140 field station staff members, the proportion being SARS-CoV-2 IgG-positive was 18%.
- Less than half of the IgG-positive individuals reported being ill during the pandemic.
- The official number of PCR-confirmed COVID-19 cases grossly underestimates the prevalence during the pandemic.

Author statements

Ethical approval

National Committee of Ethics in Health (CNES – Guinea-Bissau), approval number 116/CNES/INASA/2020.

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Competing interests

None declared.

Author contributions

All authors had had full access to all the data in the study. Benn takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis or interpretation of data: All authors.

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Disclaimer

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of any funder or sponsor.

Appendix A. Supplementary data

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References

1. Self WH. Decline in SARS-CoV-2 antibodies after mild infection among frontline health care personnel in a multistate hospital network — 12 states, april–august 2020. *MMWR Morb Mortal Wkly Rep* [Internet] 2020;**69** [cited 2021 Jul 2]. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6947a2.htm.
2. Lassaunière R, Frische A, Harboe ZB, Nielsen ACY, Fomsgaard A, Krogfelt KA, et al. Evaluation of nine commercial SARS-CoV-2 immunoassays. *medRxiv* 2020 Apr 10. https://doi.org/10.1101/2020.04.09.20056325.
3. Chisale MRO, Ramazanu S, Mwale SE, Kumwenda P, Chipeta M, Kaminga AC, et al. Seroprevalence of anti-SARS-CoV-2 antibodies in Africa: a systematic review and meta-analysis. *Rev Med Virol* 2021 Jul 6:e2271.
4. Bobrovitz N, Arora RK, Cao C, Boucher E, Liu M, Donnici C, et al. Global seroprevalence of SARS-CoV-2 antibodies: a systematic review and meta-analysis. *PLoS One* 2021 Jun 23;**16**(6):e0252617.
5. Adams J, MacKenzie MJ, Amegah AK, Ezeh A, Gadanya MA, Omigbodun A, et al. The conundrum of low COVID-19 mortality burden in sub-saharan Africa: myth or reality? *Glob Health: Sci Pract* 2021 Sep 30;**9**(3):433–43.

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Original Research

Trend analysis and risk of gallbladder cancer mortality in China, 2013–2019

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ABSTRACT

Objectives: There is a lack of comprehensive analysis of recent gallbladder cancer (GBC) mortality trends in China. This study aims to analyse trends in GBC mortality in China, with a specific focus on urban and rural area differences, and to determine possible risk factors.
Study design: This was a cross-sectional study.
Methods: Data were accessed through the Chinese Health Statistics Annual Report for 31 provinces from 2013 to 2019. Age-standardised mortality rate (ASMR) stratified by regions, gender and the years of diagnoses were analysed by Joinpoint regression analysis.
Results: The GBC ASMR was higher in females than in males and higher in urban areas than in rural areas. Mortality was primarily observed in individuals aged ≥65 years (in both sexes). A non-significant downward trend of GBC mortality was identified in urban areas from 2013 to 2019 (average annual percent change [AAPC] −1.50%; 95% confidence interval [CI]: −3.49, 0.53). However, in rural areas, the ASMR significantly increased with an AAPC of 2.64% (95% CI: 1.15, 4.15) in males and 3.85% (95% CI: 2.17, 5.56) in females. The GBC mortality rate was positively related to red meat consumption.
Conclusions: The burden of GBC mortality in rural China cannot be ignored, as results from this study show significantly increasing trends in both females and males from 2013 to 2019. In addition, red meat consumption may play a vital role in the increasing GBC mortality rate.

Introduction

Gallbladder cancer (GBC) is an uncommon malignancy with poor prognosis. The disease progresses rapidly because of the lack of perceptible symptoms in the early stage, resulting in delayed diagnosis and ultimately contributing to poor clinical outcomes. GBC is a malignancy with a high fatality rate (5-year survival rate <5%).[1]

The pathogenesis of GBC remains uncertain, and both genetic and environmental factors are associated with GBC. Family history, high parity and obesity increase the risk of GBC.[2–4] Dietary factors also play a critical role in the development of GBC. It has been reported that high consumption of mustard oil could increase the risk of GBC in India,[5] whereas preserved vegetables and salted meats showed positive associations with GBC in Shanghai, China, because such foods have been shown to have pro-inflammatory properties.[6] Several studies have found that red meat consumption is associated with an increased risk of GBC.[7–9]

As genetic and environmental factors are different throughout the world, the incidence rate of GBC varies in different countries. According to World Health Organisation (WHO) Global Cancer Observatory (https://gco.iarc.fr/today), the worldwide GBC incidence rate was $1.2/10^5$, and the mortality rate was $0.84/10^5$ in 2020. In South-Central Asia, the highest GBC incidence rate was $1.7/10^5$, and the mortality rate was $1.3/10^5$. Although the worldwide incidence and the mortality rate did not exceed $2/10^5$, the extensive variance observed between countries cannot be ignored.[10] The highest GBC incidence rate was shown by women from Chile $(27/105)^5$, followed by northern India $(21.5/10^5)$ and south Karachi, Pakistan $(13.8/10^5)$.[11,12] Although the incidence rate of GBC in the European Union has decreased by 30% between the late 1980s and 1999, the mortality rate remains notable in both males and females.[13] In most counties, GBC is more common in

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females than in males;[12,14] however, in Iceland, Costa Rica and Korea, higher mortality is seen in males.[15]

Although GBC is generally a rare disease, more attention should be paid to this disease because of the high mortality rate. A full understanding of this disease, including identification of the epidemiological risk factors in various populations, is important for the prevention of GBC. Unfortunately, there is little information about GBC in China. In Shanghai, from 1973 to 2009, the GBC incidence has risen from $1.1/10^5$ to $2.9/10^5$ in men and from $1.7/10^5$ to $3.9/10^5$ in women. The mortality trends increased with an estimated annual percent change (APC) of 2.8% in men and 2.5% in women.[16] However, these data were up to 2009 and only for residents in urban Shanghai, which is the largest and most modern city in China; thus, these results cannot represent the GBC situation in the whole of China.

To date, detailed mortality analyses of GBC in China are lacking. This investigation aims to undertake a detailed descriptive study of urban and rural GBC mortality in China and to determine possible risk factors. The GBC mortality data from 2013 to 2019 were extracted from the Chinese Health Statistics Annual Report for the current analyses.

Methods

Data source

The GBC mortality data were derived from the Chinese Health Statistics Annual Report from 2014 to 2020. GBC mortality data have only been reported in the Chinese Health Statistics Annual Report since 2014; hence, this is the start date of the data collection. As mortality data have a 1-year time lag from cancer death to data collection, the data this study extracted were for GBC deaths that occurred from 2013 to 2019. Data were reported from 31 provinces, excluding Hong Kong, Macau and Taiwan. GBC [C23] was identified according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).

Statistical analyses

The GBC crude mortality rates (CMRs) were classified by areas (urban or rural), gender (male or female) and age groups (0, 1~, 5~, 10~, ….. 80~, 85~ years [5-year intervals]). The age-standardised mortality rate (ASMR) is a weighted average of the age-specific mortality rates per 100,000 persons, where the weights are the proportions of persons in the corresponding age groups of the general population. In this study, ASMR was calculated by the Chinese population structure (the fifth National Population Census in 2010) and Segi's world standard population structure (1960). Unless stated otherwise, Segi's world standard was used for all the analyses in this study, and all rates are expressed as per 100,000 persons per year.

Joinpoint regression analyses were performed to describe the mortality time trends. The mortality time trends were stratified by areas (urban or rural), gender (male or female) and age groups (20~, 40~, 60~, 80~ years [20-year intervals]). The estimated APC and average annual percent change (AAPC) were computed by means of generalised linear models assuming a Homoscedasticity distribution. Joinpoint Regression Program, version 4.8.0.1, was used for analysis. A P value of <0.05 was considered statistically significant.

The correlations between GBC mortality rate and meat consumption were evaluated by Pearson correlation tests using SPSS18.0 software. A P-value of <0.05 was considered statistically significant.

Results

Mortality rates of GBC in rural and urban areas

From 2013 to 2019, the GBC CMRs were higher in urban than rural areas. The urban mortality rates ranged from $1.28/10^5$ to $1.38/10^5$ and remained stable over the 7 years. The highest mortality rate of $1.38/10^5$ was in 2017, accounting for 0.85% of overall cancer deaths. The ASMRs were $0.83/10^5$ and $0.85/10^5$ after being standardised by the age structure of the Chinese population and the world population, respectively. Rural GBC mortality rates ranged from $0.70/10^5$ to $1.24/10^5$ and followed an upward trend over the 7 years, resulting in an increase mortality burden caused by GBC. After adjustment by Segi's world standard population structure, the mortality decreased from $0.83/10^5$ to $0.74/10^5$ in urban areas from 2013 to 2019, whereas the mortality increased from $0.47/10^5$ to $0.57/10^5$ in rural areas over the same period. Gaps in the age-adjusted methods between the Chinese and Segi's world standard are very minimal in this study (Table 1).

ASMR of GBC in males and females

In terms of gender and area, females in urban areas were the highest contributors to GBC mortality burden, with an average ASMR of $0.93/10^5$ in the 7-year study period. This was followed by urban males, rural females and rural males. Urban females and males showed a similar trend, with a slight decrease from 2013 to 2016, then an increase in 2017, followed by a declined to 2019. Unlike urban areas, the GBC mortality rate in both males and females in rural areas gradually increased. Broadly, deaths from GBC

Table 1
Gallbladder cancer mortality in urban and rural area of China, 2013–2019.

Year	Area	Crude rate ($1/10^5$)	Ratio (%)	ASMR China ($1/10^5$)	ASMR world ($1/10^5$)
2013	Urban	1.35	0.85	0.83	0.83
	Rural	0.70	0.47	0.47	0.47
2014	Urban	1.32	0.81	0.83	0.83
	Rural	0.73	0.48	0.47	0.47
2015	Urban	1.28	0.77	0.80	0.80
	Rural	0.78	0.50	0.51	0.51
2016	Urban	1.24	0.77	0.75	0.76
	Rural	1.24	0.77	0.75	0.76
2017	Urban	1.38	0.85	0.83	0.85
	Rural	0.85	0.54	0.51	0.52
2018	Urban	1.33	0.81	0.76	0.77
	Rural	0.95	0.59	0.55	0.55
2019	Urban	1.36	0.83	0.72	0.74
	Rural	1.00	0.62	0.57	0.57

ASMR, age-standardised mortality rate.

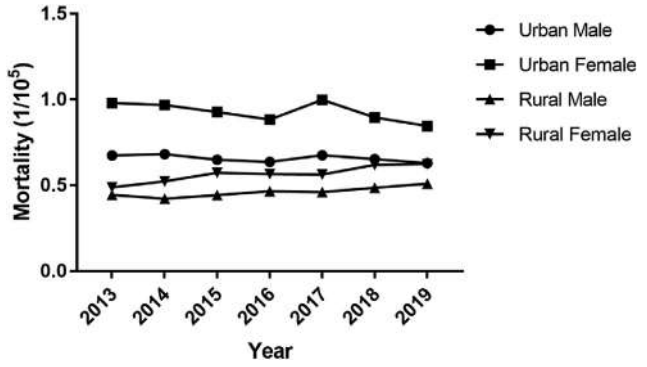

Fig. 1. ASMR of GBC by gender in urban and rural areas, 2013–2019. ASMR, age-standardised mortality rate; GBC, gallbladder cancer.

occurred more frequently among females than males and in urban areas than in rural areas (Fig. 1).

Age-specific mortality rates of GBC

In rural and urban areas, the age-specific mortality rates of GBC for different years were compared. The trend of age-specific mortality rate from 2013 to 2019 was similar in both areas. The mortality rates were very low in the population aged <40 years in both rural and urban areas. From the age of 50 years, the GBC mortality rate rapidly increased and peaked in the ≥85-year-old age group. The differences in mortality rates over the 7-year study period were negligible, with the exception of the relatively faster increasing rate in 2016 in rural areas (Supplementary Fig. S1).

After stratification by gender and area, there were almost no deaths in individuals aged <30 years in both males and females and in urban and rural areas. Overall, the most common age group in terms of mortality rate was the 60–75 years group, accounting for more than 50% of all GBC deaths. The difference between males and females within age groups can be ignored. For urban areas, the proportion of deaths began to increase at the 50~ years age group, then showed a slight increase in the 85~ age group from 2013 to 2019. As for rural areas, a similar transition was observed, except that the proportion of deaths began to decrease from the age group of 75~ years and did not increase after this age. It is worth noting that the proportion of deaths in the >85 years age group in rural areas was less than that in urban areas (Fig. 2).

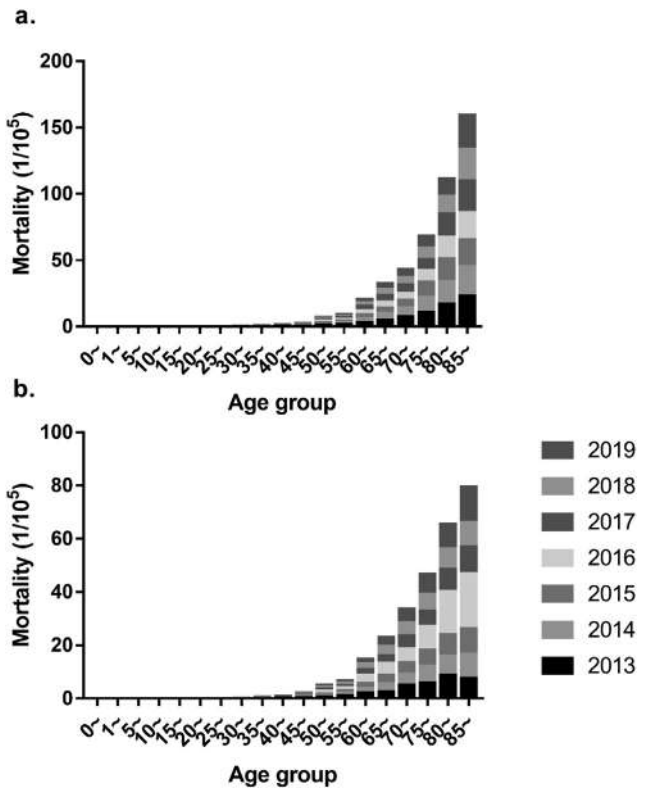

Fig. 2. Age-specific mortality rates of GBC in urban (a) and rural (b), 2013–2019.

Joinpoint analysis of the trends in mortality

From 2013 to 2019, ASMR decreased from $0.83/10^5$ to $0.74/10^5$ in urban areas, with an AAPC of −1.50% (95% confidence interval [CI]: −3.49, 0.53), whereas ASMR increased from $0.47/10^5$ to $0.57/10^5$ in rural areas, with an AAPC of 3.34% (95% CI: −4.64, 11.97), but with no statistical significance. Joinpoint analysis identified no significant Joinpoint from 2013 to 2019, which indicates the GBC mortality rate was relatively stable in this period.

When gender-specific trends were analysed, non-significant decreasing trends were also observed, with an APC of −0.91% and −1.84% in urban males and females, respectively. In rural areas, the GBC mortality rate significantly increased, regardless of gender, with an AAPC of 2.64% (95% CI: 1.15, 4.15) in males and 3.85% (95% CI: 2.17, 5.56) in females.

