Public Health 223 (2023) 110–116

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

African migrant women acquisition of clay for ingestion during pregnancy in London: a call for action

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ARTICLE INFO

Article history:
Received 13 April 2023
Received in revised form
7 July 2023
Accepted 17 July 2023
Available online 25 August 2023

Keywords:
African migrant women
Clay ingestion during pregnancy
Clay acquisition in London
Social networks
Health risks
Multilevel interventions

ABSTRACT

Objectives: This study aimed to explore how African migrant women go about acquiring clay for ingestion during pregnancy in London against a backdrop of restrictions and warnings by the Food Standard Agency and Public Health England due to the potential health risks to expectant mothers and their unborn babies.
Study design: This was a qualitative study using an interpretative phenomenological approach.
Methods: Individual in-depth interviews and a focus group discussion were used for data collection. Data collection took place between May and August 2020.
Results: Participants acquired clay from African shops and markets in London, countries of origin and online/social media platforms. Due to official restrictions and warnings, transactions were conducted under the counter based on trust between sellers and the women underpinned by shared community identities. However, clay was acquired, social networks emerged as crucial facilitators. The current top-down approach, which is also lacking a regulatory policy framework, has pushed clay transactions underground, thereby leaving pregnant women potentially ingesting toxic clay with little chances of dictation by authorities.
Conclusion: We call on the UK Health Security Agency (UKHSA) and public health practitioners to collaborate with communities to design multilevel/multisectoral interventions as well as the Food Standards Agency (FSA) to consider an appropriate regulatory policy framework.

Introduction

Pica has a slippery definition. It is defined as a disorder that manifests in eating behaviours involving ingesting non-food products such as clay.[1] Clay ingestion (CI), also known as geophagy, is a socially and culturally embedded practice practiced by women during pregnancy in many African countries.[2,3,4,5,6,7,8] Against a backdrop of migration, CI among migrant African women during pregnancy has been identified in the UK, Austria, the Netherlands and Belgium.[9,10] Scientific evidence suggests that some clays intended for human ingestion contain high levels of lead and arsenic, which can lead to low child birth weight, impaired intrauterine growth, impaired neurodevelopment and intestinal blockages.[5,4,9,2,10] Lower levels of exposure to lead is known to affect children's brain development, resulting in reduced IQ and attention span, antisocial behaviour as well as reduced educational attainment.[11] Furthermore, CI exposes pregnant women to potential helminthic infections caused by various parasitic worm species.[12,13] Despite these risks, CI is associated with health benefits under certain circumstances.[14,15,16] However, because clay chemical composition differs depending on the source, it is difficult to assess the potential dangers or benefits to health of all clays. Nevertheless, Madziva and Chinouya[8] have argued that a blanket approach to discouraging CI risks marginalizing the 'other' at the behest of western scientific tradition,[17] hence the call to integrate indigenous and biomedical knowledge, with recognition of the harmful impact of environmental changes to clay.[2] In the absence of this integration, appropriate policy responses and interventions which enable women to make informed choices are required.

In the UK, the discovery of high levels of lead and arsenic in clays intended for human ingestion led the FSA to issue repeated warnings[18,19,20,21] to pregnant and breast-feeding women.[22] Over the past 20 years, the FSA's responses have included placing clay on the

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https://doi.org/10.1016/j.puhe.2023.07.021

banned or restricted products list,[23] engaging retailers to ensure compliance with the law, i.e. either removing clay from sale or marking it unsafe for human consumption as well as seizures by environmental health officers.[10] The then Public Health England (PHE) (now UKHSA), which views CI as a 'dangerous practice', admonishes GPs and other medical professionals to dissuade pregnant and breast-feeding women from CI.[24] Despite these measures, pregnant women continue to ingest clay.[8] This suggests the top-down approach is of limited impact. Crucially, evidence of pregnant women continuing to ingest clay points to its availability in a context where it should not be sold for ingestion.[20,23] This raises questions regarding how pregnant women go about acquiring clay in this restricted context. Despite official concerns regarding the practice, there is a remarkable dearth of studies that engage with clay ingesting women in this context.[8] Previous studies[10,34] on CI in this context have focused on sample testing and alerting relevant government agencies in relation to clay toxicity. On this note, understanding women's contextualized experiences will be a starting point to closing the knowledge gap as well as informing policy responses and interventions by relevant agencies, mostly community groups, the FSA and the UKHSA against a backdrop of potential health risks.

Methods

Study design

Interpretative phenomenological approach (IPA) aims to uncover the meaning and key structures of participants' lived experiences with a phenomenon as well as the contextual forces that shape it.[25] IPA was chosen for this study owing to its suitability to address research questions relating to individual experiences regarding clay acquisition for ingestion during pregnancy among African migrant women in a particular restricted context. Applying IPA enabled researchers to fully uncover and accommodate participants' lived experiences. The analysis followed the four-stage process outlined by Willig[26] as follows: (1) encountering with the text, (2) identifying themes, (3) clustering themes, and (4) producing a summary table.

Data collection

Thirty individual interviews, each lasting 40 min to 1 h, and one focus group discussion (FGD) with seven participants lasting 1 h and 45 minutes were conducted. Semi-structured in-depth interviews were utilized due to the combination of structure and interaction this affords, which was crucial to gaining in-depth insights into participants lived experiences as told in their language.[27] Utilizing a FGD enabled collection of data generated between participants as they presented their shared and unique lived experiences.[28] Participants were purposively selected to 'represent' those self-identifying as 'black African' woman, over 18 years old, living in a London borough, and having engaged in CI during pregnancy in England in the last 10 years. Recruitment utilized a combination of purposive sampling, which resonates with IPA[29] snowballing and quota sampling. Snowballing enabled recruitment of a hard to reach small and dispersed group.[30] However, given the risk of sample heterogeneity with snowballing, quota sampling was introduced to improve diversity.

Study context and participants

The study was conducted in London with 30 participants drawn from 15 London boroughs, as listed in Table 1. Participants' ages ranged from 29 to 45 years. The table shows participant demographics.

Data analysis

All recordings were transcribed, and transcripts were anonymized and printed for IPA. After the manuscripts were printed, they were read for familiarization, followed by re-reading for coding. Major themes and subthemes were identified and categorized, followed by selection of quotes.

Ethical issues

In line with ethical requirements, participants were briefed on the aims of the study, issues of consent, confidentiality, voluntary participation and right to withdraw from the study. Informed consent was obtained from participants, and to ensure confidentiality, all participants were anonymized, and the areas where clay was acquired are presented in pseudonyms with epithets of the larger context in brackets.

Results

Clay acquisition experiences are divided into three broad themes: 'African shops and markets', 'back home' and 'online social platforms'. Language, identity and trust emerged as important subthemes in facilitating transactions, with social networks playing a facilitatory role whichever way clay was acquired.

Table 1
Participant demographics.

Number of children	Occupation	Boroughs of residence from which participants were recruited	Countries of origin
2 Participants – 1 child each	3 Hairdressers	Newham	Zimbabwe
10 participants – 2 children each	8 Nurses including managers	Barking & Dagenham	Uganda
14 participants – 3 children each	5 Social workers including managers	Redbridge	Cameroon
4 participants – 4 children each	9 Support workers/Health care assistants	Havering	South Africa
1 participant – 5 children	2 Marketing & finance workers	Richmond upon Thames	Ghana
	5 Others	Waltham Forest	Republic of Congo
		Hackney	Nigeria
		Bromley	Congo Brazzaville
		Greenwich	Guinea Bissau
		Lewisham	
		Croydon	
		Enfield	
		Tottenham	
		Westminster	
		Chelsea	

African shops and markets 'where they sell African stuff'

Despite official warnings about risks, most participants reported acquiring clay from African shops and markets: A Nigerian mother put it this way:

> *We get it [clay] from some African Shops … in Storelands [East London] where they sell African stuff, they know there are people who eat it, it's on demand (Nigerian Mother P8)*

The idea of acquiring clay where African stuff is sold was reinforced by another mother who noted:

> *… If you go to Larksenhill and Stenswan [South London] especially where they sell African stuff, you can get it. It might not be, as you know, the same quantity as you would have access in Africa (Nigerian Mother P17)*

The notion of 'African stuff' also reinforces the association of clay with African cultural products sourced from the continent. Another mother reported acquiring clay from 'proper black areas', which alludes to areas with a higher concentration of black communities. She put it this way:

> *We get it from African shops…I would say in Shallowston or Sparowsten, Larksenhill [South London] as well as the proper black areas (Cameroonian Mother P15)*

Language, identity and trust: 'you have to ask for it'

The process of acquiring clay was however complex, with participants reporting having to ask for it. One mother who travelled some distance explained:

> *I buy it [clay] from an African shop…Larkenshill [South London]. I live in East London then I will travel all the way to Larkenshill … to get the clay. That's crazy you know. But you have to ask for it, it is not something you find it easily. (Nigerian Mother P10)*

However, asking for the clay was not sufficient to facilitate a transaction. Familiarity also played an important role as noted below:

> *There is an African shop in Larksenhill [East London]… You have to ask. Even when you ask if they don't know you, they say they don't have it …so, if there is a new face, the shop owner says they don't have it. Except it is someone like me or somebody they know … (Congolese Mother P9)*

Language appeared to play a prominent role in transactions as a Ugandan mother put it this way:

> *It [clay] wasn't always displayed. It was behind the counter, and you have to ask for it, can I please have some 'emumbwa' and they will tell you they have some, they don't have some, come back someday I will have some for you…. (Ugandan Mother P11)*

Asking for clay in a native language seemed to work as a code that signaled a genuine potential customer was a community member and hence could be trusted. Thus, a shared identity through language emerged as an important aspect in facilitating transactions. A Nigerian mother explained it this way:

> *Once you go there (the shop) you have to ask for it [clay]. Sometimes you have to speak their language for them to know that you are one of them… so if you don't speak their language… they won't sell it to you… also even if they don't know you, but if you speak their language and you speak friendly to them, like you have been coming to them regularly, they might sell to you but the truth is that if they are not sure, they might not (Nigerian Mother P23)*

A shared identity through language played a central role in trust building with shop keepers most likely to sell to their 'own' community members as well as those already familiar to them. 'Community' outsiders had to rely on friends who could speak the relevant native language as one mother put it this way:

> *So, if there's African shops around, they wouldn't specifically sell it to me because one I didn't speak the language and secondly they were not too sure who I was and whether they could trust me and sell it to me. So I had to make sure that whenever we went into the shop , I was with her [friend] so she would then speak in her native language saying do you have A, B, C, D (South African Mother, P14)*

When queried further as to why clay was only sold to those who spoke the native language, she noted:

> *I think maybe because of restrictions… But because I wanted it so badly, those rules and regulations didn't really apply because you know, when you do want something, you want it … Also, when I think that something that was just costing me a pound or two pounds (South African Mother P14)*

Similar to other participants, awareness of the restrictions had not deterred this mother from acquiring clay, and moreover, the cost was no impediment. Some participants observed changes in how clay was sold, which likely resonates with the onset of the restrictions. A Cameroonian mother explained it this way:

> *I would get it [clay] here from Larksenhill [East London]… I used to ask for it because they told me that they were not selling it freely so they didn't display it. But before then … they would just put it in front of their counter but later on I realized that they were not putting it out … I would ask for it and they would take it from their drawer and sell it to me. (Cameroonian Mother P13)*

Probed if she knew why clay was no longer displayed as before; she noted:

> *They said by law they are not allowed to sell it anymore (Cameroonian Mother P13)*

Another mother who observed this change put it this way:

> *After 2014 we noticed that they [shop keepers] were hiding it when we went to buy it [clay]. They will take it from the chest drawers, the cupboard and give it to you… they don't expose it anymore as before …So I asked one of the guys about it; he said they [government) don't allow them to sell the clay anymore… (Congolese Mother P5)*

While this mother was keen to understand why this was the case, not all participants cared to know. A mother who preferred clay from her home country Cameroon explained it this way:

> *I would travel all over London to look for it [clay] … if they sold it I would get it, even if it was not the good one. And you would not see the clay unless you ask. I remember going to Larksenhill [East London], I went to every single shop in the whole market because I was looking for the Cameroonian one… they mostly have Nigerian, Ghanaian, and Congolese, it's difficult to find the one from*

Cameroon. It was not displayed; you have to ask (Cameroonian Mother – P28)

Probed if she knew why it wasn't display she responded:

I don't really know, that's not really my problem (Cameroonian Mother P28).

While this mother was rather indifferent, knowledge of the restrictions left another irate. She narrated it this way:

I went to the shop to buy it and they said they are not selling… you see, the demand for clay is very high and when women become pregnant, they go to the African shops… they said they did not have it … if they have the clay, they have to hide it and I said, "why do you have to hide it?" They said "because the system in this country does not allow it" I said "but they are not eating it, we are eating it, it's good for us, so why are they banning something that is good for us? (Ghanaian Mother P29)

The belief that CI is good for pregnant women perpetuates demand for it, with shopkeepers likely perceiving their role as helping their communities away from the prying eyes of authorities. However, equally concerning is that some participants did not know about the restrictions, which potentially points to a lack of health risk awareness. Some participants also reported acquiring clay from 'Asian' shops, as this mother explained:

I found several shops selling it … even Indian shops as well because Indian people also eat the clay… I used to buy the clay from Pakistan and Indian shops in Hornbilton, Peacoston [East London] … but last month, I went to Larksenhill [East London] and I asked for the clay, they had it hidden under the counter, they looked at me, maybe they were trying to assess me …. they took it out of the counter (Cameroonian Mother P20)

The availability of clay in Indian and Pakistan shops alludes to CI among some Indian and Pakistan communities as well.

Clay from 'back home': "she brought me bags [of clay] …"

While most participants reported acquiring clay locally, some had it sent from 'back home' via family and friends, as well as personally bringing it when they travelled. A Zimbabwean mother explained it this way:

When I got pregnant, the cravings just became more and more, I remember during that time I had a family member coming from Zimbabwe… I asked my mum to get it for me during my early pregnancy days …I had that [clay] until at about 12 weeks (Zimbabwean Mother –P3)

Another mother who perceived clay from 'back home' of good quality put it this way:

… my mum would send me, if there is someone coming from Uganda… they [back home] know where to get the good quality one[clay]. It's not like going to the shops here and you get any kind. There is a difference. (Ugandan Mother – P11)

The comparison also suggests a dual reliance on clay from back home as well as locally. A Cameroonian mother also reinforced this point:

… when my mum heard I was pregnant she sent me the clay; I think she sent me all of what was in the market … so every time I saw it, I was eating it … I didn't like the one from this country [sold locally] … the taste wasn't quite like the one I get from Cameroon. (Cameroonian Mother P22)

Those who relied on clay from 'back home' appeared to acquire it locally as a last resort. Clay acquirement from back home via family and friends indicates the existence of social networks that pregnant women tapped into. One mother expressed surprise at the amount of clay her acquaintance was able to bring from back home. She explained it this way:

When I discovered that I was pregnant, I was saying …where am I going to get clay …so I asked my mum… she said if anyone is coming to the UK then she would send them with the clay… the person who came from Zimbabwe, she brought me bags [of clay] …(Zimbabwean Mother – P19)

Some participants relied on postal services as one mother put it this way:

When I was pregnant here… when I started to feel it [morning sickness], I called my mum to tell her I needed the clay. She posted it. I started eating it and it stopped. I did that for the second one [pregnancy], for the third one [pregnancy] … (Congolese Mother P24)

The idea of pregnant women relying on their mothers to send them clay points to the crucial role they play as sources of support. In one case, clay from 'back home' was taken away by customs officials, as a Congolese mother narrated it this way:

I asked my friend who went to Congo to bring it [clay] for me because I am from Congo. When she brought it here, they [immigration and customs] threw it away at the airport, you know at Heathrow. They did not allow it to enter the country (Congolese Mother – P5)

While this was the only reported case of confiscation among participants, it indicates that officials do take action.

Social networks and reciprocity: 'when you got it [clay] you want to share it'

Social networks were important in acquiring clay as well as getting information on where to obtain it. Reliable sources of clay were shared within networks and utilized as this mother noted:

This is like a Zimbabwean community group on Facebook, so here and there people will be posting, "is there anyone selling clay, I am really craving for it", and then someone will be like yeah there is so and so, who is selling it… (Zimbabwean Mother P30)

Some participants perceived CI as a social activity shared with friends, and as highlighted earlier, the cost was no barrier. One mother put it this way:

… sometimes, my partner I'll ask him to go to Olwstopple [North London] and buy clay for me. I'll buy it for £5. It's a lot. And then I'll call a friend to say; I've got some clay. This is like cigarettes. When you got it you want to share it… I can also go to my friend's house and say I have just come to take some clay …(Congolese mother P5)

The similarity drawn with cigarettes is indicative of a social activity that is underpinned by some level of reciprocity.

Furthermore, sharing clay amongst friends appeared to denote compassion to their need for it, as narrated below:

> *… a friend came to visit me and she was talking about it saying; "oh I want some clay", and I was like "oh I have a surprise for you." I went to bring it and she was so happy… (Guinea-Bissauan Mother P27)*

While another's participant husband went to great lengths to find her clay in the local 'mountains', the taste fell short and a friend came to her rescue. She explained it this way:

> *I usually vomit in all my pregnancies … Before or after the food I eat the clay, I will not vomit. But in this case, I couldn't find it [clay] so I would just eat and throw up, eat and throw up…I could see my husband going around to the mountains here, but he couldn't find the clay that I wanted… I had a friend whom I told about it and she said that she can buy online. She ordered it for me but it was a small packet and I had to eat small pieces everyday just to have that taste… (Zimbabwean Mother P26)*

Another participant explained how her cousin helped her to acquire clay from a local farm as follows:

> *I have my cousin… so immediately she knew I was pregnant she said listen; I am going sort you out … She said where she is in Henston [South England]… there is a farm where they have got some clay … I actually paid 50 pounds for it … (Zimbabwean Mother – P19)*

While most clay sold locally appeared imported, the quote above suggests of a local source. Though the quantity was unclear, the reference to a £50 payment was the highest mentioned in the study. Overall, participants exploited and benefitted from their social networks to acquire clay.

Discussion

This study aimed to explore how African migrant women go about acquiring clay for ingestion during pregnancy in a restricted context. Clay was acquired from across London, with Larksenhill [East London] and Storelands [South London] frequently cited. Indeed, there is evidence of environmental health officers seizing clay from some of these areas.[31,32] Home to many African Communities, East and South London multicultural shops and markets stock products reflective of diverse needs, including African cultural needs;[33] hence, it is not surprising some participants travelled quite some distance to acquire clay for their needs. It was, however, highlighted that clay was not openly sold but hidden under counters, including 'drawers' and 'cupboards', hence the need to ask for it. This suggests the current top-down approach has pushed transactions underground, which raises questions of effectiveness. Previously, clay sold openly enabled accessibility to researchers (see Refs.[10,34]) and environmental health officers via compliance checks for sample testing. It was through sample accessibility that toxic clays were discovered, warnings issued and restrictions put in place. Under the counter transactions have left pregnant women potentially ingesting highly toxic clay with little chances of dictation by authorities.

Since issuing a warning and memo to public health practitioners as well as producing an educational leaflet in 2013.[24] PHE's (now UKHSA) efforts to tackle CI have been halfhearted. In 2016, the agency aptly acknowledged that education and awareness raising is probably the best way to prevent health risks, hence engagement in multi-agency work to produce educational materials to warn expectant mothers regarding the dangers of ingesting clay.[35] However, to date, no such additional educational materials have been identified. Furthermore, framing CI under 'pica'[35] in the context of a cultural heritage that considers it the norm[8] is unhelpful. Knowledge and awareness of CI's cultural dimension is pivotal in designing effective interventions. African migrant women are overrepresented in poor maternal health outcomes, including low birthweight,[36] and potential contributing factors such as exposure to toxic metals through ingesting contaminated clay deserve appropriate attention.

Findings indicate that clay transactions between shopkeepers and customers were based on trust built on shared identities and languages. This points to the existence of shared community networks, which could be harnessed in the design of interventions. The diversity of our sample identifying with various parts of the African continent is indicative of the heterogeneous nature of the African community, which is often assumed to be homogeneous.[37] Future interventions need to be co-designed with community as a way of capturing this complex diversity.

Against a backdrop of some shopkeepers admitting to participants selling clay was against official guidance; it can be postulated that there is a need for collaborative intervention approaches that include sellers so they can effectively improve the health outcomes of pregnant women by sharing knowledge of the danger of CI. The language used by some participants alludes to a chasm between 'us' and 'they', i.e. 'us', which can be a powerful tool for designing culturally informed interventions. Informed conversations and interventions with key stakeholders amongst the wider Black and Ethnic Minority populations can help clarify the risk and perceived benefits of CI during pregnancy. Here, 'they', pointing to those in authorities, are perceived as lacking understanding of 'our' cultural heritage, thereby creating an opportunity for co-designing evidence-informed interventions that are led by communities and those in authority. To some extent, the top-down approach that problematizes CI as 'pica' and a dangerous practice without understanding of its cultural roots has contributed to this chasm. Further top-down measures risk consigning the practice deeper underground, hence the call for community-led interventions. Evidence indicates that some pregnant women are most likely to see clay sellers before midwives for the booking appointment,[7] hence the need to design interventions that are led from downstream.

While clay intended for ingestion is on the FSA banned or restricted list,[20] the guidance is advisory with no explicit underpinning regulation. The lack of regulation, as previously acknowledged by the FSA,[20] limits understanding of the risks amongst communities, as clay is not a food product. The ingredients in clay are also unknown, as they are sourced from various sources. Despite evidence of large commercial consignments of clay being seized by officials,[19] this does not offer sustainable solutions to improving health outcomes for women who may ingest clay during pregnancy. Explicit guidance through a joined-up approach between relevant agencies underpinned by a regulatory policy framework and funding of community groups to support intervention initiatives may contribute towards improving health outcomes for women and their babies.

Whether clay was acquired via online platforms, locally or abroad, findings indicate that social networks, including family and friends, played a facilitatory role. Evidence of clay sharing with friends suggests the practice is both an individual and social activity. The social networking theory alludes to health behaviours being partially driven by an individual's network due to the flow of resources.[38] In this study, participants received information support (where to get clay), instrumental support (help in acquiring clay) and material support (being given clay). Against this

backdrop, the inclusion of networks in interventions is pivotal, as a lack of support from these can hinder behaviour change.[39]

CI is also influenced by the larger contextual environment; hence, in addition to the intrapersonal and interpersonal influences, the Socio Ecological Model identifies organizational, community and policy levels of influence on individual health behaviour.[40] With regards to CI influences, the community level can be linked to the African community, which is made up of diverse subcommunities, with the policy level, as already noted, building evidence-informed policies to improve health outcomes for women and their babies. On this note, multilevel interventions that target all identified levels of influence[41] are more likely to be effective. Increasing risk awareness through information and education at the intrapersonal level can be replicated at the interpersonal and community levels while supporting this with an appropriate policy framework. While CI is highly prevalent in many African countries[7] of origin, with studies[2,3,14] equally pointing to potential health risks, to date no official restrictive measures regarding clay sales have been identified in those countries as well as other European countries. This presents potential opportunities for international collaborations among relevant agencies in tackling CI among pregnant women.

In order to boast effectiveness, interventions must be community led, as learned from successful HIV interventions among African communities by Chinouya.[42] On this note, we call upon public health practitioners to collaborate with communities in developing robust, culturally sensitive interventions. We also call on the FSA to engage with other relevant agencies to consider an appropriate policy framework.

The limitation of this study is that women interviewed may not be representative of the experiences of all migrant African women who ingest clay during pregnancy in London. Despite this, the findings provide us with in-depth insight into how pregnant women go about acquiring despite the official restrictions in place.

Author statements

Ethical approval

The study was granted ethical approval by London Metropolitan University Ethics Review Committee (ID-016).

Funding

This study was funded by the Rescaling Fund, London Metropolitan University.

Competing interests

The authors have no competing interests to declare.

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Public Health 223 (2023) e12–e13

Contents lists available at ScienceDirect

Public Health

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Letter to the Editor

A "Tail" of three cities. Public health and acute atrophy of vigilance

As infections with the COVID-19 virus spread, we witnessed the declaration of the outbreak as a global public health emergency on March 11, 2020. The response in combating the public health and economic devastation demonstrated successes and failures.

Vigilance is a state of heightened concern often in response to a threat, which can be exhibited by individuals, societies, and institutions. We recently evaluated the evolution of vigilance following the last major infectious disease outbreak before the COVID-19 pandemic in Canada, South Korea, and the United States.[1] In summary, there were differences in maintained vigilance.

The concept of atrophy of vigilance[2] is typically discussed in terms of a major, one-time catastrophic event that prompts a heightened vigilance reflected in new policy (e.g. the Exxon Valdez oil spill and Hurricane Katrina). Before the manifestation of COVID-19, each jurisdiction suffered a major threat with clear socio-economic consequences, that is, MERS in South Korea, SARS in Canada, and H1N1 and Ebola in the United States. When COVID arrived, Canada and the United States had to face their atrophy of vigilance, the latter exacerbated by palpable degrees of political chaos.[3] South Korea, on the other hand, appeared to maintain their learnings from MERS with continued practices of vigilance manifesting in fewer cases and deaths.[4]

New vigilance in urgent public health measures was established during the prolonged pandemic to varying degrees. In Toronto, there was a series of four "stay-at-home" orders over the course of the pandemic. In New York City, one such order lasted 8 weeks. There were no such orders in Seoul. Instead, South Korea acted strongly with prepared public health measures reflected by fewer infections and deaths through the first three pandemic waves.