When age-specific GBC mortality trends were explored, decreasing trends in urban and increasing trends in rural areas were observed in all age groups, although no significant trends were identified. The highest AAPC was observed in the age group of 20~ years, at −3.51% (95% CI: −16.76, 11.84) and 27.06% (95% CI: −3.76, 67.76) in urban and rural areas, respectively (Table 2 and Supplementary Fig. S2).

Correlation between GBC mortality rate and meat consumption

This study showed that GBC mortality rate was positively associated with total meat consumption and red meat consumption, with correlation coefficients of 0.772 and 0.652, respectively. Red meat accounted for 87.91% of the total meat consumption, which implied that red meat may play a vital role for the increasing GBC mortality rate. However, the correlation was not significant after the data were stratified by urban and rural areas, which may be a result of the limited number of years of available data. The mean meat consumption in urban areas was higher than in rural areas (total meat: 29.13 vs 23.79 kg; red meat: 24.79 vs 21.73 kg), coinciding with the higher GBC mortality rate in urban areas (Table 3).

Table 2
The trends of gallbladder cancer mortality by area, gender and age group, China, 2013–2019.

Variable	Urban [AAPC (95% CI)]	Rural [AAPC (95% CI)]
Total	−1.50 (−3.49, 0.53)	3.34 (−4.64, 11.97)
Gender		
Male	−0.91 (−2.19, 0.40)	2.64[a] (1.15, 4.15)
Female	−1.85 (−4.23, 0.60)	3.85[a] (2.17, 5.56)
Age group in years		
20~	−3.51 (−16.76, 11.84)	27.06 (−3.76, 67.76)
40~	−2.73 (−7.33, 2.10)	2.48 (−4.55, 10.04)
60~	−1.74 (−3.62, 0.16)	3.02 (−3.48, 9.95)
80~	−0.12 (−2.14, 1.95)	4.19 (−10.36, 21.09)

AAPC, average annual percent change; 95% CI, 95% confidence interval.
[a] $P < 0.05$, means AAPC is significantly different from zero.

Table 3
Correlation between gallbladder cancer mortality rate and meat consumption in China, 2013–2019.

Variables	N	Mean ± SD	Correlation coefficient	*P* value
Mortality rate ($1/10^5$)	14	0.67 ± 0.15		
Total meat (kg)	14	26.46 ± 3.10	0.772	0.001
Red meat (kg)	14	23.26 ± 2.05	0.652	0.012

Total meat includes white meat and red meat. Red meat includes pork, beef and mutton.

Discussion

GBC is an orphan disease because of the relatively low incidence and mortality rate in the world; however, it cannot be neglected because of increasing incidence and mortality trends in recent years. It is essential to investigate GBC burden among the Chinese population for all provinces in China. The China Health Statistics Annual Report is an annual statistical publication that reflects the development of China's health services and the health status of residents. The important causes of mortality among residents are noted in this report, including 17 types of malignant tumours, one of which is GBC. GBC was added to the report in 2014, indicating that it is an increasingly important disease-causing mortality in the Chinese population. The results provide mortality trends in GBC in different areas of China. In the present study, the mortality rate of GBC was higher in urban than in rural areas. This result may be attributable to a higher prevalence of obesity and high cholesterol in older adults in urban areas, which increase the risk of GBC.[17,18]

The highest ASMR was $0.85/10^5$ in urban areas in 2017, which is slightly higher than the world ASMR of $0.84/10^5$. Fortunately, this ASMR decreased to $0.74/10^5$ in 2019. GBC mortality rate decreased in urban areas during the 7-year study period (2013–2019), but it was not statistically significant. This result may be because individuals in urban areas have easier access to health services and better diagnostic modalities, resulting in appropriate staging and treatment of GBC. This study found a significantly increasing mortality rate in rural areas from 2013 to 2019, with an AAPC of 2.64% (95% CI: 1.15, 4.15) in males and 3.85% (95% CI: 2.17, 5.56) in females. It has been reported that poor socio-economic conditions are associated with elevated GBC incidence, although the underlying mechanisms remain uncertain.[19] Furthermore, it is undeniable that people who live in rural areas have limited access to health care. Therefore, more attention should be paid to gallbladder health in rural residents. Although the current mortality rate is relatively low, the latent risk cannot be ignored.

In our study, GBC mortality occurred more frequently in females than males. This result is in line with WHO's observation that worldwide GBC deaths in females is 1.78 times that reported in males. In most countries, such as Saudi Arabia, the United States and India,[20–22] females are at a higher risk of GBC than males. This is most likely attributable to the high oestrogen hormone levels in females, which increases the saturation of cholesterol in the bile and subsequentially the risk of gallstone formation. Gallstones are a predisposing condition for GBC.[23–25] However, some countries, such as Iceland, Costa Rica and Korea, report higher GBC mortality rates in males than females.[15] In addition, older age was also a risk factor for GBC mortality. The results of the present study show that the most common age for GBC mortality was the 60–75 years age group, accounting for >50% of GBC mortality, whereas those aged <50 years were less affected by GBC. These findings are in accordance with studies from Saudi Arabia and Shanghai and reflect the reality of ageing populations.

A variety of risk factors driving GBC have been studied. Pre-existing gallbladder disease (e.g. gallstones and chronic cholecystitis), environmental exposures (e.g. diet, arsenic and tobacco) as well as genetic factors all play key roles in GBC pathogenesis.[25–28] In this study, GBC mortality rate was positively related to red meat consumption, which was consistent with Pandey and Shukla's study that showed red meat was associated with an increased risk of GBC.[7] Several studies have investigated the potential role of meat intake on the risk of cancers, including dietary heterocyclic amines and other mutagens formed in cooked meat[29] and how meat intake may impact the intestinal microbiome by altering microbial community structure and metabolism, although the results are inconclusive.[30] It is worth noting that the present study is based on ecological evidence and more details about meat intake and other related factors correlating with GBC are needed to explore this association. Further studies are required to identify risk factors, such as dietary and lifestyles habits, to prevent the increasing GBC mortality rate in rural China and keep GBC a 'silent' disease in the future.

Nevertheless, in the present study, the difference in mortality rates between the gender and age groups in the different years was small, and the decreasing trend in GBC mortality in urban areas was not statistically significant. Such results may be because of the very low mortality and the limited years of data available. A longer time span of data collection would ensure more robust results.

Conclusions

In conclusion, this study showed a significantly increasing GBC mortality burden in rural areas of China; thus, more attention should be paid to rural residents. Additional research is required to evaluate whether meat intake has a causal relationship to GBC, so policy makers can take effective measures to prevent the increasing GBC mortality rate in China.

Author statements

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Ethical approval

Not required. This article is based on data from a published Statistical Yearbook.

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Competing interests

The authors declared no competing interests.

Appendix A. Supplementary data

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References

1. Levy AD, Murakata LA, Rohrmann CA. Gallbladder carcinoma: radiologic-pathologic correlation. *Radiographics* 2001;**21**:295.

2. Hsing AW, Bai Y, Andreotti G, Rashid A, Deng J, Chen J, et al. Family history of gallstones and the risk of biliary tract cancer and gallstones: a population-based study in Shanghai, China. *Int J Cancer* 2007;**121**:832–8.
3. Dhiman RK, Chawla YK. Is there a link between oestrogen therapy and gallbladder disease? *Expet Opin Drug Saf* 2006;**5**:117–29.
4. Larsson SC, Wolk A. Obesity and the risk of gallbladder cancer: a meta-analysis. *Br J Cancer* 2007;**96**:1457–61.
5. Mhatre S, Rajaraman P, Chatterjee N, Bray F, Goel M, Patkar S, et al. Mustard oil consumption, cooking method, diet and gallbladder cancer r isk in high- and low-risk regions of India. *Int J Cancer* 2020;**147**:1621–8.
6. Nelson SM, Gao Y-T, Nogueira LM, Shen M-C, Wang B, Rashid A, et al. Diet and biliary tract cancer risk in Shanghai, China. *PLoS One* 2017;**12**:e0173935.
7. Pandey M, Shukla VK. Diet and gallbladder cancer: a case-control study. *Eur J Cancer Prev* 2002;**11**:365–8. the official journal of the Eu ropean Cancer Prevention Organisation (ECP).
8. Papier K, Fensom GK, Knuppel A, Appleby PN, Tong TYN, Schmidt JA, et al. Meat consumption and risk of 25 common conditions: outcome-wide analys es in 475,000 men and women in the UK Biobank study. *BMC Med* 2021;**19**:53.
9. Tavani A, La Vecchia C, Gallus S, Lagiou P, Trichopoulos D, Levi F, et al. Red meat intake and cancer risk: a study in Italy. *Int J Cancer* 2000;**86**:425–8.
10. Shaffer EA. Gallbladder cancer: the basics. *Gastroenterol Hepatol* 2008;**4**:737–41.
11. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. *Int J Cancer* 2006;**118**:1591–602.
12. Schmidt MA, Marcano-Bonilla L, Roberts LR. Gallbladder cancer: epidemiology and genetic risk associations. *Chin Clin Oncol* 2019;**8**:31.
13. Levi F, Lucchini F, Negri E, La Vecchia C. The recent decline in gallbladder cancer mortality in Europe. *Eur J Cancer Prev* 2003;**12**:265–7. the official journal of the European Cancer Prevention Organisation (ECP).
14. Alqahtani SA, Alghamdi IG. Epidemiology of gallbladder cancer in Saudi Arabia. *Cancer Manag Res* 2020;**12**:9527–37.
15. Hariharan D, Saied A, Kocher HM. Analysis of mortality rates for gallbladder cancer across the world. *HPB* 2008;**10**:327–31. the official journal of the International Hepato Pancreato Bilia ry Association.
16. Zhang M, Wu C, Zuo B, Gong W, Zhang Y, Yang Y, et al. Trends of gallbladder cancer incidence, mortality, and diagnostic approach in urban Shanghai between 1973 and 2009. *Tumori* 2020;**106**:392–9.
17. Liu H, Zhang Y, Ai M, Wang J, Jin B, Teng Z, et al. Body mass index can increase the risk of gallbladder cancer: a meta-analysis of 14 cohort studies. *Med Sci Monitor Basic Res* 2016;**22**:146–55.
18. Ding L, Liang Y, Tan ECK, Hu Y, Zhang C, Liu Y, et al. Smoking, heavy drinking, physical inactivity, and obesity among middle-aged and older adults in China: cross-sectional findings from the baseline survey of CHARLS 2011-2012. *BMC Publ Health* 2020;**20**:1062.
19. Nemunaitis JM, Brown-Glabeman U, Soares H, Belmonte J, Liem B, Nir I, et al. Gallbladder cancer: review of a rare orphan gastrointestinal cancer with a focus on populations of New Mexico. *BMC Cancer* 2018;**18**:665.
20. Dutta U, Bush N, Kalsi D, Popli P, Kapoor VK. Epidemiology of gallbladder cancer in India. *Chin Clin Oncol* 2019;**8**:33.
21. Rahman R, Simoes EJ, Schmaltz C, Jackson CS, Ibdah JA. Trend analysis and survival of primary gallbladder cancer in the United States: a 1973-2009 population-based study. *Cancer medicine* 2017;**6**:874–80.
22. Konstantinidis IT, Deshpande V, Genevay M, Berger D, Fernandez-del Castillo C, Tanabe KK, et al. Trends in presentation and survival for gallbladder cancer during a period of more than 4 decades: a single-institution experience. Chicago, Ill : 1960 *Arch Surg* 2009;**144**:441–7. discussion 7.
23. Jones MW, Gnanapandithan K, Panneerselvam D, Ferguson T. *Chronic cholecystitis*. Treasure Island (FL): StatPearls Publishing; 2020. PMID: 29261986.
24. Everson GT, McKinley C, Kern Jr F. Mechanisms of gallstone formation in women. Effects of exogenous estrogen (Premarin) and dietary cholesterol on hepatic lipid metabolism. *J Clin Invest* 1991;**87**:237–46.
25. Pilgrim CH, Groeschl RT, Christians KK, Gamblin TC. Modern perspectives on factors predisposing to the development of gallbladder cancer. *HPB* 2013;**15**:839–44. the official journal of the International Hepato Pancreato Biliary Association.
26. Sharma A, Sharma KL, Gupta A, Yadav A, Kumar A. Gallbladder cancer epidemiology, pathogenesis and molecular genetics: recent update. *World J Gastroenterol* 2017;**23**:3978–98.
27. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. *Clin Epidemiol* 2014;**6**:99–109.
28. Iyer P, Barreto SG, Sahoo B, Chandrani P, Ramadwar MR, Shrikhande SV, et al. Non-typhoidal Salmonella DNA traces in gallbladder cancer. *Infect Agents Cancer* 2016;**11**:12.
29. Augustsson K, Skog K, Jägerstad M, Dickman PW, Steineck G. Dietary heterocyclic amines and cancer of the colon, rectum, bladder, and kidney: a population-based study. *Lancet* 1999;**353**:703–7.
30. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 2014;**505**:559–63.

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Original Research

Validity and reliability of the Greek version of modified Baecke questionnaire

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ABSTRACT

Objectives: The purpose of this study was to translate and investigate the validity and reliability of the modified Baecke Physical Activity Questionnaire (mBQ) in the Greek adult population.
Study design: This is a cross-cultural study.
Methods: The cross-cultural adaptation of the mBQ was performed according to official guidelines. The prefinal Greek translation was tested in 30 healthy participants. The reliability was determined (n = 100) by filling out the mBQ, two times, 1 week apart. For validation (n = 45), the scores between the mBQ and the International Physical Activity Questionnaire (IPAQ) were compared, and the correlation between mBQ and VO_2max and between mBQ and interview (METS) were assessed.
Results: High statistical significant of test–retest reliability was found (intraclass correlation coefficient = 0.84; standard error of measurement = 0.48; smallest detectable difference = 16.7%; Cronbach's alpha = 0.92). Statistical significant correlation between the mBQ and the IPAQ (r = 0.425, $P = 0.005$), high correlation between the mBQ and METS (r = 0.691, $P = 0.000$), and moderate correlation between mBQ and VO_2max (r = 0.388, $P = 0.08$) were found.
Conclusion: The Greek mBQ was found to be reliable and valid for assessing the level of physical activity in the Greek population.
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Introduction

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. There is incontrovertible evidence that participation in regular activities promotes many health benefits by improving physical and psychological well-being.[1,2] The health benefits can be achieved by following international guidelines that recommend a weekly routine of 150 min of moderate exercise.[3] On the contrary, physical inactivity is associated with more than 35 chronic diseases/conditions.[4] Many studies have shown that physical inactivity is an important modifiable risk factor for many common diseases such as cardiovascular diseases, osteoporosis, type II diabetes, and depression.[3,5,6] Moreover, 9% of premature mortality is attributed to physical inactivity by making it similar to the risk factors of obesity and smoking. The limitation of physical inactivity might increase the life expectancy of the world's population to 0, 68 years.[7] As a result, it would be quite helpful for health professionals to have accurate, valid, and reliable measures for evaluating the level of PA and functional status of their patients. In this way, they could improve patients' well-being and prevent multiple potential diseases.