Smart and aggressive public health strategies work

Non-pharmacologic interventions (e.g. protection, isolation) were part of the initial public health strategy in all three cities. Travel restrictions were implemented. Vaccine development and rollout were impressive as was antiviral availability.

Albeit tardy, the realization that aerosol transmission was paramount to COVID-19 infectivity led to North American recognition that mask wearing was a vital barrier between infected individuals and potential hosts. Canada was hampered by supply and scientific debate dismissive of the precautionary principle, resulting in an early failure in conveying a cohesive recommendation on barrier face coverings. The United States also faced supply problems and divisiveness on mask wearing. In contrast, Seoul was ahead of this due in part to a history of common use against air pollution and a genuine concern for fellow citizens.

The other distinction of Seoul in the early phases of the pandemic was the intensity of its testing, tracing, isolation, and quarantine. Learning from MERS, the importance of early testing and isolation was realized and executed without debate. The three pillars of early and free testing, expansive tracing technology, and mandatory isolation and quarantine were clearly effective. This precautionary isolation of the "contacted" from the "infected" served to promptly separate the actively and potentially sick from the well and, for the most part, kept the pandemic at bay. Here, NYC was hampered by federal CDC testing delays during the critical early period.[5]

Acute atrophy of vigilance

This new pandemic vigilance was short lived and was followed by an acute atrophy that can be measured in months vs years (e.g. decade) that are observed in sudden catastrophic events. This more acute atrophy of vigilance during the global pandemic was observed in Toronto and New York City with a steady growth of divisiveness, particularly around masking and vaccination.

By the first months of 2022, masking recommendations were lifted in all three cities. When strains on the hospital system in Toronto emerged in the fall of 2022, renewed indoor masking recommendations fell short of a mandate placing the onus on individual decisions. City officials nevertheless urged provincial authorities to intensify visibility and reach on masking and vaccination benefits—a clear recognition of atrophy of vigilance. Another indication of acute atrophy was vaccination rates. In Toronto, for example, as of November 2022, 87% received one dose of vaccine, 84% received two doses of vaccine, and 54% received three doses of vaccine. In New York City, these percentages were 89%, 80%, and 40%, respectively.

Then came Omicron

All three cities suddenly experienced a dramatic upswing in cases and deaths with the Omicron variant. The tail indicating infectivity and illness in Seoul was most dramatic. A perfect storm for the case surge in Seoul was driven by both biology and policy. First was Omicron's increased transmissibility. Second, Seoul shifted policy by reducing its testing, tracing, isolation, and quarantine, mimicking the west's "living with COVID." Also, the effects on the ongoing presidential political campaign may also have played a role, given the sensitivities of the electorate to positions taken by the incumbent party candidate related to non-pharmacologic interventions.

Importantly, the 2022 surge in Seoul did not reflect a higher case fatality rates vs others. The strategy of "select and focus" was effective as case fatality rates remained below the others. Nevertheless, one may interpret "living with COVID" as an acceptance of more

https://doi.org/10.1016/j.puhe.2023.01.032

deaths, particularly in the elderly and susceptible simply by the dramatic increase in the case count denominator.

In conclusion, this comparison highlights that smart and aggressive public health strategies of Seoul were effective to win the battle that was missing with MERS. Rather than atrophy of vigilance, public health was given constant attention to be prepared at the time of COVID-19 arrival.[6] The high transmissibility of the omicron variant and the social fatigue after 2 years of admirable compliance let infections through the cracks in preventative methods.

This tale illustrates that public health measures effectively implemented can win. We witnessed what we term an "acute atrophy of vigilance" within the prolonged pandemic, even in Seoul. This acute atrophy reflected "how tired of it all" we became. Toronto and NYC finished their "season of COVID-19," having many highlight reels, but along with a supply of "bloopers" not to be repeated. In conclusion, Seoul's public health measures won. Omicron scored a late goal to prevent a shutout.

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10 January 2023
Available online 10 March 2023

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Public Health 223 (2023) 24–32

Contents lists available at ScienceDirect

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Original Research

Emotional dependence as a predictor of emotional symptoms and substance abuse in individuals with gambling disorder: differential analysis by sex

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ARTICLE INFO

Article history:
Received 9 April 2023
Received in revised form
7 July 2023
Accepted 17 July 2023
Available online 17 August 2023

Keywords:
Gambling
Emotional dependence
Women
Sex differences
Comorbidity

ABSTRACT

Introduction: Emotional dependence, anxious-depressive symptoms and substance use have been associated with gambling disorder (GD). Although anxiety and depression have been predominantly related to female gamblers and substance abuse to male gamblers, the role of emotional dependence in GD is unknown. Moreover, sex differences remain underexplored.
Objectives: First, to explore possible differences in emotional dependence, anxious-depressive symptoms and substance abuse by group (GD and non-GD) and sex (women vs men). Second, to analyse the predictive role of emotional dependence in alcohol and drug abuse and anxious-depressive symptoms in patients with GD as a function of sex.
Methods: Instruments to measure gambling (SOGS), emotional dependence (CDE), anxious-depressive symptoms (SCL-90-R) and substance abuse (MULTICAGE CAD-4) were administered to 108 people with GD diagnosis (60 women and 48 men) and 429 without GD (342 women and 87 men).
Study design: The research is an analytical cross-sectional study.
Results: The results showed that the group with GD scored significantly higher than the non-GD group on alcohol abuse, symptoms of depression and anxiety, and emotional dependence, but not on drug abuse. In the group with GD, emotional dependence predicted alcohol and drug abuse in women, and emotional dependence predicted anxiety and depressive symptoms in men.
Conclusion: The findings suggest that women with GD who consume alcohol or drugs would benefit from therapies addressing loneliness, borderline expression, attention-seeking and affective expression. Men with GD who report anxious-depressive symptomatology would benefit from therapeutic strategies to deal with separation anxiety and attention-seeking.

Gambling Disorder (GD) is the diagnostic category used in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [DSM-5][1] to define a persistent and recurrent pattern of gambling associated with significant distress and impairment in the person's life. In European countries, problem gambling reaches three percent, while in some non-European countries, the rate rises to six percent.[2,3]

Apart from the general diagnostic criteria, it has been observed that the clinical picture of patients with GD may vary considerably according to sex. As a result, even though studies point to a higher prevalence in men,[4,5] being female is associated with an added social stigma when suffering from an addictive behaviour.[6] Hence, females' increasing participation in gambling activities has been explored in recent years.[7,8]

Considering the sex differences in GD profiles, it has been argued that motivations for gambling differ according to sex,[9–11] with women being more likely to gamble to escape from loneliness, boredom or to cope with everyday life difficulties.[12,13] In contrast, men enter gambling-related treatment at a younger age than women and are involved in more illegal conflicts.[14,15] In the case of females, the telescoping effect has been suggested, referring to a later age of onset but with a faster progression to GD than males.[16] However, some findings sharply contrast with this phenomenon, arguing that the convergence of the age of onset in gambling activities of both sexes diminishes any telescoping

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https://doi.org/10.1016/j.puhe.2023.07.023

effect.[17] The literature shows a lack of sex-specific research on gambling in women.

The comorbidity of substance use disorders (SUDs) and emotional disorders has been extensively studied concerning GD. A systematic review of sex differences in GD found that male problem gambling was related to substance and alcohol use, whereas females suffering from GD were more likely to have comorbid psychiatric diagnoses, especially depression and anxiety.[18,19,29] SUDs are a mental health condition defined by the problematic use of a substance such as alcohol, drugs, or prescription medications. Similar to GD, the individual consumes heavily and despite harmful consequences, affecting their ability to function in daily life. The available studies of SUDs have indicated that although a higher proportion of male adults tend to show problematic alcohol and drug use than females, recent data indicate that this sex difference does not occur among adolescents.[21–23] More specifically, it has been suggested that this sex parity among young people is driven by prescription drug use, with girls reporting higher rates than boys, as well as a similar pattern of current alcohol use and binge drinking.[24]

Concerning comorbid emotional disorders, results are still inconsistent and mixed.[20,25,26] However, an investigation conducted by Andronicos et al. (2015)[18] found that the significance of psychopathology was similar for men and women with GD, especially in terms of the presence of affective disorders and SUDs, but the reported precipitating risk factors are likely to differ.[27,28]

Emotional dependence has been studied for its relationship with addictive disorders and maladaptive psychological symptomatology.[29–31] Emotional dependence is defined as an extreme affective need that a person feels towards another person, habitually the partner, in the course of their different relationships.[32] Some professionals have even argued for including emotional dependence as a diagnostic category within non-substance-related addictions.[33] This approach is based on the fact that addictive behaviour involves an object of obsession, either a substance or a person.[34] In addition, it has been observed that brain reward pathways are similar for substance and non-substance addictions and relationship addiction.[35] In the same vein, similar clinical characteristics have been suggested for GD and emotional dependence, such as craving, the activation of the brain reward and dopaminergic system, tolerance, abstinence syndrome, the loss of control or severe disruption of daily life.[36,37] Furthermore, Echeburúa et al. (2014)[38] suggested that GD also involves emotional dependence. In fact, the results obtained by Estévez et al. (2018)[39] found a positive relationship between emotional dependence and impulsive behaviours, as well as with psychological symptomatology, including depression, anxiety, hostility or somatisation.[31] Sex differences in emotional dependence remain incongruent. While some studies have found higher emotional dependence scores in men,[30,39,40] other studies have found it in women,[41] and still others have found no significant differences.[42]

However, to our knowledge, no studies have explored the role of emotional dependence in comorbid substance use and psychological symptoms in patients suffering from GD. Additionally, the scarcity of existing studies on the predictive role of emotional dependence for addictive behaviours and associated symptomatology sheds no light on whether the manifestation might differ between women and men suffering from GD. Therefore, the objectives of this study were, firstly, to explore the existence of sex differences in alcohol and drug abuse, symptoms of anxiety and depression, and emotional dependence in a group of people with and without GD. Secondly, we wished to examine the differences in the relationship between age, emotional dependence, alcohol and drug abuse, and symptoms of anxiety and depression in the group of women and men with GD. Thirdly, we analysed the association and predictive role of emotional dependence in alcohol and drug abuse and symptoms of anxiety and depression in the clinical sample with GD as a function of sex.

Hypothesis

Based on the objectives stated above, we hypothesise that emotional dependence will predict symptoms of anxiety and depression in women with GD. In men with GD, we hypothesise that emotional dependence will predict alcohol and drug abuse.

Method

Study design

The research is an analytical cross-sectional study.

Participants

The sample comprised 60 women and 48 men with GD and 342 women and 87 men without GD as a control group. Table 1 shows the sociodemographic characteristics of the four groups. All participants were over 18 years old. Significant differences among the four groups were found in age, $F(3, 533) = 81.46$, $P < 0.05$, SOGS scores (Lesieur & Blume, 1987), $F(3, 533) = 1752.273$, $P < 0.05$, marital status, $\chi^2(1, 18) = 141.619$, $P < 0.05$, employment status, $\chi^2(1, 27) = 254.466$, $P < 0.05$, and educational level, $\chi^2(1, 18) = 275.185$, $P < 0.05$.

The clinical sample, that is, women and men with GD diagnosis, was recruited through GD treatment associations belonging to the FEJAR (Spanish Federation of Rehabilitated Gamblers). Inclusion criteria for this group were attending treatment at a GD treatment centre and scoring as a gambler on the South Oaks Gambling Screen questionnaire [SOGS].[43] In the case of the sample without GD (general sample), the exclusion criterion was to score as a gambler on the SOGS (for more information, see the description of the SOGS in the instruments section).

Procedure and sampling

The present study used a non-probability sampling method. Concretely, this type of sampling has been selected due to the problematic sample localisation, as it is a population of men and women with GD diagnosis.

On the one hand, clinical participants with a GD diagnosis were outpatients recruited through GD treatment associations belonging to the FEJAR. FEJAR is a Spanish organisation aimed at rehabilitating GD, which comprises multiple associations throughout the country with the same purpose.

On the other hand, the non-clinical sample (i.e., without GD) was recruited from the general population. The questionnaire was diffused on social networks (e.g., WhatsApp, Instagram, e-mail, Facebook, or LinkedIn), university bulletin boards, journals of divulgative scientific articles and informative websites.

The sample recruitment time was approximately one year (i.e., from the summer of 2021 to the summer of 2022). The questionnaire was the same for both samples, the group of people with GD (clinical sample) and those without GD (general sample). The sample without GD completed the survey via an online link to the questionnaire or a QR code that accessed the same questionnaire. The GD clinical sample completed the questionnaires either online or offline (pencil and paper). According to Herrero-Fernández (2015),[44] a questionnaire's application method (pencil and paper vs online) does not affect the results obtained.

Table 1
Sociodemographic data of the sample.

	Male gambler	Female gambler	Male non-gambler	Female non-gambler
Age (M, DT)	41.33 (12.32)	49.07 (12.70)	27.48 (10.22)	26.80 (11.32)
Gambling – SOGS (M, DT)	9.42 (2.30)	9.13 (2.17)	0.64 (0.89)	0.23 (0.55)
Employment status				
Working	68.8%	45%	40.2%	23%
Unemployed	4.2%	23.3%	2.3%	2.7%
Student	6.3%	1.7%	34.5%	49.6%
Retired	8.3%	15%	1.1%	0.9%
Student and worker	0%	1.7%	21.8%	21.8%
Jobless	2.1%	3.3%	–	0.6%
Other	10.4%	10%	–	1.5%
Marital status				
Single	35.4%	41.7%	66.7%	48%
Married	33.3%	31.7%	9.2%	8.2%
Partner in law	12.5%	0%	2.3%	2.6%
Separated or divorced	14.6%	16.7%	–	3.2%
Widowed	2.1%	6,7%	–	0.9%
Other	2.1%	3.3%	21.8%	37.2%
Educational level				
Without education	8.3%	3.3%	–	–
Primary	8.3%	33.3%	1.1%	0.3%
High school	8.3%	6.7%	–	0.6%
Secondary school	6.3%	10%	13.8%	16.2%
Professional training	47.9%	30%	19.5%	8.8%
University studies	18.8%	16.7%	65.5%	74%
Other	2.1%	–	–	–

To access the questionnaire, participants had to read the study information and provide informed consent. The duration of the application was about 30 minutes. The questionnaire included general information about the main goals of the study. We ensured participants of their response confidentiality and anonymity and their voluntary participation. No compensation was provided for participation in this study.

Instruments

Gambling disorder

GD was assessed with the SOGS.[43] The Spanish version was adapted by Echeburúa et al. (1994).[45] It is a 20-item screening questionnaire. The scale contains items related to gambling activity patterns, debts, sources of money to gamble and emotions involved in gambling. The response format is a dichotomous scale with *Yes/No* response options. According to this tool, scores between 0 and one indicate no gambling risk, scores between two and three indicate gambling risk, and scores of four or more suggest the potential presence of GD. Therefore, to belong to the non-GD group of the present study (general sample), the participants had to score between 0 and one point; otherwise, they were excluded from the general sample. The instrument presents good psychometric properties, showing appropriate internal consistency for the original scale ($\alpha = 0.94$), and the convergent validity with DSM-IV criteria was 0.94. In the present study, Cronbach's alpha for the SOGS was 0.63.

Emotional dependence

We used the Emotional Dependence Questionnaire[46] ('Cuestionario de Dependencia Emocional' – CDE, in Spanish), which consists of 23 items. Each item is scored on a six point Likert response format ranging from 0 (*completely false*) to five (*it describes me perfectly*). The CDE assesses emotional dependence as a global construct through the sum of its items. It presents six subscales: (1) separation anxiety, (2) affective expression of the partner, (3) plan modification, (4) fear of loneliness, (5) borderline expression, and (6) attention-seeking. The original scale shows structural validity for both sexes and the presence or absence of a partner. Cronbach's alpha for the total original scale was 0.93. In the present study, Cronbach's alpha for the CDE was 0.92.

Alcohol and drug abuse

MULTICAGE CAD-4.[47] This questionnaire consists of 32 items that assess eight impulse-control disorders and addictions. In this study, we used two of the eight factors (i.e., Alcohol and Drug Abuse). Each factor contains four items, providing a total of eight items. Each factor is evaluated by reproducing the CAGE schema[48]: Self-Perception of the problem, Perception by Cohabitants, associated feelings of Guilt, and signs of Abstinence. The response format consists of a dichotomous scale *Yes/No*. According to the tool, scores between 0 and one indicate '*no problem*', two affirmative answers indicate the '*possible existence of the problem*', three affirmative answers indicate '*very probable existence of the problem*' and four affirmative answers indicate '*certain existence of the problem*'. The cut-off point was set by the authors at two affirmative responses to indicate problem behaviour and/or the presence of addiction. Cronbach's alpha for the total original scale was 0.86. Each subscale has an alpha above 0.70. For the present study, Cronbach's alpha was 0.82 for Alcohol and 0.92 for Drug Abuse.