There is no globally accepted gold standard for assessing the level of PA in a population, as it is considered a complex and multidimensional exposure variable. However, there are many direct and indirect methods for measuring habitual PA.[8,9] For direct

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measurement of physical performance, it could be used the activity monitor by using different tools, such as accelerometers, pedometers, heart rate monitors, etc.[10] One of the most valid direct methods for measuring energy expenditure in free-living adults is the doubly labeled water method. This method allows participants to maintain their habitual activities, causing only minimal inconvenience. However, it is considered unsuitable for use in large population studies because of its high cost and time-consuming process.[11,12]

On the other hand, indirect methods include data collection procedures such as self-reporting questionnaires, PA diaries, and interviews.[10] Each method has its advantages and limitations. Although all previous referred technological tools have raised the objectivity and accuracy of PA estimation, they are quite costly and sometimes time wasting. Contrary to the above, self-reported questionnaires could be used in large samples and cover longer time frames leading to recall bias. The advantages of using questionnaires for assessing PA are considerable because they are convenient, time-saving, cost-effective, and easy to access, and they have scoring flexibility.[13] All these advantages make them the most suitable and efficient choice for measuring PA performance in large populations even if there is always a risk of participants to underestimate or overestimate their answers during filling it.

A various number of available questionnaires exist for measuring PA,[14,15] one of the most frequently used is Baecke Questionnaire (BQ). The advantages of being short, self-administrated, and easy to fill make the BQ an attractive and preferable assessment tool for use in a busy clinical setting. Baecke Habitual Activity Questionnaire was developed by Baecke et al. for measuring PA in healthy populations.[16] Some years later, Voorrips et al. slightly modified this questionnaire to capture PA performance in the elderly by adding and modifying some questions.[17] Based on BQ Pols et al. developed a modified version (modified Baecke Questionnaire [mBQ]) by adding three more questions. Therefore, the BQ consists of 16 questions against its modified version that includes 19 questions. Moreover, the original version is self-administrated against modified, which is interview administrated by clinicians.[18] The present study selected the modified version, as there is no significant difference between self-administrated questionnaires and interview administrated by clinicians.[19] We consider that the presence of a clinician during the filling of questionnaires provides a scientific approach in our methodology, even if a self-administrated questionnaire can collect more subjects. Moreover, the modified version may be considered more evolved, as it includes three more questions than the original. Both original and modified versions can be applied in patients such as patients with HIV, obesity, cardiovascular diseases, hip disorders, etc.[20–25] As a consequence, the validity and reliability of BQ and the modified version as PA measurement tools have been assessed in both healthy and unhealthy populations. Besides, the questionnaires are valid and reliable in many different languages such as Dutch,[26] French,[27] Persian,[28] Korean,[29] Brazilian,[30] Chinese,[31] Japanese,[20] and Spanish.[32] However, the validity and reliability of the questionnaire have not been assessed yet in Greek adults.

Methods

The purposes of the present study were to translate, modify, and investigate the validity and reliability of the mBQ in the Greek adult population. The present study was divided into three phases: (1) translation and cross-cultural adaptation process, (2) assessment of the test–retest reliability, and (3) assessment of the validity. The protocol of studies was approved by the Ethics Committee of the Department of Physiotherapy of the University of Thessaly, Greece.

Phase 1: translation and cross-cultural adaptation

The plan of translation and cross-cultural adaptation of the mBQ was based on the methods indicated in the scientific literature.[33] The whole process consists of the following five steps (Fig. 1):

Step I: forward translation

Two professionals translators, who were native Greek speakers and fluent in both English and Greek, translated the original English version of the questionnaire into Greek by working independently. Therefore, two independent Greek translations (T1 and T2) of the questionnaire were produced. Two reports were also written by both translators indicating their comments on any difficulties that faced during the translation process.

Step II: Synthesis

The results of both translations (T1 and T2) were compared and synthesized by the two translators after discussing any discrepancies between the translations. The translators reached consensus on one common Greek questionnaire.

Step III: Backward translation

The common Greek language version (T12) was back-translated into English by two official English translators who have been in an English-speaking country for more than 5 years. The back translations (BT1 and BT2) were produced without the two translators being aware or informed of the study concept. Moreover, the translators examined whether there was a semantic, conceptual, and experiential equivalence between the English original to the back-translated one.

Step IV: Harmonization

To produce the prefinal Greek language translation, the four Greek translators organized a harmonization meeting where they discussed any discrepancies between the original and translated versions. Furthermore, they evaluated semantic, idiomatic, experiential, and conceptual equivalences and reached consensus on a prefinal version of the questionnaire that was eligible for pilot testing.

Step V: Pilot study of the prefinal version

A pilot study was conducted for examining the comprehensibility, linguistic validation, and completeness of the prefinal version of the questionnaire. The prefinal Greek translation was tested in 30 healthy participants. The sample was selected randomly. The inclusion criteria for the sample were age >18 years, Greek native speakers, Greek inhabitants, and sufficient cognitive functioning. After signing an informed consent form, the participants filled the questionnaire under the supervision of an examiner. The examiner documented any problems and difficulties that occurred during the administration of the questionnaire. Each participant after filling the questionnaire participated in an interview organized by the examiner. At the end of the interview, each participant was asked to provide comments related to the completeness of the questionnaire and identify any words or phrases that were difficult to understand. Finally, any discrepancies that remained were discussed among the three translators and the examiner/interviewer to conclude to a consensus final version.

Fig. 1. Phases of translation and cross-cultural adaptation.

Phase 2: assessment of test–retest reliability

The final version of the mBQ was tested on 100 participants (55 males and 45 females). The inclusion criteria of the sample were the same as the pilot's study. To assess test–retest reliability, the participants were requested to complete the mBQ on two occasions, 1 week apart.

Phase 3: assessment of validity

For examining the construct validity of the mBQ, three different measurement methods were used. These methods included (1) the measurement of VO_2max during Astrand-Rhyming Test as seems to exist a quite linear relationship between the mean habitual daily energy expenditure and VO_2max[34] and has been used as a standard measurement for validating also other habitual PA questionnaires,[21,35] (2) an interview about participants' activities during a typical work and non-work day, and (3) concurrent validity was measured by comparing the results of the final Greek mBQ with the results of the Greek version of the International PA Questionnaire (IPAQ).[36]

Design and participants

For the validation study, 45 healthy subjects participated (23 males and 22 females, age range 18–60 years). The sample was convenient, and the exclusion criteria were (1) age <18 years, (2) poor health status, (3) poor Greek language comprehension, (4) diagnosed with cardiovascular diseases, (5) cardiac pacemaker, (6) medication that prevents exercise activity, (7) neurological disorders with effect on the lower body, (8) musculoskeletal disorders or injuries on the lower body in the last 3 months, and (9) PAR-Q health risk assessment form.[37]

For the concurrent validity of the mBQ and the IPAQ questionnaires, the same sample as with the test–retest reliability study was used. The data were collected at the Laboratory of Human Activity and Rehabilitation of the Department of Physiotherapy of the University of Thessaly, Lamia, Greece, under the supervision of two physiotherapists/researchers.

Procedure

All participants filled the PAR-Q questionnaire for examining if they could participate in the study and completed a consent form after they got informed about the whole process of the study. Before participants started the measurements, the researchers completed a form with the body size measurements (height and weight) and the age of each participant.

Astrand-Rhyming test for VO_2max assessment. VO_2max was assessed with the indirect method known as Astrand-Rhyming cycle ergometer test.[38] This method is recommended for people of various ages.[39,40] Each participant performed a 6-min submaximal exercise test by using the ergometer bike (Monark). Before starting the test, the researcher adjusted seat height to fit the subject. Moreover, the heart rate of participants was monitored continuously during testing by the Garmin Vivofit Heart Rate Monitor. Heart rate monitoring is necessary during the testing because of the linear relationship between VO_2max and heart rate to predict VO_2max.[38,40] Initially, subjects rested for 2 min for measuring resting heart rate; after that, there is a 5 min warm-up period at a low intensity to allow the participant to practice and get familiar with the pace. The researcher instructed the participants to maintain a steady cadence throughout the test and recorded the participants' heart rate (HR) at 5 and 6 min. These values were used for determining VO_2max by using the Astrand-Rhyming nomogram, and the results were then normalized to age. Once the test was completed, the participants should cool down until HR and breathing rate return to normal.[38] The test could be interrupted if threatening

symptoms appeared on participants or when the HR reached 85% of the age-predicted maximum heart rate. After a relaxing period, the participants took part in an interview related to their daily routine.

Interview for daily routine activities. Interview was one more measurement tool, which was used for assessing the validation of questionnaire results. The interview aimed to gather sufficient information about the participants' PA during the week to calculate the total amount of energy expenditure (METs) per week, so the questions were related to the job, sports, and leisure time of the interviewee.[41] Through these opened-ended questions, the volunteer was able to describe the activities he performed during a typical working day as well as a typical non-working day.[27] For calculating METS of daily activities of each participant, a Compendium of Physical Activities was used. The Compendium provided a list with several activities linked to their respective metabolic equivalent intensity levels (e.g. for resting, the MET level was 0.9 [sleeping] and the level of MET for running was 18 [running at 10.9 mph]).[41] The interview began with a general process description and the building of rapport between interviewer and participant. The average duration of the interview was 30 min and was recorded using a laptop microphone that was connected to a computer. The program used for the interview was audacity 2.1.1. After completing the interview process, the participant filled the mBQ.

Modified Baecke Questionnaire. The questionnaire includes three different categories of questions that are related to household activities, sports and, leisure time activities in the previous 12 months. The overall number of questions is 19. The questions about work have three to five possible answers, categorizing the activity from inactive to very active. Participants were instructed to consider studying or household activities as their work in case that was their main daily activity. The questions of sports activities include the activity type, the frequency of activity performance, and the number of months annually that the activity is performed. The questions on leisure time activities have five possible answers. Participants have to choose only one answer for each question of the questionnaire. All items result in a separate score. The sum of the answers' scores obtained from each category represents the level of individual PA. The total score of the questionnaire varies from 3 to 15, with higher scores representing higher levels of PA.[18] After completing the whole process, participants got informed about their results via emails (Appendix 1).

International Physical Activity Questionnaire. The IPAQ is considered a quite valid and reliable measurement tool of physical activities.[36,42] It was developed by the World Health Organization in 1988.[43] There are four long (31 questions) and four short (nine questions) versions of the IPAQ that can be self-administered or answered via phone call.[44] All forms have been assessed as validated against accelerometer measurements. However, many researchers prefer to use the short form, as it has equivalent psychometric properties to the long form. IPAQ has been investigated and used in a variety of different populations until now.[36,42] Greek adults are one of them, as the reliability and validity of the IPAQ have already been examined in the Greek language. Therefore, it is considered an acceptable tool for assessing the validation against the mBQ in terms of evaluation of physical activities.[45]

Statistical analysis

The analysis of test–retest reliability was performed with descriptive and inductive statistical analysis using the program 'Statistical Package for the Social Sciences' (SPSS, version 22.0). For checking test–retest reliability, the intraclass correlation coefficient (ICC) was used, along with the standard measurement error (standard error of measurement [SEM]) and the smallest detectable difference (SDD) between variables (parametric tests). The Spearman rho correlation coefficient was used for the correlation between the mBQ and the IPAQ questionnaire. The significance test was performed at level $P < 0.05$.

The analysis of validity was performed in IBM SPSS Statistics (v. 22.0). The variability control of variables was tested using the Kolmogorov–Smirnov statistical test where a variable is considered to have a normal distribution if the statistical significance value P is greater than the value $\alpha = 0.05$. According to the results of the Kolmogorov–Smirnov statistical test, all variables were found to have a statistically non-significant difference with the normal distribution and are considered to be of normal form. In addition to the descriptive analysis of the data, a correlation test was performed between the variables using the Pearson correlation factor. The probability level at which the statistical test was performed was defined as $\alpha = 0.05$. For concurrent validity testing, statistical correlation tests were performed between each parameter of the mBQ and the IPAQ. The normality of the data was tested with the Kolmogorov–Smirnov test that showed that data of BQ data were normally distributed, whereas the data of IPAQ questionnaire were irregularly distributed.

Results

Translation and cross-cultural adaptation process

The mBQ was translated into Greek and then culturally adapted. Difficulties arising during its development were considered minor. The 30 participants of the pilot study did not face any discrepancies in meaning or terminology in the Greek version of the questionnaire. Furthermore, the participants did not request assistance in interpreting the questionnaire and were able to understand all the statements in the questionnaire, so no modification to the text was required.

Test–retest reliability

For examining reliability, 100 participants (55 males and 45 females) completed the mBQ twice, 1 week apart (Table 1). The reliability was very good (ICC = 0.84, SEM = 0.48, SDD = 16.7%), and a Cronbach α of 0.92 was obtained.

Validity

For assessing construct validity, 45 healthy participants (23 males and 22 females) with a mean age of 26.8 (±10.40) years (range: 18–59 years) took part in three different tests (VO_2max measurement, METS measurement, and BQ; Table 2). According to the results, a low correlation was found, in the total sample (n = 45), between the Baecke total and VO_2max sections (r = 0.388, $P = 0.008$), whereas in the same sections, a moderate correlation was found (r = 0.577, $P = 0.004$) in the male sample (n = 23). The

Table 1
Participant characteristics.

Participants	n	Age (mean ± SD)	Height (mean)	Weight (mean)
Total	100	26.5 ± 9.5	173.8	71.6
Males	55	28 ± 10.2	179.4	81.6
Females	45	24.6 ± 8.2	178	59.4

Table 2
Participant characteristics.

Participants	n	Age (mean ± SD)	Height (mean)	Weight (mean)
Total	45	26.80 ± 10.40	1.7184	69.8767
Males	23	27.91 ± 11.208	1.7926	81.5239
Females	22	25.64 ± 9.609	1.6409	57.7000

Table 3
Concurrent validity between the mBQ and the IPAQ.

IPAQ	Baecke total	Work	Sport	Leisure
IPAQ total	**0.425****	**0.372****	**0.247***	0.50
IPAQ A	**0.349****	**0.234***	**0.300****	-0.031
IPAQ B	0.137	0.118	0.080	0.102
IPAQ C	**0.365****	0.163	**0.205***	**0.362****

Statistical significance *<0.001, **<0.005.

final correlation in the study was between the interview (the results were calculated with the METs as a unit of measurement) and the modified Baecke. The results showed that there was a moderate to high correlation between Baecke total and METs, more specifically in the whole sample (n = 45; r = 0.691, $P = 0.000$), in the sample of women (n = 22; r = 0.758, $P = 0.000$), and in the sample of athletes (n = 14; r = 0.792, $P = 0.001$).

For examining concurrent validity between the mBQ and the IPAQ questionnaires, the same sample as with test–retest reliability study was employed. Findings revealed that the correlation between total Baecke and total IPAQ score was low positive (r = 0.425, $P = 0.005$) (Table 3).

Discussion

The increasing problem of physical inactivity along with the need to have a measuring tool for assessing PA in Greek population led to the adaptation of the mBQ in Greek language. The original version of the BQ is in the English language,[16] so its translation and cross-cultural adaptation in Greek population were necessary. The need of using validated and reliable tools for measuring levels of PA led to the assessment of its psychometric properties (namely, the validation and reliability). This questionnaire was chosen in many studies, as it is short, simple, valid, reliable, and easy to use.

Table 4
The modified Baecke Questionnaire in different languages.