Symptoms of depression and anxiety

We used the *Symptom Checklist-90-Revised* (SCL-90-R)[49], adapted to Spanish by González de Rivera et al. (1989).[50] The SCL-90-R is a self-administered questionnaire that assesses 90 psychological symptoms. It is divided into nine dimensions related to psychopathological symptoms and three global distress indices. In this study, two psychological symptoms were used: (1) Depression, composed of 13 items that tap signs related to depressive disorder (e.g., despondency, anhedonia, self-destructive thoughts, etc.) and (2) Anxiety, composed of 10 items that refer to clinical manifestations of both acute and generalised anxiety, as well as signs of emotional stress or psychosomatic manifestations. The level of distress caused by each symptom is assessed on a 5-point Likert scale ranging from 0 (*no symptom-related distress*) to 4 (*maximum distress*). Internal consistency is very good for the overall scale, and higher than 0.70 for all subscales. In the current study, Cronbach's alpha was 0.92 for the dimension of Depression and 0.94 for Anxiety.

Ethics

The research obtained the ethics committee's approval from the first author's university (ref: ETK-17/20-21). This study was performed following the principles of the Declaration of Helsinki.

Statistical analyses

First, mean differences for alcohol, drugs, anxiety, depression and emotional dependence were calculated with the analysis of variance (*ANOVA*) among four groups (male gamblers, female gamblers, male non-gamblers and female non-gamblers). Post-hoc analyses were carried out for intergroup comparisons using Scheffe's test. The effect size of mean differences was calculated with eta squared (η^2) values.

Second, the correlation between alcohol, drugs, anxiety, depression, emotional dependence and age was analysed in the clinical sample of female and male gamblers. The analyses were carried out separately in both groups: female gamblers and male gamblers. Fisher's *z*-test was carried out to determine the significance of the differences of correlations between both groups.

Third, hierarchical regression analyses were conducted to assess the predictive role of emotional dependence in substance abuse and emotional symptoms, controlling for the effect of age, employment and marital status, and educational level. The analyses were again carried out separately in both groups. In the case of female gamblers, the predictive role of emotional dependence on alcohol, drug abuse, anxiety and depression was calculated based on the correlational results. In the case of male gamblers, the predictive role of emotional dependence was analysed for anxiety and depression also based on the correlational results.

Additionally, baseline data on the SOGS scores[43] and age of the four sample groups were compared through *ANOVA*, while chi-square analyses were used to compare marital status, employment status and educational level.

Results

First, mean differences between male gamblers, female gamblers, male non-gamblers and female non-gamblers were analysed for alcohol, drugs, anxiety, depression and emotional dependence (Table 2). Results indicated that differences were significant for all variables except for drug abuse. The eta squared (η^2) values showed that the effect size was small ($\leq$0.03) for alcohol; moderate (0.03–0.06) for emotional dependence—affective expression and attention-seeking; and large (>0.06) for symptoms of anxiety, depression, total emotional dependence and emotional dependence—separation anxiety, plan modification, fear of loneliness and borderline expression.

A post-hoc analysis using Scheffe's test was then performed for intergroup comparisons. Post-hoc analyses showed that, in the case of alcohol abuse, female gamblers scored significantly lower than male and female non-gamblers. Regarding emotional dependence, both male and female gamblers scored higher than male and female non-gamblers on anxiety, depression, total emotional dependence, separation anxiety, affective expression, fear of loneliness, plan modification and borderline expression. In the case of plan modification, male non-gamblers also scored higher than female non-gamblers, and in the case of attention-seeking, all males (gamblers and non-gamblers) scored higher than female non-gamblers. In anxiety and depression, female non-gamblers scored higher than male non-gamblers. There were no significant differences between male and female gamblers in any of the study variables.

Secondly, the correlation between alcohol, drugs, anxiety, depression, emotional dependence and age was analysed in the clinical sample of female and male gamblers (Tables 3 and 4). In the case of female gamblers, alcohol and drug abuse correlated significantly with total emotional dependence and with emotional dependence—separation anxiety, affective expression, fear of loneliness and attention-seeking. Anxiety correlated significantly with total emotional dependence and with emotional dependence—separation anxiety, affective expression, fear of loneliness, borderline expression and attention-seeking. Depression correlated significantly with total emotional dependence and with emotional dependence—separation anxiety, fear of loneliness, borderline expression and attention-seeking. In turn, alcohol and drug abuse correlated with each other; anxiety and depression correlated with each other; and anxiety and alcohol abuse correlated with each other.

In the case of male gamblers, alcohol and drug abuse correlated significantly with each other but not with emotional dependence. Anxiety and depression correlated significantly with all variables of emotional dependence except for attention-seeking, and they correlated significantly with each other. Concerning age, no significant relationships were found with the study variables in the sample of male gamblers, except for the relationship between age and anxiety, which was negative. In contrast, significant relationships were found in the sample of female gamblers, where age correlated negatively with alcohol abuse, anxiety, total emotional dependence and emotional dependence—separation anxiety, affective expression and attention-seeking. Additionally, Fisher's *z*-test was carried out to determine the significance of differences of the correlations between both groups. Significant differences were found in the relationships among total emotional dependence, fear of loneliness, attention-seeking and alcohol; affective expression and drugs; total emotional dependence and separation anxiety, and depression; and attention-seeking and all the emotional dependence scales except for separation anxiety.

Thirdly, hierarchical regression analyses were conducted to assess the predictive role of emotional dependence in alcohol and drug abuse, anxiety and depression, controlling for the effect of age, employment and marital status, and educational level in the group of female gamblers (Table 5). The results showed that emotional dependence was a predictor of alcohol abuse for women gamblers; more specifically, the predictor variables were borderline expression and attention-seeking. The effect of sociodemographic data was non-significant. Emotional dependence was not a predictor of anxiety, depression or drug abuse in female gamblers.

In the group of male gamblers, the predictive role of emotional dependence was analysed for anxiety and depression, controlling for the effect of age (Table 6). The results showed that emotional dependence was a predictor of depression in men; more specifically, the predictor variable was separation anxiety. When controlling for the effect of sociodemographic data, it was a non-

Table 2
Comparison between male and female gamblers and non-gamblers on alcohol, drugs, anxiety, depression and emotional dependence.

	Male gamblers (n = 48)	Female gamblers (n = 60)	Male non-gamblers (n = 87)	Female non-gamblers (n = 342)	
	M (DT)	M (DT)	M (DT)	M (DT)	F (df)
1. Alcohol	1.56 (1.50)	0.85 (1.37)a,b	2.05 (2.12)a	1.89 (2.43)b	4.01 (3507)*
2. Drugs	1.79 (1.77)	0.52 (1.18)	1.40 (2.12)	1.39 (2.43)	2.55 (3490)
3. Emotional dependence	66.15 (21.39)a,b	61.83 (23.15)c,d	47.63 (14.96)a,c	47.03 (15.77)b,d	24.01 (3474)*
4. Emotional dependence – Separation anxiety	20.07 (8.56)a,b	18.70 (8.84)c,d	14.54 (5.64)a,c	14.79 (6.18)b,d	12.36 (3489)*
5. Emotional dependence – Affective expression	13.70 (4.77)a,b	13.45 (5.39)c,d	9.74 (4.21)a,c	11.07 (4.61)b,d	10.74 (3496)
6. Emotional dependence – Plan modification	10.65 (4.57)a,b	10.08 (4.83)c,d	7.79 (3.52)a,c,e	6.45 (2.75)b,d,e	33.97 (3487)*
7. Emotional dependence – Fear of loneliness	8.56 (4.52)a,b	8.92 (4.43)c,d	5.30 (2.48)a,c	6.29 (3.37)b,d	16.73 (3488)*
8. Emotional dependence – Borderline expression	6.28 (3.50)a,b	5.74 (2.92)c,d	4.32 (1.68)a,c	4.11 (1.35)b,d	24.88 (3488)*
9. D Emotional dependence – Attention-seeking	6.00 (2.73)a	4.94 (2.83)	5.58 (2.37)b	4.52 (2.10)a,b	8.59 (3498)*
10, Anxiety	22.23 (10.10)a,b	22.66 (11.46)c,d	10.34 (8.32)a,c,e	14.11 (10.89)b,d,e	22.39 (3498)*
11. Depression	31.88 (13.16)a,b	32.55 (14.19)c,d	15.05 (10.13)a,c,e	20.52 (12.34)b,d,e	32.86 (3492)*

* = p<.05 / a,b,c,d * Scheffe's test results.

Table 3
Correlation of alcohol, drugs, anxiety, depression and emotional dependence in female gamblers.