Study	Language	Sample	Methods	Results		
				Reliability	Validity	Mean total score (SD)
[a]Philippaerts et al. (1998)[26]	Dutch	90 (males)	**Reliability:**1-month test–retest **Validity:** **(1)** physical activity between three levels of professional status **(2)**means of a principal components analysis study	ICC = 0.88 0.20 <Kappa values < 0.73.	Based on component-loading matrix of the physical activity variables	7.9 (±1.4) 8.0 (±1.4) 8.8 (±1.8)
[a]Florindo et al. (2003)[30]	Portuguese-Brazilian	21 (males)	**Reliability:** Test–retest (45 days) **Validity:** 1)VO_2max 2)%DHR	ICC = 0.77	(1) r = 0.17 ($P = 0.470$) (2) r = 0.48 ($P = 0.027$)	7.39 (±1.29)
[a]Lee et al. (2004)[29]	Korean	507 (males = 318, females = 189)	Unclear-Korean language	Cronbach's alpha coefficient: 0.73 (work) 0.78 (sport) 0.35 (leisure)	Based on factor-loading matrix of the items about physical activity	7.4
[a]Ono et al. (2007)[20]	Japanese	61 (females)	**Reliability:** Two-week test–retest **Validity:** measured step counts (validity)	ICC = 0.87	rho = 0.49 ($P < 0.01$)	7.6 (±1.4)
[b]Vilaró et al. (2007)[32]	Spanish	55	**Reliability:** Test–retest (2 weeks to 1 month) **Validity:** (1)SGRQ (2)PM6M (3)FEV_1%	ICC = 0.96 *Cronbach's alpha coefficient = 0.97*	rho = −0.45 ($P < 0.05$) rho = 0.54 ($P < 0.05$) rho = 0.31 ($P < 0.05$)	12.8 (IQR: 25–75% = 9–17.1)
[a]Vol et al. (2011)[27]	French	702	**Reliability:** (1) Two-week test–retest (2) Overtime test–retest (2 months) **Validity:** interview	ICC = 0.87 Kappa >0.60	rho = 0.39 ($P < 0.0001$)	8.31 (±1.21)
[a]Ho et al. (2015)[31]	Chinese	198 (males = 94, females = 104)	**Reliability:** Two-week test–retest **Validity:** 3-day activity diary	ICC = 0.65–0.90 *Cohen's κ: 41.0% (males) 56.7% (females)*	r = 0.61 ($P < 0.01$)	8.81 (±1.47)
[a]Sadeghisani et al. (2015)[28]	Persian	**Pilot:** 20 **Reliability:** 32 **Validity:** 126 (males = 66, females = 60)	**Reliability:** Test–retest (3–7 days after the first session) **Validity:** IPAQ	ICC = 0.88 *Cronbach's alpha coefficient > 0.7*	r = 0.36 ($P = 0.00$) (sitting position excluded) r = 0.19 ($P = 0.03$) (sitting position included)	8.26 (±1.33)

[a] Based on the original Baecke Questionnaire.
[b] Modified of modified Baecke Questionnaire.

Test–retest reliability and validity of the BQ and mBQ have been already examined in different populations speaking different languages (Table 4). Although the mBQ includes three more questions at the leisure time activities filled in comparison to BQ, the results of validity and reliability were still comparable. Most translations and cross-cultural adaptations were based on the original version. However, the results in most studies were similar. More specifically, many ICC values of BQ and mBQ questionnaires in different languages were reported as acceptable values, suggesting it as a reliable tool.[28] For example, ICC values of the BQ/mBQ in Japanese (ICC = 0.87),[20] Persian (ICC = 0.88, Cronbach's alpha coefficient >0.7),[28] Flemish (ICC = 0.88, 0.20 <Kappa values < 0.73),[26] Spanish (ICC = 0.96, Cronbach's alpha coefficient = 0.97),[32] Chinese (ICC = 0.65–0.90),[31] Korean (Cronbach's alpha coefficient: 0.73 [work],0.78 [sport], 0.35 [leisure]),[29] and French (ICC = 0.87, Kappa >0.60).[27] The results of the present study show that ICC value was 0.84. Therefore, the ICC value is consistent with those obtained for the BQ/mBQ in different language populations.

For assessing the concurrent validity of the mBQ, we used the IPAQ. As stated by Papathanasiou et al., the Greek version of IPAQ is a valid and reliable tool to evaluate the level of physical activities in Greek speakers.[45] The results showed a statistically significant correlation between the mBQ and the IPAQ ($r = 0.425$, $P = 0.005$). For evaluating the construct validity of the mBQ, the METS calculation via interview was used. The correlation between the mBQ and the interview ($r = 0.691$, $P = 0.000$) was the highest compared with other methods used. Similar results were obtained by Vol et al. in their study conducted for the adaptation of the questionnaire in French.[27] This could be explained, as the interview is considered the most appropriate tool to prove the validity of a questionnaire. Moreover, the measurement of VO_2max was used for assessing the construct validity of the mBQ. Nevertheless, the correlation between the questionnaire and VO_2max, although lower than the interview ($r = 0.388$, $P = 0.008$), was statistically significant. Another study also found low correlation between total Baecke and VO_2max ($r = 0.17$, $P = 0.470$).[30] Even if seems to be a quite linear relationship between the mean habitual daily energy expenditure and VO_2max, there are some other variables, such as body mass, age, gender, etc., that affect this relationship[34] and may be responsible for the low correlation between total Baecke and VO_2max. Moreover, the nature of BQ that measures PA during work, leisure, or sports throughout the past year and not only in the present time could be another explanation for the low correlation.

The present study has a few limitations that have to be addressed. The first limitation is that the mBQ referred to activities of the past year, whereas the IPAQ concerns the activities of the last week. Therefore, the comparison of results between the two questionnaires is quite difficult. However, IPAQ was used to correlate with the mBQ, as it is the only one PA questionnaire that has been tested for reliability and validity in Greek culture. Another limitation was that the sample included only the age range of 18–59 years, so its validity has not still been proven for use in the elderly and minors in Greece. The final limitation was that only healthy participants were included in the present study. These limitations suggest further research to prove the validity of the mBQ in a wider age range as well as the application in various diseases.

The results of the present study have great clinical significance. It is the first time that the mBQ has been interculturally adapted and controlled in terms of validity and reliability in Greece. The mBQ can be a useful and easy-to-use tool for Greek clinicians and researchers for evaluating and monitoring PA in Greece, so it has an important clinical contribution except for scientific ones. Furthermore, it was the first time that mBQ was used and correlated with the IPAQ questionnaire for PA in the Greek population. The present study helped to investigate the validity and reliability of the questionnaire as a commonly accepted clinical tool. Last but not least, it is important to be clarified when the original or the modified version of the BQ is used according to research good practice.

Conclusion

In conclusion, the modified Greek BQ was found to be a reliable and valid tool for measuring habitual PA in the Greek population. That means the mBQ could be a valuable tool for Greek healthcare professionals in both clinical and research environments. Moreover, further research is needed to evaluate the validity of the questionnaire to children and the elderly, as well as its use in different patient groups.

Author statements

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Ethical approval

The questionnaire and methodology for this study were approved by the Human Research Ethics committee of the University of Thessaly (Ethics approval number: 1008/01-9-2015).

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Competing interests

None declared.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Clinical messages

- The Greek version of Modified Baecke is reliable and valid.
- It is a useful and easy-to-use tool for Greek clinicians and researchers.
- It is necessary the clarification between the use of the original or modified version of the BQ in studies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.11.017.

References

1. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *Cmaj* Mar 14 2006;**174**(6):801–9. https://doi.org/10.1503/cmaj.051351.
2. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Publ Health Rep* Mar-Apr 1985;**100**(2):126–31.
3. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol* Sep 2017;**32**(5):541–56. https://doi.org/10.1097/hco.0000000000000437.

4. Booth FW, Roberts CK, Thyfault JP, Ruegsegger GN, Toedebusch RG. Role of inactivity in chronic diseases: evolutionary insight and pathophysiological mechanisms. *Physiol Rev* Oct 1 2017;**97**(4):1351–402. https://doi.org/10.1152/physrev.00019.2016.
5. Teychenne M, Ball K, Salmon J. Sedentary behavior and depression among adults: a review. *Int J Behav Med* Dec 2010;**17**(4):246–54. https://doi.org/10.1007/s12529-010-9075-z.
6. Warburton DE, Bredin SS. Reflections on physical activity and health: what should we recommend? *Can J Cardiol* Apr 2016;**32**(4):495–504. https://doi.org/10.1016/j.cjca.2016.01.024.
7. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* Jul 21 2012;**380**(9838):219–29. https://doi.org/10.1016/s0140-6736(12)61031-9.
8. Paffenbarger Jr RS, Blair SN, Lee IM, Hyde RT. Measurement of physical activity to assess health effects in free-living populations. *Med Sci Sports Exerc* Jan 1993;**25**(1):60–70. https://doi.org/10.1249/00005768-199301000-00010.
9. Lamonte MJ, Ainsworth BE. Quantifying energy expenditure and physical activity in the context of dose response. *Med Sci Sports Exerc* Jun 2001;**33**(6 Suppl):S370–8. https://doi.org/10.1097/00005768-200106001-00006. discussion S419-20.
10. Adamo KB, Prince SA, Tricco AC, Connor-Gorber S, Tremblay M. A comparison of indirect versus direct measures for assessing physical activity in the pediatric population: a systematic review. *Int J Pediatr Obes* 2009;**4**(1):2–27. https://doi.org/10.1080/17477160802315010.
11. Skender S, Ose J, Chang-Claude J, Paskow M, Brühmann B, Siegel EM, et al. Accelerometry and physical activity questionnaires - a systematic review. *BMC Publ Health* Jun 16 2016;**16**:515. https://doi.org/10.1186/s12889-016-3172-0.
12. Hertogh EM, Monninkhof EM, Schouten EG, Peeters PH, Schuit AJ. Validity of the modified Baecke questionnaire: comparison with energy expenditure according to the doubly labeled water method. *Int J Behav Nutr Phys Activ* May 27 2008;**5**:30. https://doi.org/10.1186/1479-5868-5-30.
13. Silsbury Z, Goldsmith R, Rushton A. Systematic review of the measurement properties of self-report physical activity questionnaires in healthy adult populations. *BMJ Open* Sep 15 2015;**5**(9):e008430. https://doi.org/10.1136/bmjopen-2015-008430.
14. Armstrong T, Bull F. Development of the world health organization global physical activity questionnaire (GPAQ). *J Publ Health* 2006;**14**(2):66–70. https://doi.org/10.1007/s10389-006-0024-x. 2006/04/01.
15. de Courten M. Developing a simple global physical activity questionnaire for population studies. *Australas Epidemiol* 2002;**9**(2):6–9.
16. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* Nov 1982;**36**(5):936–42. https://doi.org/10.1093/ajcn/36.5.936.
17. Voorrips LE, Ravelli AC, Dongelmans PC, Deurenberg P, Van Staveren WA. A physical activity questionnaire for the elderly. *Med Sci Sports Exerc* Aug 1991;**23**(8):974–9.
18. Pols MA, Peeters PH, Bueno-De-Mesquita HB, Ocke MC, Wentnik CA, Kemper HCG, et al. Validity and repeatability of a modified Baecke questionnaire on physical activity. *Int J Epidemiol* Apr 1995;**24**(2):381–8. https://doi.org/10.1093/ije/24.2.381.
19. Cook DJ, Guyatt GH, Juniper E, Griffith L, McIlroy W, Willan A, et al. Interviewer versus self-administered questionnaires in developing a disease-specific, health-related quality of life instrument for asthma. *J Clin Epidemiol* Jun 1993;**46**(6):529–34. https://doi.org/10.1016/0895-4356(93)90125-k.
20. Ono R, Hirata S, Yamada M, Nishiyama T, Kurosaka M, Tamura Y. Reliability and validity of the Baecke physical activity questionnaire in adult women with hip disorders. *BMC Muscoskel Disord* Jul 5 2007;**8**:61. https://doi.org/10.1186/1471-2474-8-61.
21. Florindo AA, Latorre Mdo R, Santos EC, Negrão CE, Azevedo LF, Segurado AA. Validity and reliability of the Baecke questionnaire for the evaluation of habitual physical activity among people living with HIV/AIDS. *Cad Saúde Pública* Mar 2006;**22**(3):535–41. https://doi.org/10.1590/s0102-311x2006000300008.
22. Richardson MT, Ainsworth BE, Wu HC, Jacobs Jr DR, Leon AS. Ability of the atherosclerosis risk in communities (ARIC)/Baecke questionnaire to assess leisure-time physical activity. *Int J Epidemiol* Aug 1995;**24**(4):685–93. https://doi.org/10.1093/ije/24.4.685.
23. Tomlinson DJ, Erskine RM, Morse CI, Onambélé GL. Body fat percentage, body mass index, fat mass index and the ageing bone: their singular and combined roles linked to physical activity and diet. *Nutrients* Jan 18 2019;**11**(1). https://doi.org/10.3390/nu11010195.
24. Hajian-Tilaki K, Heidari B. Prevalences of overweight and obesity and their association with physical activity pattern among Iranian adolescents aged 12-17 years. *Publ Health Nutr* Dec 2012;**15**(12):2246–52. https://doi.org/10.1017/s1368980012001048.
25. Porter AK, Schilsky S, Evenson KR, Florido R, Palta P, Holliday KM, et al. The association of sport and exercise activities with cardiovascular disease risk: the atherosclerosis risk in communities (ARIC) study. *J Phys Activ Health* Sep 1 2019;**16**(9):698–705. https://doi.org/10.1123/jpah.2018-0671.
26. Philippaerts RM, Lefevre J. Reliability and validity of three physical activity questionnaires in Flemish males. *Am J Epidemiol* May 15 1998;**147**(10):982–90. https://doi.org/10.1093/oxfordjournals.aje.a009389.
27. Vol S, Bedouet M, Gusto G, Leglu C, Beslin E, Decou P, et al. Evaluating physical activity: the AQAP questionnaire and its interpretation software. *Ann Phys Rehabil Med* Nov 2011;**54**(8):478–95. https://doi.org/10.1016/j.rehab.2011.09.001.
28. Sadeghisani M, Dehghan Manshadi F, Azimi H, Montazeri A. Validity and reliability of the Persian version of Baecke habitual physical activity questionnaire in healthy subjects. *Asian J Sports Med* Sep 2016;**7**(3):e31778. https://doi.org/10.5812/asjsm.31778.
29. Lee JY, Yun YH, Park EC, Seo HW, Lee JH, Shin HR, et al. Reliability and validity of the modified Korean version of Baecke questionnaire on physical activity. *Epidemiol Health* 2004;**26**(2):20–31.
30. Florindo AA, do Rosario Dias de Oliveira Latorre M. Validation and reliability of the Baecke questionnaire for the evaluation of habitual physical activity in adult men. *Revista Brasileira de Medicina do Esporte* 2003;**9**:129–35. Accessed 3.
31. Ho SC, Yu R, Chan S. Comparison of the modified Chinese Baecke Questionnaire with a 3-day activity diary in a Hong Kong Chinese population. *Asia Pac J Publ Health* Mar 2015;**27**(2):Np2358–71. https://doi.org/10.1177/1010539511416805.
32. Vilaró J, Gimeno E, Sánchez Férez N, Hernanco C, Díaz I, Ferrero M, et al. Actividades de la vida diaria en pacientes con enfermedadpulmonar obstructiva crónica: validación de la raducciónespañola y análisis comparativo de 2 cuestionarios. *Med Clínica* 2007;**129**(9):326–32.
33. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. *Value Health* Mar-Apr 2005;**8**(2):94–332. https://doi.org/10.1111/j.1524-4733.2005.04054.x.
34. Berthouze SE, Minaire PM, Castells J, Busso T, Vico L, Lacour JR. Relationship between mean habitual daily energy expenditure and maximal oxygen uptake. *Med Sci Sports Exerc* Aug 1995;**27**(8):1170–9.
35. Pereira MA, FitzerGerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, et al. A collection of Physical Activity Questionnaires for health-related research. *Med Sci Sports Exerc* Jun 1997;**29**(6 Suppl):S1–205.
36. Hagströmer M, Oja P, Sjöström M. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. *Publ Health Nutr* Sep 2006;**9**(6):755–62. https://doi.org/10.1079/phn2005898.
37. Adams R. Revised physical activity readiness questionnaire. *Can Fam Physician* Apr 1999;**45**:1004–5. 992, 995.
38. Astrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. *J Appl Physiol* Sep 1954;**7**(2):218–21. https://doi.org/10.1152/jappl.1954.7.2.218.
39. Buono MJ, Roby JJ, Micale FG, Sallis JF. Predicting maximal oxygen uptake in children. *Modif Astrand-Ryhming Test* 1989;**1**(3):278–83.
40. Buttar KK. A review: maximal oxygen uptake (VO 2 max) and its estimation methods. *Int J Phys Educ Sports Health* 2019;**6**(6):24–32.
41. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* Sep 2000;**32**(9 Suppl):S498–504. https://doi.org/10.1097/00005768-200009001-00009.
42. Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the international physical activity questionnaire short form (IPAQ-SF): a systematic review. *Int J Behav Nutr Phys Activ* Oct 21 2011;**8**:115. https://doi.org/10.1186/1479-5868-8-115.
43. Chun MY. Validity and reliability of Korean version of international physical activity questionnaire short form in the elderly. *Korean J Fam Med* May 2012;**33**(3):144–51. https://doi.org/10.4082/kjfm.2012.33.3.144.
44. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* Aug 2003;**35**(8):1381–95. https://doi.org/10.1249/01.mss.0000078924.61453.fb.
45. Papathanasiou G, Georgoudis G, Papandreou M, Spyropoulos P, Georgakopoulos D, Kalfakakou V, et al. Reliability measures of the short international physical activity questionnaire (IPAQ) in Greek young adults. *Hellenic J Cardiol* Jul-Aug 2009;**50**(4):283–94.

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Original Research

Vulnerable migrants' access to healthcare in the early stages of the COVID-19 pandemic in the UK

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ABSTRACT

Objectives: To understand the living conditions, changes in the service user profile, and needs of vulnerable migrants trying to access healthcare in the early stages of the COVID-19 pandemic.
Study design: Mixed methods study; using quantitative questionnaire data collected from migrant service users of Doctors of the World UK (DOTW UK) with qualitative data from free-text notes.
Methods: DOTW UK provides drop-in clinics to vulnerable migrants. Consultations switched to remote during the UK's first lockdown. We compared patient profile, well-being, healthcare access and reason for consultations of individuals attending the virtual clinic between March and September 2020 to those of the prepandemic periods between 2011 and 2018.
Results: During the pandemic, consultations dropped to under half of the prepandemic numbers, with the shift to remote consultations attracting more users outside of London. DOTW UK's user base changed to include a greater proportion of asylum seekers, younger adults (18–34) and individuals reporting good health. Socio-economic conditions and housing stability deteriorated for the majority of users. Those in the greatest need of healthcare appeared to be less able to access remote services. General practitioner (GP) registration remained the most common reason for contacting the virtual clinic with a lack of knowledge of the healthcare system being the main barrier to access.
Conclusion: The shift to virtual consultations may have exacerbated existing inequalities in healthcare access for vulnerable migrants. Given that many clinical services continue to operate remotely, it is important to consider the impact such actions have on vulnerable migrants and find ways to support access.

Introduction

The advent of the coronavirus (COVID-19) global pandemic has had a wide impact on populations across the world but with marked disparities in infection and survival rates. Early in the pandemic, it was evident that social and economic inequalities shaped people's vulnerability to the disease.[1] In the United Kingdom (UK) and United States (US), Black, Asian and minority ethnic (BAME) groups including migrants were found to experience higher infection rates.[2] The pandemic generated economic and social conditions with potential for a deleterious effect on migrant health. Findings from the UK Household Longitudinal Survey showed that migrant men experienced worse economic impacts and mental health than those born in the UK. During the UK's first lockdown, they were more likely to experience job loss, financial hardship and a reduction in working hours,[3] and BAME migrants received a lower level of financial protection.[3,4] Migrant women faced more barriers to access healthcare services during the pandemic.[5] Filipino migrants were more likely to be working in front-line positions, which increased their risk of exposure to the disease;[6] those without documents were particularly vulnerable: working and living in crowded and unsafe conditions with few social distancing or hygiene measures and fearful of accessing healthcare services.[6] Research looking at forced migrant survivors of sexual and gender-based violence found that they lived on very low incomes and had to choose between purchasing food, hygiene products and mobile phone data.[7,8] Research with healthcare providers, asylum seekers and refugees identified the digitisation of primary care and the severing of connections to support networks

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as a barrier to healthcare access.[9] Undocumented migrants' struggles to register with a general practitioner (GP) also presented an obstacle to vaccination.[10]

Clearly, the pandemic and associated measures are experienced differently according to socio-economic and migration status. However, there is a gap in knowledge about the impact of the pandemic on the most vulnerable migrants, namely rejected asylum seekers and undocumented migrants known to struggle with healthcare access prepandemic.[11] Such migrants are unidentifiable in routine or specialised surveys. This article brings new knowledge of the needs of vulnerable migrants trying to access healthcare in the early stages of the COVID-19 pandemic. Using a unique dataset from vulnerable migrant service users assembled by DOTW UK via cross-referenced social and medical questionnaires and free-text notes, we compare the health concerns and well-being status of individuals attending the clinic during and before the pandemic. We explore patterns of change in DOTW UK's service user base and the pandemic's impact on migrant groups known to struggle to access healthcare.

Methods

The data collected by DOTW UK represent a cohort of service users at risk of vulnerability. As a non-governmental organisation, DOTW UK uses consultations with volunteer doctors and nurses to support excluded people to access healthcare. From 2011 until the pandemic, most consultations were provided in a face-to-face format by clinics based in London and Brighton (now defunct). All consultations switched to a telephone service on 17th March 2020 in the UK's first lockdown. Data were collected during a phone conversation with a volunteer caseworker concerning service users' demographic profile, well-being, healthcare access and the reason for making contact (service user information form and social form) and during the consultation with a volunteer GP where this was necessary (medical form); all forms included space for free-text notes. Detailed information on the process of data collection is published elsewhere.[12]

We focus on DOTW UK's migrant service users, which include undocumented migrants, asylum seekers, refugees, European Union (EU) citizens, non-EU citizens with valid visas and refused asylum seekers. We exclude British citizens because they form a small minority of DOTW UK's service users (0.3%). With appropriate anonymisation, quantitative data were extracted from the service user information form and matched to the social and medical forms.[c] We focus on what we term the 'pandemic' period, from the DOTW UK move to remote consultations in March 2020, until the end of September 2020, and the comparative 'prepandemic' periods of the same months in 2011–2018, to explore the differences in trends between these two periods. We analyse a sample of free-text notes (those collected in April and July 2020) which we term qualitative data.

Quantitative analysis

Based on the matched results from service user and social forms, we compare 6268 unique service user consultations across the two periods (5947 before and 321 during the pandemic). Incomplete/erroneous data were corrected following discussions with DOTW UK: service users with missing information were removed from datasets and misspellings were manually corrected. The data contain missing information for some variables, which we excluded from the calculations. The effective sample sizes used in our analyses and missing data are included in the figures.

Questions asked are mainly consistent between the two periods. The sociodemographic indicators included sex, age, economic situation, immigration status and housing situation. Geographic location refers to consultations in London vs other locations. Well-being status is defined as self-reported general and psychological health. Questions about psychological health differed during pandemic/prepandemic periods. In 2011–2018, service users were asked 'how is your psychological health?' From 2020, DOTW UK used the Patient Health Questionnaire-2 (PHQ-2) question 'Over the last 2 weeks, how often have you been bothered by feeling down/depressed/hopeless?'

We use descriptive statistics, usually percentage distributions given the nature of the variables, to compare prepandemic and during-pandemic data. For each percentage, we compute 95% confidence intervals to assess differences across answer categories. We use a chi-squared test (significant at 0.05 unless specified) to assess the differences in answer distributions. When appropriate, we compare results across immigration statuses, using confidence intervals and chi-squared tests. Throughout, we use a minimum cell count of five observations.

Qualitative analysis

We use free-text notes to enable us to make sense of patterns observed in the quantitative analysis. We extract all available free-text notes for migrant service users for April and June 2020. From a total of 107, we exclude 12 as they were UK nationals or contained no data. The remaining 96 sets of notes range from a few lines to several pages and outline details of health concerns and life situations, providing an account of engagement until the problem was resolved or the contact was lost. A content analysis consists of two stages: first, we summarise characteristics of the individual case focusing on 1) service users' current health status, 2) the health services required, 3) their life situation, 4) any barriers and facilitators to accessing health services and 5) how their health concerns were resolved (or not). Then, we compare across cases to understand the range of concerns faced by service users.

The Ethical Review Committee of the University of Birmingham granted full ethical approval. All data were anonymised by DOTW UK before they were securely shared with the authors. DOTW UK's service users gave consent for data sharing when data were collected. Data were stored on encrypted devices.

Results

Number of consultations

The number of consultations from March to September in 2011–2018 was 5947, and it was 321 in 2020. Fig. 1 shows that the monthly trend of pandemic consultations is similar to the prepandemic period but dropped to under half that of the prepandemic period.

Sociodemographic characteristics

Table 1 shows that sex was equally distributed throughout the periods with females accounting for approximately 49% (2982/6024) of consultations. Service users were younger during the pandemic with a significant increase in the proportion of 18–34-year-olds from 42.7% (2476/5793) in the prepandemic period to 50.8% (163/321), and the 35–59 age group decreased from 49.6%

[c] The match was performed using unique consultation identifiers – note that any repeat consultations with the same service user are also excluded so that we only have unique service users in the data.

Fig. 1. Yearly averaged number of consultations during the prepandemic and pandemic periods ($N = 6268$). Values before the pandemic are averaged.

Table 1
Variable descriptions and descriptive statistics for service users prepandemic and during pandemic periods.

Variables	Prepandemic (%)	Prepandemic (*N*)	Pandemic (%)	Pandemic (*N*)	Chi- squared value	*P*-values
Sex (*N* = 6024)						
Female	49.6	2845	48.2	137	0.190	0.663
Male	50.4	2895	51.8	147		
Age group (*N* = 6114)						
0–17	2.8	164	3.1	10	8.815	0.032
18–34	42.7	2476	50.8	163		
35–59	49.6	2876	41.4	133		
60+	4.8	277	4.7	15		
Location of residence (*N* = 6100)						
London	89.8	5191	82.3	261	17.468	0.000
Outside of London	10.2	592	17.7	56		
What have you been helped with today? (*N* = 6026)						
GP registration	84.9	4843	76.6	246	15.771	0.000
NHS cost	53.2	3035	22.1	71	117.539	0.000
Antenatal care	3.3	189	8.7	28	25.621	0.000
Immigration (2013–2018, $N = 4627$)	15.4	661	6.5	21	18.444	0.000
A&E/walk in	5.2	294	4.7	15	0.144	0.704
Second care charging	2.8	160	3.1	10	0.107	0.744
Dentist	5.5	314	2.8	9	4.368	0.037
Termination of pregnancy	0.7	40	2.5	8	12.337	0.000
Foodbank	1.9	109	1.6	5	0.204	0.652
The proportions of GP registration by immigration status						
Undocumented ($N = 3621$)	87.3	3006	77.3	136	14.542	0.000
Asylum ($N = 797$)	81.8	576	86	80	0.997	0.318
Others ($N = 1158$)	85.9	959	63.4	26	15.672	0.000
In the last 3 months approximately how much money per month did you have to live on? (2013–2018, *N* = 4032)						
Above poverty threshold	17.7	664	9	25	13.976	0.000
Below poverty threshold	82.3	3089	91	254		
Housing situation of service users (*N* = 5992)						
Roofless/houseless	3.2	182	5.8	18	2246.552	0.000
Insecure/inadequate house	2.4	137	63	196		
Secure tenancy	91.6	5203	17.4	54		
Others	2.8	159	13.8	43		
Have you experienced any obstacles/barriers when accessing healthcare? (*N* = 5863)						
Lack of knowledge	25.4	1410	23.4	75	0.693	0.405
Admin barrier	25.1	1390	11.8	38	28.884	0.000
Fear of arrest	10.4	579	6.9	22	4.260	0.039
Language barrier	12.9	714	5.6	18	14.701	0.000
Financial barrier	3.7	206	4.7	15	0.764	0.382
Denied health coverage	8.1	450	4.4	14	5.881	0.015
Other barrier	2	109	2.2	7	0.072	0.789
Denied by healthcare provider ($N = 5598$)	15.3	808	1.9	6	44.002	0.000

Note: Percentages may not add up to 100% due to rounding. The prepandemic period represents March to September in 2011–2018 unless specified. The pandemic period represents March to September in 2020. The observation numbers ('*N*'s) are presented for each variable unless specified. EU citizens and non-EU citizens with valid visas make up the 'others' immigration status.'

(2876/5793) to 41.4% (133/321). The share of those over 59 or under 18 years remained similar.

During the pandemic, more service users (91%, 254/279) reported their monthly income as below the poverty line (£836 per month), a significant increase from prepandemic (82.3%, 3089/3753). Free-text notes indicated that most had no employment during the pandemic and relied on support from family and friends.

About 91% (5681/6268) of service users reported an immigration status, which we categorised as follows:

- Undocumented/no legal status: e.g. those who refused asylums, visa-overstayers
- Asylum seekers and refugees: ongoing asylum claims; granted refugee status
- Others: e.g. EU citizens; non-EU with a valid visa

Fig. 2 shows the proportion of asylum seekers which increased from 13.6% (732/5371) to 30% (93/310) during the pandemic. The share of undocumented migrants and others dropped from 65.1% (3498/5371) to 56.8% (176/310), and from 21.2% (1141/5371) to 13.2% (41/310), respectively. Analysis of free-text notes indicates that a number of service users had sought help while living in hotel accommodation; two of whom were concerned about the impact of poor quality hotel food on their health. The notes identified a few instances of "other" service users seeking advice having been trapped in the UK after travel plans were disrupted by the pandemic.

Housing

DOTW UK's location is in London. The shift to remote interactions saw the share of service users residing outside of London increase significantly, from 10.2% (592/5783) in the prepandemic period to 17.7% (56/317). During the pandemic, the proportion of service users living in secure tenancies reduced by 74.2% to only 17.4% (54/311) (Table 1). Undocumented migrants in particular reported a decline in housing stability from 92.7% (3196/3447) in secure housing to 18.5% (32/173). Analysis of notes showed that most now lived in shared rented accommodation with friends or family, often with the rent paid for by family members. The notes indicate that most felt safe for now, however, a small number reported living in exploitative circumstances or being concerned about housing stability. Some 46% (40/87) of asylum seeker service users were in 'other' types of housing during the pandemic, most likely hotels.