	1	2	3	4	5	6	7	8	9	10	11
1. Alcohol	–										
2. Drugs	0.56**	–									
3. Emotional dependence	0.49**/a	0.46**	–								
4. Emotional dependence – Separation anxiety	0.43**	0.37*	0.92**	–							
5. Emotional dependence – Affective expression	0.34*	0.50**/a	0.83**	0.71**	–						
6. Emotional dependence – Plan modification	0.22	0.28	0.59**	0.39**	0.34*	–					
7. Emotional dependence – Fear of loneliness	0.48**/a	0.35*	0.76**	0.63**	0.56**	0.28*	–				
8. Emotional dependence – Borderline expression	0.19	0.20	0.79**	0.70**	0.56**	0.37**	0.61**	–			
9. Emotional dependence – Attention-seeking	0.60**/a	0.30*	0.75**/a	0.64**	0.60**/a	0.38**/a	0.49**/a	0.56**/a	–		
10. Anxiety	0.31*	0.17	0.48**	0.48**	0.39**	0.21	0.43**	0.44**	0.24*	–	
11. Depression	0.11	0.05	0.32*/a	0.33*/a	0.22	0.02a	0.43**	0.37**	0.10*	0.65*	–
12. Age	−0.32*	−0.21	−0.31*	−0.35*	−0.30*	0.01	−0.25	−0.15	−0.32*	−0.28*	−0.26

* = $P < 0.05$, ** = $P < 0.01$, /a = $P < 0.05$ in Fisher's test.

significant predictor. Emotional dependence did not predict anxiety in men. As emotional dependence was not correlated with alcohol and drug abuse in male gamblers, regression analyses were not performed in this group.

Discussion

Existing research has identified many psychological variables that influence the onset, maintenance or relapse of GD. However, to our knowledge, no studies have explored the predictive role of emotional dependence in patients with GD, and even fewer have analysed sex differences. In fact, most studies on emotional dependence have focused on its relationship with violence or emotional symptoms and have been conducted in general population samples,[51,52] but almost nothing is known about the relationship of emotional dependence with addictions, and there are no explorations in samples with GD.

To this end, the present study first examined sex differences in alcohol and drug abuse, symptoms of anxiety and depression, and emotional dependence in groups with and without GD. The results showed that the group with GD scored significantly higher than the non-GD group on these variables (i.e., alcohol abuse, symptoms of depression and anxiety, and emotional dependence), except for drug abuse. However, even if the differences in drug abuse between the group of people with GD and those without GD were not significant, men with GD obtained the highest scores on drug abuse, followed by men and women without GD, respectively. Regarding sex differences, female gamblers were found to have lower scores on alcohol and drug abuse than both female and male non-gamblers. Concerning the other study variables (i.e., symptoms of depression and anxiety and emotional dependence), both females and males with GD scored higher than non-gamblers. These results align with previous findings indicating that women suffering from GD tend to exhibit less substance abuse comorbidity than men with GD.[20,53] That is, the manifestation of multiple addictions is not as common in the case of women when they already suffer from an addictive disorder such as GD. Alcohol is one of the most widely consumed substances in young people of the general population, in both females and males.[24,54,55] This might explain why the group of women and men from the general population of the study—who were younger than the group with GD— scored higher than the group of women with GD in alcohol abuse. Regarding symptoms of anxiety, depression, and emotional dependence, previous evidence supports our results showing that people with GD are more likely to obtain higher scores than those not at risk of gambling.[11,56,57]

Secondly, differences in the relationship between age, emotional dependence, alcohol and drug abuse, and symptoms of anxiety and depression were analysed in the group of women and men with GD. There were no significant differences between males and females with GD, but the variables were related differently. Alcohol and drug abuse, symptoms of anxiety and depression, and emotional dependence were positively related in women with GD. Moreover, significant negative relationships were found with age, indicating that the older the person, the less alcohol abuse and emotional dependence. These findings may also corroborate to some extent the previous hypothesis about alcohol consumption being related to the non-GD sample because of their younger age (and not to women with GD, who are older). Concerning men with GD, alcohol and drug abuse were significantly associated with each other but not with emotional dependence. In contrast, anxiety, depression and emotional dependence did show significant relationships with each other. No significant differences were found

Table 4
Correlation of alcohol, drugs, anxiety, depression and emotional dependence in male gamblers.

	1	2	3	4	5	6	7	8	9	10	11
1. Alcohol	–										
2. Drugs	0.45**	–									
3. Emotional dependence	0.19a	0.21	–								
4. Emotional dependence - Separation anxiety	0.19	0.23	0.90**	–							
5. Emotional dependence - Affective expression	0.14	−0.01a	0.76**	0.59**	–						
6. Emotional dependence - Plan modification	0.16	0.13	0.73**	0.58**	0.55**	–					
7. Emotional dependence - Fear of loneliness	0.11a	0.29	0.68**	0.49**	0.33*	0.51**	–				
8. Emotional dependence - Borderline expression	0.09	0.24	0.72**	0.57**	0.50**	0.38*	0.56**	–			
9. Emotional dependence – Attention-seeking	0.24a	0.09	0.44**/a	0.45**	0.33*/a	0.06a	0.05a	0.20a	–		
10. Anxiety	0.17	0.26	0.45**	0.46**	0.32*	0.33*	0.43**	0.34*	−0.07	–	
11. Depression	0.08	0.23	0.63**/a	0.64**/a	0.45**	0.42**/a	0.58**	0.51**	0.04	. 75**	–
12. Age	−0.05	−0.15	−0.30	−0.30	−0.19	0.01	−0.23	−0.29	−0.22	−0.31*	−0.19

* = $P < 0.05$, ** = $P < 0.01$, /a = $P < 0.05$ in Fisher's test.

Table 5
Regression analysis of emotional dependence as a predictor of alcohol in female gamblers controlling for the effect of age, employment and marital status, and educational level.

	t	*B*	*SE B*	*β*	*F (df)*	R	R^2	Adjust.R^2	R^2 change
Alcohol									
Step 1					3.552 (4,44)*	0.49	0.24	0.18	0.24*
Age	−0.95	−0.02	0.02	−0.15					
Employment status	−1.73	−0.15	0.09	−0.23					
Educational level	0.88	0.11	0.12	0.13					
Marital status	−1.60	−0.23	0.14	−0.25					
Step 2					4.395 (10,38)*	0.73	0.54	0.41	0.29*
Age	−0.43	−0.01	0.02	−0.06					
Employment status	−1.15	−0.09	0.08	−0.14					
Educational level	−0.14	−0.02	0.11	−0.02					
Marital status	−1.14	−0.15	0.13	−0.16					
ED − Separation anxiety	0.51	0.02	0.03	−10					
ED − Affective expression	−0.37	−0.02	0.04	−0.06					
ED − Plan modification	0.67	0.02	0.04	−08					
ED − Fear of loneliness	1.87	0.10	0.06	0.33					
ED − Borderline expression	−2.06*	−0.18	0.09	−0.35					
ED − Attention-seeking	3.19*	0.24	0.08	0.48					

* = $P < 0.05$. ED = emotional dependence.

in age in men with GD. This finding suggests, as the existing evidence has also shown, that women and men suffering from GD may manifest similarities in their apparent symptomatology, but the relationship of the psychological variables may not be the same for both sexes.[11,58]

Thirdly, the predictive role of emotional dependence on alcohol and drug abuse and anxious-depressive symptoms was explored for women and men with GD, controlling for the effect of age. In the case of women with GD, emotional dependence was found to predict alcohol and drug abuse but not symptoms of depression and anxiety. Concretely, fear of loneliness, borderline expression and attention-seeking predicted alcohol abuse, whereas affective expression of the partner predicted drug abuse. For men with GD, emotional dependence predicted anxiety and depressive symptoms but not alcohol and drug abuse. Specifically, attention-seeking predicted anxiety and depression, whereas separation anxiety only predicted depression. These findings are groundbreaking, as we have not found previous studies examining the differential predictive role of emotional dependence in comorbid alcohol and drug abuse and psychological symptomatology in female and male patients with GD.

In line with our results, other studies indicate that dependent personality traits are associated with an increased risk of engaging in health-damaging behaviours.[30] We found no specific studies about the relationship between GD and emotional dependence on the partner, but in substance addictions, there is ample evidence suggesting the relationship between emotional dependence and consumption.[59,60] In fact, psychodynamic theories suggest that emotional dependence may be rooted in fixations from the oral stage, and this may explain the subsequent search for addictive substances (i.e., oral stimulation[61,62]). Moreover, emotional dependence has been shown to predict addictive behaviours and to be related to symptoms of anxiety and depression.[11,63]

The literature does not agree on whether emotional dependence is more prevalent in men or women. Some research has found a greater tendency among men,[30,40,64] while other studies have found emotional dependence to be more prevalent among women.[65] However, the results of this study do not indicate whether one sex (women vs men) is more emotionally dependent than the other, but rather that in the case of people with GD, emotional dependence predicts one or another type of comorbid symptomatology depending on their sex. That is, emotional dependence is related to alcohol and drug abuse in the case of women with GD and to symptoms of anxiety and depression in the case of men with GD.