Health

We look at the health status through measures of general and psychological health (Fig. 3). The proportion of service users with good general health during the pandemic increased (from 38.7%, 2171/5603 to 47.4%, 144/304). Likewise, the share of service users with good psychological health increased significantly, while those with fair or bad psychological health status decreased significantly. Analysis of notes indicated that users with no or minor current health problems tended to contact DOTW UK to help them to register with a GP (possibly in case they got infected with COVID-19) while pregnant women who contacted DOTW UK for help with access to antenatal care were also in good health.

Breaking general health status down by the immigration status (Fig. 4), some variation was observed during the pandemic (significant at 0.10 level) but the general health of undocumented and other service users showed little difference. The health profile of service users within the asylum seeker/refugee category was more skewed toward poorer outcomes. Asylum seekers also showed significantly poorer psychological health than undocumented and "others" during the pandemic.

Reasons for consultation

Of 5705 service users, 59.8% before the pandemic and 38% of 321 service users during the pandemic gave two or more reasons for engaging with DOTW UK. GP registration was the main reason for consultations (84.9% before, 4843/5705 and 76.6% during, 246/321, respectively) although for undocumented migrants and "others" the proportion consulting for GP registration was reduced (see Table 1). Our analysis of notes indicates a range of reasons for needing GP registration, from seeking registration in case a health problem should arise (sometimes following a prior refusal) or to access medication, to more complex situations, including multiple acute health problems and/or the need to be classified as extremely vulnerable to receive help during the pandemic. Help with National Health Service (NHS) costs was a highly ranked reason in both

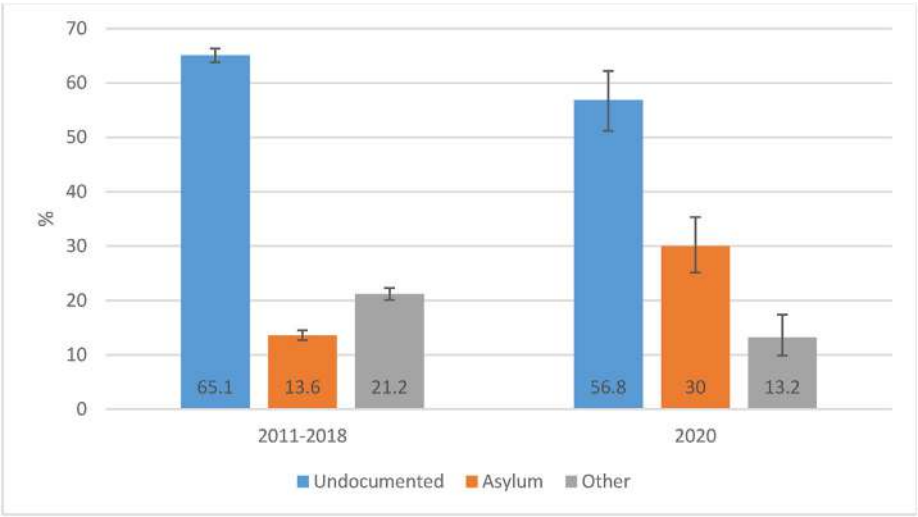

Fig. 2. Immigration status of service users visiting DOTW UK prepandemic ($N = 5371$, 576 observations missing) and pandemic ($N = 310$, 11 missing) periods.

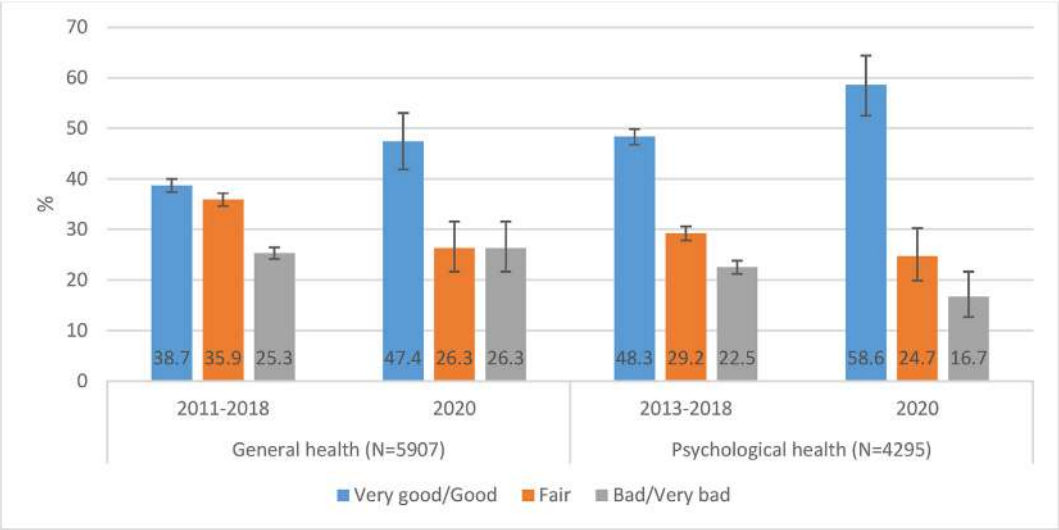

Fig. 3. Self-reported health status of service users during prepandemic and pandemic periods. For general health, $N = 5603$ (344 missing) in the prepandemic period and $N = 304$ (17 missing) during the pandemic period. For psychological health, $N = 4032$ (1915 missing, because 2011 and 2012 data do not have information about psychological health) during the prepandemic period and $N = 263$ (58 missing) during the pandemic period.

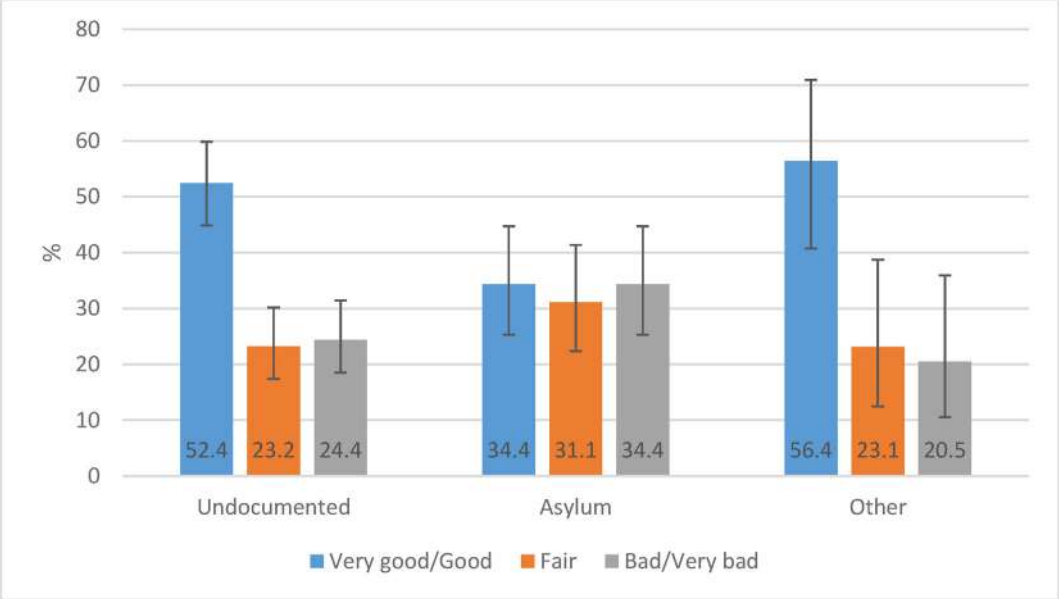

Fig. 4. Self-reported general health by the immigration status of service users who visited DOTW UK during the pandemic period ($N = 297$, 24 missing). $N = 168$, 90 and 39, for undocumented migrants, asylum seekers and others, respectively. This is a small sample because this figure only covers the pandemic period.

periods. Notes showed a few instances of service users needing help with bills incurred while receiving hospital care.

Barriers to healthcare access

As noted above, help to access healthcare was the main reason for consulting. Users faced multiple barriers including lack of understanding of the healthcare system (23.4%, 75/321). Administrative barriers (11.8%, 38/321) were important although reduced from prepandemic times. The notes recorded that some GP practices refused to register new patients during the pandemic with individuals struggling to communicate with practices registering remotely. The notes also evidenced that technological or financial barriers impeded GP registration (i.e. poor access to devices and data). A few service users worried that they might be detained by immigration services if they tried to register. Finally, financial barriers were raised linked to the ability to pay for medication or secondary care. Most barriers were resolved by DOTW UK although the notes revealed that seeking resolution could be a lengthy process, requiring multiple interventions by DOTW UK.

Discussion

In this study, we sought to understand the living conditions, changes in service user profile and needs of vulnerable migrants trying to access healthcare in the early stages of the COVID-19 pandemic. There were clear differences in the number and needs of service users accessing DOTW UK's services prepandemic and

during the pandemic. As services shifted to remote, consultations reduced markedly and the profile of service users changed to younger users and asylum seekers. An increase in the number of asylum seekers being housed in hotels in London during the pandemic[d] was one factor driving this change as they were not supported by accommodation providers to access GP registration. Additionally, it may reflect that they were given free access to Wi-fi and thus able to engage remotely with DOTW UK.[13]

There was a reduction in older users, undocumented migrants and individuals with poor health which could mean that those in the greatest need were being excluded, perhaps because of a digital divide evidenced in some groups of migrants prepandemic and mentioned in the free-notes around access to GPs.[15] The relative decrease in undocumented service users may relate to difficulties accessing the necessary devices, telephone minutes and data when destitute.[7] Certainly we find evidence that the shift to virtual consultations increased existing inequalities in healthcare access for vulnerable migrants reinforcing previous work.[9] The income and living conditions of users declined with more reporting low incomes and living in insecure housing reflecting evidence elsewhere of migrants experiencing higher likelihood of financial hardships,[3,16] unsurprising given the predominance of vulnerable migrants in service industries worst hit in lockdown.[17] Such hardship may have promoted movement from rented housing to sharing with friends and family.

Although the numbers of users reporting good health increased in the pandemic, we find that asylum seekers were more likely to report poor general and psychological health reflecting concerns expressed by the Refugee Council of the healthcare implications of living in hotels.[13] Our findings reflect the alarm expressed by NGOs, particularly after an incident in which an asylum seeker, suffering from deteriorating mental health after a lengthy hotel residence, stabbed six others and was shot dead by police.[14]

The need to register with a GP continued to be the most important reason for contacting DOTW UK with the main barrier to registration being a lack of knowledge, reflecting the importance of cultural health capital to enable meaningful healthcare access.[18] In addition, we suggest that anxiety associated with the possibility of COVID-19 infection prompted some migrants to register with healthcare providers although they were in good health.

The proportion of individuals reporting being denied access to healthcare and facing administrative barriers reduced during the pandemic. This may reflect a more open attitude to offering healthcare to undocumented migrants as public health officials promoted the importance of attending to the health of all, although organisations such as the Joint Council for the Welfare of Immigrants (JCWI) reported that migrants remained fearful of using such services.[19]

Limitations

Our data analysis covers only the early pandemic period. Over time, service users may have become more accustomed to remote provision and returned in larger numbers. The questionnaire data do not cover the whole population, because of the incomplete match between service users, social and medical forms and missing information. The variable for psychological health was defined using different questions prepandemic and during-pandemic because DOTW UK updated their questionnaire. The qualitative data only constitute the notes made by volunteers, which provided 'snapshots' but did not respond to systematised questions. Given the shift in data collection from face-to-face to phone conversations may also have affected the nature of responses.

Conclusions

Our paper offers the first quantitative analysis of vulnerable migrants' living conditions and healthcare needs in the COVID-19 pandemic. We highlight a reduction in the number of service users accessing DOTW UK's services. Users reported barriers to access associated with GP registration and healthcare costs. Service users were younger, reported better health and were more likely to be asylum seekers. The reduction in older users and those in poorer health may relate to barriers encountered engaging with DOTW UK via remote consultations. Given that many clinical services continue to operate remotely 18 months after the introduction of the first lockdown, it is important to consider the policy implications of such provision on vulnerable migrants such as older migrants and those in worse health. It is necessary to find ways to provide face-to-face services for excluded groups and to ensure that GP surgeries register patients regardless of the immigration status. Further research is needed to examine the longer-term effects of the pandemic on vulnerable migrants.

Author statements

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Ethical approval

This work has been approved by the ethical committees of the University of Birmingham and Doctors of the World and subjects gave informed consent to the work.

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Competing interests

None declared.

References

1. Cash-Gibson L, Pericàs JM, Martinez-Herrera E, Benach J. Health inequalities in the time of COVID-19: the globally reinforcing need to strengthen health inequalities research capacities. *Int J Health Serv* 2021 Jul 1;**51**(3):300–4.
2. Bhatia M. COVID-19 and BAME group in the United Kingdom. *Int J Community Soc Develop* 2020 Jun 1;**2**(2):269–72.
3. Shen J, Bartram D. Fare differently, feel differently: mental well-being of UK-born and foreign-born working men during the COVID-19 pandemic. *Eur Soc* 2021 Feb 19;**23**(sup1):S370–83.

[d] During the pandemic, the UK's asylum dispersal system which moves people on a no-choice basis into residential housing across the UK was suspended and evictions from dispersal accommodation ceased for failed asylum seekers and new refugees. Many recently arrived asylum seekers were housed in contingency accommodation, with over 40 hotels in use in London alone. Hotel accommodation is intended for short stays but asylum seekers spent many months with limited access to laundry, cooking and other facilities. In some cases, right-wing activists entered the hotels unchallenged to harass occupants and there were reports of high concentrations of COVID-19 cases because of overcrowding in hotels.

4. Hu Y. Intersecting ethnic and native–migrant inequalities in the economic impact of the COVID-19 pandemic in the UK. *Res Soc Stratif Mobil* 2020 Aug 1;**68**:100528.
5. Germain S, Yong A. COVID-19 highlighting inequalities in access to healthcare in england: a case study of ethnic minority and migrant women. *Fem Leg Stud* 2020 Nov 1;**28**(3):301–10.
6. Galam R. Care and solidarity in the time of Covid-19: the pandemic experiences of Filipinos in the UK. *Philippine Stud: Historical Ethnographic Viewpoints* 2020;**68**(3/4):443–66.
7. Pertek S, Phillimore J, McKnight P. *Forced Migration, SGBV and COVID-19: understanding the impact of COVID-19 on forced migrant survivors of SGBV* [Internet]. 2020. Available from: https://www.birmingham.ac.uk/Documents/college-social-sciences/social-policy/iris/2020/sgbv-covid-19.pdf. [Accessed 10 November 2021].
8. Phillimore J, Pertek S, Akyuz S, Darkal H, Hourari J, Ozcurumez S. "We are forgotten": forced migration, sexual and gender based violence and COVID-19. *Violence Against Women* 2021 Sep 17:1–27.
9. Knights F, Carter J, Deal A, Crawshaw AF, Hayward SE, Jones L, et al. Impact of COVID-19 on migrants' access to primary care and implications for vaccine roll-out: a national qualitative study. *Br J Gen Pract* 2021 Apr 16;**71**(709):583–95.
10. Deal A, Hayward SE, Huda M, Knights F, Crawshaw AF, Carter J, et al. Strategies and action points to ensure equitable uptake of COVID-19 vaccinations: a national qualitative interview study to explore the views of undocumented migrants, asylum seekers, and refugees. *J Migration Health* 2021 Jan 1;**4**:100050.
11. Karl-Trummer U, Novak-Zezula S, Metzler B. Access to health care for undocumented migrants in the EU: a first landscape of NowHereland. *Eurohealth* 2010;**16**(1):13–6.
12. Lessard-Phillips L, Lindenmeyer A, Phillimore J, Hamid F, Jones L. *Vulnerable migrants and wellbeing: a pilot study* [Internet]. 2019 Feb. Available from: https://mk0nuffieldfounpg9ee.kinstacdn.com/wp-content/uploads/2019/02/Final-report-February-2019-Project-433831.pdf. [Accessed 10 November 2021].
13. Refugee Council. *Refugee Council raises serious concerns over increasing use of hotels as contingency accommodation for asylum seekers* [Internet]. 2021 Apr. Available from: https://www.ein.org.uk/news/refugee-council-raises-serious-concerns-over-increasing-use-hotels-contingency-accommodation. [Accessed 10 November 2021].
14. Brooks L. *Police name man shot dead by officers after Glasgow knife attack* [Internet]. The Guardian; 2020. Available from: http://www.theguardian.com/uk-news/2020/jun/27/glasgow-hotel-attack-stabbing-suspect-park-inn-mental-health. [Accessed 10 November 2021].
15. Samkange-Zeeb F, Borisova L, Padilla B, Bradby H, Phillimore J, Zeeb H, et al. Superdiversity, migration and use of internet-based health information – results of a cross-sectional survey conducted in 4 European countries. *BMC Publ Health* 2020 Aug 20;**20**(1):1263.
16. Burton-Jeangros C, Duvoisin A, Lachat S, Consoli L, Fakhoury J, Jackson Y. The impact of the covid-19 pandemic and the lockdown on the health and living conditions of undocumented migrants and migrants undergoing legal status regularization. *Front Public Health* 2020 Dec 16;**8**:940.
17. Williams CC, Kayaoglu A. COVID-19 and undeclared work: impacts and policy responses in Europe. *Serv Ind J* 2020 Oct 25;**40**(13–14):914–31.
18. Shim JK. Cultural health capital: a theoretical approach to understanding health care interactions and the dynamics of unequal treatment. *J Health Soc Behav* 2010 Mar 1;**51**(1):1–15.
19. Gardner Z. *Migrants deterred from healthcare during the COVID-19 pandemic* [Internet]. 2021. Available from: https://www.jcwi.org.uk/Handlers/Download.ashx?IDMF=fa346f70-cb08-46c1-b366-9a1f192ff4f3. [Accessed 10 November 2021].

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Original Research

Years of potential life lost and productivity costs due to COVID-19 in Turkey: one yearly evaluation

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ABSTRACT

Objectives: The aim of the study is to calculate the years of life lost (YLL) and years of potential life lost (YPLL) due to COVID-19, according to age groups in Turkey in the first year of the pandemic and the cost of this burden.
Study design: This is an observational study with quantitative analyses.
Methods: YLL due to premature deaths was calculated for men and women by interpolating the number of deaths and the expected life expectancy. YPLL was calculated according to the age 65 years. Productivity loss is an estimation of the cost of time lost at work-related activities—in a scenario analysis—using predetermined wage rates with the human capital theory.
Results: Men lost 205,177 (67.57%) years of life, whereas women lost 125,330 (32.43%) years of life. The YLL average age in men was 63.66 ± 14.66 years, and the YLL average age in women was 66.07 ± 15.46 years. The average YLL age in men was younger than in women ($P < 0.001$). Men lost 65,180 (70.16%) YPLL, whereas women lost 27,723 (29.84%) YPLL. The average YPLL age in women was younger than in men ($P < 0.001$). During one year of the pandemic, premature death cost Turkey 227,396,694 USD, the cost for one premature death was 14,187 USD, and the cost of any year of life lost was 1261 USD.
Conclusion: YLL and YPLLs are very closely associated with COVID-19 deaths in the country. The economic dimensions of the pandemic with human losses are quite high.

Introduction

The COVID-19 pandemic has affected the whole world in all possible dimensions. More than a year after the beginning of pandemic, more than 190 million people were diagnosed with the disease and more than 4 million people lost their lives.[1] COVID-19 has a broad spectrum of infection, mostly affecting the elderly and those with underlying medical problems.[2,3]

A better understanding of the impact of the COVID-19 pandemic on public health can only be achieved by measuring the burden of the disease. There can be several ways of showing the burden of a disease. Therefore, classical epidemiological indicators such as incidence, prevalence, mortality rate, and case fatality rate have been used.[4] Although prevalence and incidence can show the magnitude and severity of the problem for a given condition, still they are insufficient to explain health outcomes. The number of cases is affected by the laboratory conditions and contact tracing practices in countries. Although the mortality rate, particularly the case fatality rate, may show the importance of disease, they are not enough to show the burden of disease. The case fatality rate (CFR) is a crude mortality rate. On the other hand, different formulas that give different results can be used for the CFR. It is known that when calculations are done with formulas that take into account the period between diagnostification of disease and death, CFR takes a higher value.[5] Considering this limitation, the Global Burden of Disease study used premature deaths to calculate the burden of disease. Reporting the early death and disease costs according to diseases has an impact on policy makers' priorities.[6,7] In this context, years of life lost (YLL), which is the age at which deaths occur and the number of deaths, may be more guiding in the establishment of disease control programs and the allocation of economic resources. In this context, YLL, a concept derived from the early age at death and the frequency of death, can be more guiding

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in establishing disease control programs and in allocating economic resources.[7]

Apart from that, social and economic preventions of premature death can be expressed with two more measures. These are YPLL and cost of productivity lost (CPL), which are helpful variables to measure the burden of disease.[8,9] Such an analysis could show the COVID-19-related disease burden and loss of productivity. Calculation of the cost of productivity loss is an economic assessment that does not take into account other economic aspects of COVID-19 (e.g. quarantine, contact tracing, reduction in consumption, direct costs of health care, etc.). It is an economic evaluation based on the loss of production in the society from the individual loss.

Different approaches and responses to the pandemic were seen in different countries since the onset of the disease. Turkey has followed policies to suppress COVID-19 infection. First of all, it was tried to reduce the burden of health services by reducing cases and deaths through shutdown practices. Pandemic approaches according to patients' age are considered to take the disease under control. Some measures, such as the curfew for individuals aged ≥65 years and those aged <20 years, were aimed at age groups; on the other hand, age was taken into consideration in determining priority groups in vaccination applications.

The disease burden of the COVID-19 pandemic is not fully understood, as it is a new disease. However, the calculation of YLL and CPL in the pandemic will play an important role for policy makers decisions. The first COVID-19 official case in Turkey was reported on March 11, 2020. The aim of the study was to calculate the YLL and YPLL due to COVID-19 according to age groups in Turkey in the first year of the pandemic and the cost of this burden.

Methods

Sources of data

The study data were obtained from the surveillance data published on the website of the Ministry of Health, and the necessary data for the calculation of population-adjusted values were obtained from the website of the Turkish Statistical Institute (TUIK). The approval for this study was taken from research ethics committee of Ankara Yıldırım Beyazıt University. Deaths due to COVID-19 were coded by gender and age group. The population of Turkey was used to calculate death, YLL, and YPLL rates per 100,000 population (male: 41,915,985, female: 41,698,377, total 83,614,362).[10] For calculation of YLL, population, number of deaths, and standard life expectancy (LE) for gender and each age range were taken from selected sources.[11,12] YPLL was calculated according to the age 65 years, as this is the retirement age in Turkey.

YLL formula[13,14]:

$$YLL = \frac{KC\,e^{ra}}{(r+\beta)^2}\left[e^{-(r+\beta)(L+a)}[-(r+\beta)(L+a)-1] - e^{-(r+\beta)a}[-(r+\beta)a-1]\right] + \frac{1-K}{r}\left(1-e^{-rL}\right)$$

where a = age of death (years), r = discount rate (usually 3%), β = age-weighting constant (e.g. β = 0.04), K = age-weighting modulation constant (e.g. K = 1), C = adjustment constant for age weights (e.g. C = 0.1658), and L = standard life expectancy at age of death (years).

YPLL formula[15]:

$$YPLL = \sum_{i=0}^{N} di \times (W_U - W_L)$$

where d_i is the number of deaths at the mid-point of each age group; W_U is the upper limit of working age (65 years), and W_L is the lower working age (from 15 to 65 years).

For calculation of the productivity loss, annual average wages, labor employment ratio, discount rate, and inflation rate values were used. These values were taken from Organisation for Economic Co-operation and Development (OECD) and International Labour Organization (ILO) Turkey data.[16,17]

Study design

First, the distribution of deaths due to COVID-19 by gender and each age group was calculated according to death rate per 100,000 population and percentage of total number of deaths (% death). YLL was calculated for men and women by interpolating the number of deaths in each age group and the expected LE for that age group. YLL in the specific gender and age group was calculated as a percentage (% YLL) of the total number of YLLs and the rate of YLL in 100,000 populations. Similar evaluation was done in YPLL.

The human capital theory was used to estimate the productivity loss due to premature death because of COVID-19 pandemic in Turkey. The human capital theory measures the amount of potential social productivity and charges with market values of output lost due to disease-related morbidity and mortality.[9]

It is an estimation of the cost of time lost at work-related activities—in a scenario analysis—using predetermined wage rates with the human capital theory. The formula used in the first step in calculating the productivity loss is the sum of the estimated value of earning for people in the labor force ($Y_{ns}W_{ns}P_{nas}$) that takes into account the annual average earning (Y), labor employment ratio (W), and the probability of survival (P) for each age group (n) and sex (s). That estimate was adjusted for changes in labor productivity (g) and discounted (i) to convert the lifetime earning into a present

Table 1
Number of deaths from COVID-19 by gender and age groups, their rates, and percentage distributions per 100,000 people in the population.

Age groups	Male			Female			Total		
	Deaths	Deaths per 10^5	%Deaths	Deaths	Deaths per 10^5	%Deaths	Deaths	Deaths per 10^5	%Deaths
0–4	27	0.7	0.1	21	0.7	0.2	48	0.7	0.2
5–14	12	0.2	0.1	12	0.2	0.1	24	0.2	0.1
15–24	246	2.5	1.4	134	1.4	1.2	380	2.0	1.3
25–49	657	6.8	3.6	312	3.3	2.8	969	5.1	3.3
50–64	3227	43.7	17.8	1312	17.9	11.7	4539	30.8	15.5
65–69	4255	134.5	23.5	2235	66.7	20.0	6490	99.6	22.2
70–79	5502	356.3	30.4	3262	167.9	29.2	8764	251.3	29.9
80-+	4193	735.1	23.1	3883	405.6	34.8	8076	528.6	27.6
Total	18,119	42.6	100.0	11,171	23.0	100.0	29,290	32.9	100.0

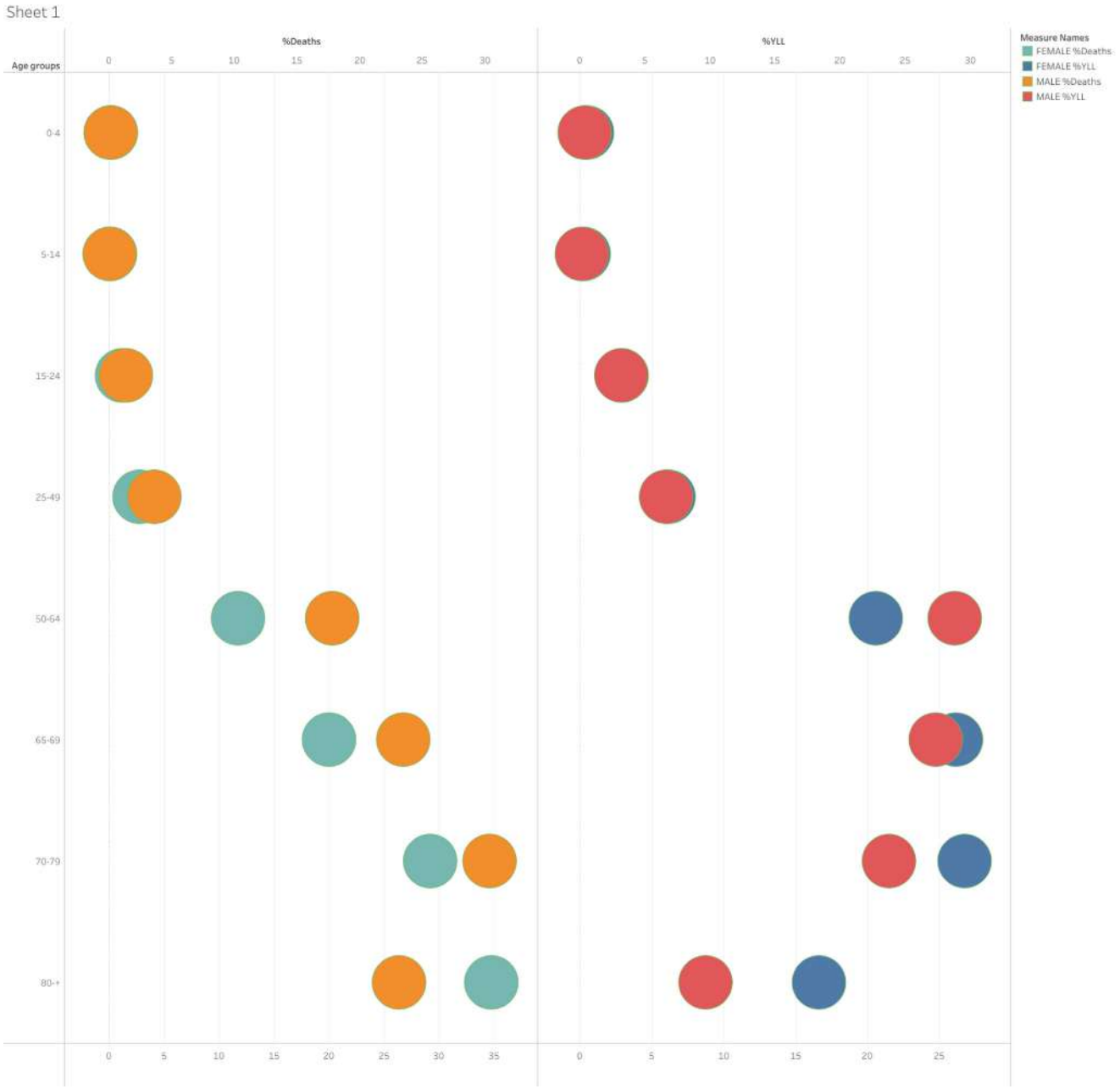

Fig. 1. Percentage distribution of deaths and years of life lost (YLL) due to COVID-19 by gender and age groups.

value. The discounted rate adjustment is used to express the value of the future costs in present value. Finally, to express the productivity loss in constant prices, we deflated average earnings using the average of the last 5 years of deflation of gross product of Turkey. This procedure is necessary to adjust the effect of inflation (α). İnflation is an increase in the general level of prices of goods and services in an economy over a period usually as measured by the Gross National Product.[9,18,19] Costs were expressed in US Dollars ($1 = 7,3670 TL) on the midday of the working period (August 15, 2020).

Statistical analysis

The study database was prepared in Excel program. Population and COVID-19 deaths by age groups for men and women were recorded in this Excel database. SPSS 15.0 program was used for the study data analysis. The mean and standard deviation of the classified arrays were calculated in the distribution of YLL and YPLL by age groups. The *t*-test was used to compare the groups. Statistical significance level was accepted as $P < 0.05$.

Results

In the first year of the pandemic, 29,290 people died from COVID-19, 18,119 of which were men (61.86%) and 11,171 were women (38.14%). The average age at death in men was 69.79 ± 13.19 years, and the average age at death in women was 72.68 ± 13.12 years. The average age at death in men was younger than in women ($P < 0.001$). Death due to COVID-19 was higher in

Table 2
Years of life lost (YLL) due to COVID-19 by gender and age groups, rates, and percentage distributions per 100,000 people in the population.

Age groups	Male			Female			Total		
	YLLs	YLL per 10^5	%YLL	YLLs	YLL per 10^5	%YLL	YLLs	YLL per 10^5	%YLL
0–4	810	21.5	0.4	635	21.3	0.5	1445	21.4	0.5
5–14	349	5.3	0.2	353	5.6	0.3	702	5.4	0.2
15–24	6566	66.7	3.2	3658	38.9	2.9	10,224	53.1	3.4
25–49	13,631	141.8	6.6	7750	82.3	6.2	21,381	112.4	7.0
50–64	59,104	800.2	28.8	25,793	351.4	20.6	84,897	576.5	28.0
65–69	56,123	1773.8	27.4	32,771	978.5	26.1	88,894	1364.8	29.3
70–79	48,745	3156.2	23.8	33,532	1726.1	26.8	82,277	2359.5	27.1
80-+	19,849	3479.7	9.7	20,838	2176.6	16.6	40,687	2663.1	13.4
Total	205,177	419.2	100.0	125,330	300.6	100.00	303,653	360.5	100.0

Table 3
Numbers of potential years of life lost (YPLL) from COVID-19 by gender and age groups, rates, and percentage distributions per 100,000 people in the population.

Age groups	Male			Female			Total		
	YPLL	YPLL per 10^5	%YPLL	YPLL	YPLL per 10^5	%YPLL	YPLL	YPLL per 10^5	%YPLL
15–24	1209	12.3	1.9	1344	13.6	4.8	2553	13.3	2.8
25–49	30,144	313.5	46.2	14,292	148.6	51.6	44,436	233.5	47.8
50–64	33,827	458.0	51.9	12,087	163.6	43.6	45,914	311.8	49.4
Total	65,180	158.8	100.0	27,723	69.8	100.0	92,903	133.7	100.0

Table 4
Cost of premature death in the population aged >15 years ($, August 15, 2020).

Gender	Total premature mortality cost	Premature mortality cost per death	Premature mortality cost per YLL
Men	1,331,149,879 ₺	73,625.54 ₺	6524.66 ₺
	180,690,902.6 $	9993.96 $	885.66 $
Women	344,081,569.8 ₺	30,892.58 ₺	2767.22 ₺
	46,705,792.01 $	4193.37 $	375.62 $
Total	1,675,231,449 ₺	104,518.13 ₺	9291.88 ₺
	227,396,694.6 $	14,187.34 $	1261.28 $

YLL, years of life lost.

men aged 50–64 and 65–69 years and in women aged ≥80 years ($P < 0.001$) (see Table 1).

Men lost 205,177 (67.57%) years of life, whereas women lost 125,330 (32.43%) years of life. The YLL average age in men was 63.66 ± 14.66, and the YLL average age in women was 66.07 ± 15.46. The average YLL age in men was younger than in women ($P < 0.001$). YLL was found to be high in the 50–69 years age group in men, whereas in women, YLL was high in young ages and those aged ≥80 years ($P < 0.001$) (Fig. 1, Table 2).

%YLL/%mortality ratio was calculated according to age groups for both genders in the study. In men, the ratio was 0.38, 0.41, 0.43, 0.55, 0.62, 0.86, 1.28, and 2.39 for 0–4, 5–14, 15–24, 25–49, 50–64, 65–69, 70–79, and ≥80 years age groups, respectively, whereas in women, it was 0.37, 0.39, 0.41, 0.45, 0.57, 0.77, 1.09, and 2.09 respectively.

A highly positive correlation was found between death and YLL rates per 100,000 people in the population in men (r = 0.917; $P = 0.001$), in women (r = 0.929; $P = 0.001$), and in total (r = 0.982; $P < 0.001$).

Men lost 65,180 (70.16%) of the YPLL, whereas women lost 27,723 (29.84%). The average age of YPLL in men was 47.05 ± 10.59 years, whereas in women, it was 47.87 ± 11.28 years. The average YPLL age in women was younger than in men ($P < 0.001$). YPLL was found to be high in men included in 50–64 years age group and in women in 25–49 years age group and those who were old ($P < 0.001$) (see Table 3).

During 1 year of the pandemic, premature death cost Turkey 227,396,694 USD, the cost for one premature death was 14,187 USD, and the cost of any year of life lost was 1261 USD (see Table 4).

Discussion

Factors such as death due to COVID-19, number of cases, fatality rate, vaccination rate, and mutation contribute in the pandemic uncertainty day by day. Turkey has been one of the most affected countries since the World Health Organization declared the new coronavirus disease a pandemic. Calculation of cost of potential productivity lost and productive YLL help to understand better the impact of this pandemic on public health. The rapidly changing epidemiology of the ongoing pandemic makes it more difficult for the local health services to fight the disease. The burden of disease and the demand for healthcare services are increasing with the epidemic growth; countries are focusing on preventing and treating the conditions that cause the disease. Healthcare measures presented in this study are predicted to be very helpful in guiding the policy and decision makers.

Information about the economic impact of the current pandemic also strengthens the data pool of epidemiology. It was found from this study that there is a significant difference between the average age at death and the average age of YLL in the 1-year period of the pandemic in Turkey, a country with a population of 84 million. There was found a 6-year difference in men (mean age at death: 69.79 years; mean age at YLL: 63.67 years) and women (72.68; 66.07, respectively). When the analyses are made in terms of productivity, it shows that COVID-19 has brought more social burden than expected. High YLL and YPLL values are related to the age at which the disease was diagnosed, age at death, and survival time.[20] As COVID-19 is an infectious disease, the period between diagnosis and death is short. Therefore, although YLL is expected to be seen in advanced ages, where deaths are

predominant, premature deaths are collected in the 50–69 years age group. The YLL men/women ratio is lower, 0.95, in 5–14 years age group and higher, 2.24, in 50–64 years age group. The high YLL and YPLL values in young age groups in women comparing to men are due to the higher LE of women.

High % YLL/% mortality ratio indicates high mortality. Considering the values in this study, COVID-19 is the most mortal in men and women aged >70 years. The high % YLL/% mortality ratio can be considered as an indicator using two values. It can be considered as a good indicator to evaluate the age distribution of deaths. A similar indicator might be to show a strong positive correlation between death rates and YLL.

The study of Nurchis et al. stated that the high disease burden of COVID-19 is mainly caused by death. Almost 99.48% of Disability-adjusted life years (DALYs) were from YLL.[13] Studies show that 45 years and older age group contributes to more than 70% of YPLL in all countries.[5] In their studies across 81 countries, Arolas et al. found that more than 20.5 million years of life were lost to COVID-19 globally, three-quarters of YLL are from people dying in ages below 75 years, and almost one-third of them from deaths below 55 years. Also, it was found that men had 45% more YLL than women.[21] Most of the data in articles come from developed countries. The tragedy is in undeveloped and developing countries, which have worse health systems.[5]

In this study, the human capital theory was used to calculate the production loss. Compensation of loss in women was lower than in men. This is because the participation rate of women in labor force in Turkey is lower than that of men. This situation is similar to the results in other developing countries. In this study, the labor force participation rate was 72% for men and 34% for women, according to OECD Turkey 2020 data.[16]

There are some limitations to this study. Restrictions caused by COVID-19 pandemic, diagnostic treatment costs, and productivity losses of patients were not included in the evaluations. One of the most important limitations is the use of only non-reliable production data in calculations. As the household activity is not charged, women's death due to COVID-19 pandemic is calculated less than its real values. In the Nurchis et al. study, it was stated that the productivity loss was largely due to premature deaths, and the number of deaths in the 60–69 years working age group was 10 times higher than in the 40–49 years age group.[13] There was a total productivity loss of around 143 million Euros for the 60–69 years age group, which represents 0.08% of national GDP, which is lower than the loss in younger age groups. In this study, although the productivity loss because of absenteeism is lower than the productivity loss due to early death, the impact was found to cause an average individual loss of approximately 915 Euros and a societal loss of roughly 100 million Euros at both the individual and societal level.[13] Currently, national administration is making great efforts to manage and control the pandemic by channeling their available healthcare resources and measures to prevent an increase in cases.

The results of the first year of the COVID-19 pandemic related to the burden of disease, such as YLL and YPLL, showed that the losses were higher than those calculated by deaths. In the control measures such as quarantine practices, vaccination priorities to be applied in COVID-19, and future pandemics, decisions should be made by using not only death data but also indicators related to disease burden.

Author statements

Ethical approval

This study was approved by University of Ankara Yıldırım Beyazıt Ethics Board.

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Competing interests

None declared.

References

1. *WHO Weekly epidemiological update*. 20 July 2021 [Internet]. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19—20-july-2021.
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med [Internet]* 2020;**382**(13):1199–207. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31995857.
3. Davies NG, Klepac P, Liu Y, Prem K, Jit M, Pearson CAB, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med [Internet]* 2020 Aug 16;**26**(8):1205–11. Available from: http://www.nature.com/articles/s41591-020-0962-9.
4. Oh I-H, Ock M, Jang SY, Go D-S, Kim Y-E, Jung Y-S, et al. Years of life lost attributable to COVID-19 in high-incidence countries. *J Kor Med Sci [Internet]* 2020;**35**(32). Available from: https://jkms.org/DOIx.php?id=10.3346/jkms.2020.35.e300.
5. Mohanty SK, Dubey M, Mishra US, Sahoo U. Impact of COVID-19 attributable deaths on longevity, premature mortality and DALY: estimates of USA, Italy, Sweden and Germany. *medRxiv [Internet]* 2020 Jan 1. 2020.07.06.20147009. Available from: http://medrxiv.org/content/early/2020/07/07/2020.07.06.20147009.abstract.
6. Wyper GMA, Assunção RMA, Colzani E, Grant I, Haagsma JA, Lagerweij G, et al. Burden of disease methods: a guide to calculate COVID-19 disability-adjusted life years. *Int J Publ Health [Internet]* 2021 Mar 5;**66**. Available from: https://www.ssph-journal.org/articles/10.3389/ijph.2021.619011/full.
7. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet (London, England)* 2012 Dec;**380**(9859):2197–223.
8. Khorasani S, Rezaei S, Rashidian H, Daroudi R. Years of potential life lost and productivity costs due to premature cancer-related mortality in Iran. *Asian Pac J Cancer Prev [Internet]* 2015 Mar 18;**16**(5):1845–50. Available from: http://koreascience.or.kr/journal/view.jsp?kj=POCPA9&py=2015&vnc=v16n5&sp=1845.
9. Hanly PA, Sharp L, Khorasani S, Rezaei S, Rashidian H, Daroudi R. The cost of lost productivity due to premature cancer-related mortality: an economic measure of the cancer burden. *Asian Pac J Cancer Prev [Internet]* 2015 Mar 26;**14**(1):224. Available from: http://koreascience.or.kr/journal/view.jsp?kj=POCPA9&py=2015&vnc=v16n5&sp=1845.
10. [Internet] *The results of address based population registration system, 2020*. TURKSTAT; 2021 [cited 2021 Feb 4]. Available from: https://data.tuik.gov.tr/Bulten/Index?p=The-Results-of-Address-Based-Population-Registration-System-2020-37210&dil=2.
11. Turkey, The Mınıstry Of Health Of Yearbook, Health Statıstıcs 2019. *Republic of Turkey Ministry of health general directorate of health information systems, 2021* [Internet]. 2021. Available from: https://sbsgm.saglik.gov.tr/Eklenti/40566/0/health-statistics-yearbook-2019pdf.pdf.
12. TUİK. *İstatistiklerle aile, 2020* [Internet]. 2021. Available from: https://data.tuik.gov.tr/Bulten/Index?p=Istatistiklerle-Aile-2020-37251#:~:text=ADNKS sonuçlarına göre%2C 2020 yılında Türkiye'de toplam 22 milyon,4 bin 518 olduğu görüldü.
13. Nurchis MC, Pascucci D, Sapienza M, Villani L, D'Ambrosio F, Castrini F, et al. Impact of the burden of COVID-19 in Italy: results of disability-adjusted life years (DALYs) and productivity loss. *Int J Environ Res Publ Health [Internet]* 2020 Jun 13;**17**(12):4233. Available from: https://www.mdpi.com/1660-4601/17/12/4233.
14. Prüss-Üstün A, Mathers C, Corvalán C, Woodward A. Introduction and methods: assessing the environmental burden of disease at national and local levels. *WHO Environ Burd Dis* 2003. Ser No 1.
15. Najafi F, Karami-Matin B, Rezaei S, Khosravi A, Soofi M. Productivity costs and Years of Potential Life Lostassociated with five leading causes of death: Evidence from Iran (2006-2010). Med J Islam Repub Iran [Internet]. 30:412. Available from: https://www.marketwatch.com/press-release/the-global-gambling-mar- ket-is-expected-to-reach-revenues-of-over-525-billion-by-2023-2018-09-18.
16. [Internet] *OECD economic surveys: Turkey 2021*. OECD; 2021 (OECD Economic Surveys: Turkey). Available from: https://data.oecd.org/turkey.htm.
17. [Internet] *Statistics on unemployment and supplementary measures of labour underutilization*. International Labour Organization; 2021 [cited 2021 Apr 20]. Available from: https://ilostat.ilo.org/topics/unemployment-and-labour-underutilization.

18. Metintas S, Ak G, Metintas M. Potential years of life and productivity loss due to malignant mesothelioma in Turkey. *Arch Environ Occup Health [Internet]* 2020 Nov 16;**75**(8):464–70. Available from: https://www.tandfonline.com/doi/full/10.1080/19338244.2020.1747380.
19. Ortiz-Ortiz KJ, Pérez-Irizarry J, Marín-Centeno H, Ortiz AP, Torres-Berrios N, Torres-Cintrón M, et al. Productivity loss in Puerto Rico's labor market due to cancer mortality. *P R Health Sci J [Internet]* 2010 Sep;**29**(3):241–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20799511.
20. Gardner JW, Sanborn JS. Years of potential life lost (YPLL)—what does it measure? *Epidemiology [Internet]* 1990 Jul;**1**(4):322–9. Available from: http://journals.lww.com/00001648-199007000-00012.
21. Pifarré i Arolas H, Acosta E, López-Casasnovas G, Lo A, Nicodemo C, Riffe T, et al. Years of life lost to COVID-19 in 81 countries. *Sci Rep [Internet]* 2021 Dec 18;**11**(1):3504. Available from: http://www.nature.com/articles/s41598-021-83040-3.