Table 6
Regression analysis of emotional dependence as a predictor of depression in male gamblers controlling for the effect of age, employment and marital status, and educational level.

	t	*B*	SE B	β	*F (df)*	R	R^2	Adjust.R^2	R^2 change
Depression									
Step 1					1.228 (4,35)	0.35	0.12	0.02	0.12
Age	−1.87	−0.36	0.19	−0.32					
Employment status	0.68	0.56	0.83	0.11					
Educational level	−0.05	−0.08	1.51	−0.01					
Marital status	1.65	3.08	1.86	0.30					
Step 2					4.379 (10,29)*	0.78	0.60	0.46	0.48*
Age	−0.04	0.16	−0.04	−0.27					
Employment status	−0.48	0.72	−0.10	−0.66					
Educational level	0.35	1.15	0.04	0.30					
Marital status	2.39	1.45	0.23	1.65					
ED − Separation anxiety	0.88	0.32	0.56	2.76*					
ED − Affective expression	0.41	0.46	0.15	0.88					
ED − Plan modification	−0.44	0.52	−0.15	−0.84					
ED − Fear of loneliness	0.79	0.47	0.28	1.70					
ED − Borderline expression	0.44	0.61	0.12	0.71					
ED − Attention-seeking	−0.94	0.73	−0.20	−1.30					

* = $P < 0.05$. ED = emotional dependence.

In sum, the findings of the present study highlight that emotional dependence plays a specific role in GD, which differs from other clinical and community samples. In addition, these results add to the evidence that there are sex differences in the manifestation and psychological vulnerability factors of GD that must be considered when preventing, assessing, diagnosing or treating this disorder. More specifically, this study provides insights for establishing intervention strategies according to sex and people's particular needs. In this sense, the results suggest that working on loneliness, borderline expression and attention-seeking would benefit women with GD who consume alcohol, whereas addressing affective expression would be recommended for women with GD who consume drugs. Regarding men with GD, we suggest therapeutic strategies to address attention-seeking and separation anxiety if anxious-depressive symptomatology is detected.

Limitations and contributions

This study presents some limitations. Firstly, it is a cross-sectional study, so we cannot establish causal relationships. In future studies, it would be advisable to explore the directionality of the relationships through longitudinal research methodologies. Moreover, screening instruments were used for anxiety, depression, alcohol and drug abuse. Therefore, we recommend administering other complementary tests or qualitative methodologies to confirm the specificity of the diagnosis and control for the effect of social desirability. The findings obtained in this study are based on sex differences, so it would be appropriate to carry out studies based on gender differences in the future. Nonetheless, we have attempted to interpret the results from a gender perspective. There are also sociodemographic differences between the clinical and non-clinical samples that may have influenced the results. For example, the size of the non-clinical sample is larger, and their age is younger. Therefore, the results should be interpreted cautiously. Future studies are recommended to collect a larger clinical sample size to develop cohort analyses that provide a more complete profile of the differences found.

However, it is important to note that the present study allows us to extend our knowledge about GD in relation to some psychological variables that are frequently present in clinical practice. Despite this, to our knowledge, the relationship of emotional dependence, GD and comorbid psychopathology has not been explored in previous scientific literature. In addition, this study provides further evidence on the clinical profile of women with GD, which has been underexplored.

Conclusion

In light of the results, we can conclude that the associated risk factors and difficulties that trigger women and men to engage in gambling are different, even if the symptomatic expression seems to be the same (e.g., GD or emotional dependence). Moreover, empirical studies on women with GD remain very scarce and contradictory, leading to the assumption of parameters and therapeutic strategies based on research on men with GD. Hence, the findings of this research provide new empirical evidence suggesting that the complex underlying links of psychological factors predisposing to GD are closely related to the patient's sex.

Author statements

Acknowledgements

We are especially thankful to the active collaboration of FEJAR (Spanish Federation of Rehabilitated Gamblers) and all the gambling treatment associations that comprise it.

Ethical approval

The Institutional Review Board of the first author's university approved the study (ETK-17/20-21). This study was performed following the principles of the Declaration of Helsinki. Informed consent was obtained from all the participants included in the study.

Funding

Research funded by the Delegación del Gobierno para el Plan Nacional sobre Drogas [PNSD; Government Delegation for the National Plan on Drugs] (Ref: 2020I007). The funders played no role in the study design, data collection and analysis, decision to publish, or manuscript preparation. The research was also supported by a predoctoral grant for training university teachers from the Spanish Ministry of Universities (FPU20/03045).

Competing interests

All authors declare no conflicts of interest or financial interest.

Consent

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

Data availability

The data sets generated during and/or analysed during the current study are not publicly available due to confidentially.

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Public Health 223 (2023) e3–e4

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Letter to the Editor

Extreme disparities in the access to outpatient treatment for COVID-19 observed at a tertiary hospital in Florence, Tuscany, Italy

We read with interest the study by Fabiani et al. recently published by the journal.[1] The authors use national data from Italy to assess differences in outcomes between Italian and non-Italian patients.[1] The study shows marked differences in COVID-19 incidence with the migrant cohort having a lower burden.[1] However, data from the study suggest a tendency toward underdiagnosis and worse outcomes, including a higher rate of hospitalization. The data are similar to studies from the United States.[2] Access to vaccine administration was also difficult for migrant patients, which contributed to the disproportionate burden of COVID-19 in this population.[2,3] In the United States, access to early treatments for mild or moderate COVID-19 was also challenging for these patients.[3] No data from European countries on these dynamics have been reported to date. Here, the widespread presence of universal health systems should, in theory, reduce patients' disparities related to this issue.[4] However, a recent study estimated that migrants have higher chances to have unmet need for medical care than Italian citizens (odds ratio (OR) 1.27). This probability increases if the patient is an irregular migrant (OR 1.59).[4]

We analyzed data from our outpatient and inpatient cohorts admitted at the Careggi University Hospital, a tertiary care center in Florence, Italy. The hospital receives patients from three provinces (Florence, Prato, and Pistoia), an area populated by ≈ 1.500.000 inhabitants where ≈12% of the resident population is foreign born.

We included records from two pre-existing electronic data sets: outpatients seen at our COVID-19 early treatment clinic (March 2021 to February 2022) and inpatients (May 2021 to February 2022). We excluded patients who were hospitalized for reasons other than COVID-19 and had received antivirals or monoclonal antibodies due to incidental COVID-19 diagnosis. We collected demographics and clinical data (vaccination status and comorbidities). Continuous variables were described as means; categorical variables were described as proportions. A Chi-squared or rank-sum test was used to test for differences where appropriate. STATA 13 (STATACorp, USA) was used for data analysis.

We included 574 inpatients, of whom 154 were foreign born (26.9%) and 292 outpatients, with 16 foreign born (5.9%) ($P < 0.00001$).

Italians were older (mean age 66 ± 17.3 vs 47 ± 14.3 years, $P < 0.0001$). This difference was equally present in the inpatient (69 ± 17.2 vs 43 years, $P < 0.0001$) and in the outpatient cohorts (61 ± 15.6 vs 53 ± 13.9 years, $P = 0.0306$).

Foreign-born patients were less vaccinated than Italians (30% vs 60%, respectively, $P < 0.0001$). This difference was accounted for by inpatients (27% vs 52%, $P < 0.0001$), whereas outpatients did not show significant differences in vaccination status (62% vs 71%, $P = 0.558$), differences in comorbidity distributions are shown in the supplementary data.

Our report points out the presence of a potential barrier to access to COVID-19 early treatments for foreign-born patients seen at a tertiary center in Italy. The proportion of foreign-born subjects among hospitalized patients (26.9%) was higher than the prevalence of foreign-born subjects living in the catchment area of the hospital (12%), whereas the proportion of foreign-born subjects among patients accessing early treatment service was significantly lower (5.9%). Some ethnic groups are especially hard to reach, as shown by the disproportion between the number of Chinese patients requiring hospitalization and their absence in the outpatient clinic. The ethnic groups found in our center are representative of the composition of the migrant population living in the area serviced by our center. Most of the migrant population present in Italy consists of economic migrants, which explains the relative absence of migrants from other high-income countries.[5]

Referrals for COVID-19 early treatments in Italy are initiated by general practitioners or by outreach units that have been instituted during pandemic to follow up COVID-19 patients not requiring hospital-based care. Our findings on comorbidities and vaccination status confirm that migrant people are disadvantaged in terms of access to preventive medicine and primary care.[2] Recent reviews found that migrants are disproportionally at risk for hospitalization and death by COVID-19 while also being excluded from preventive interventions. Nevertheless, data on admissions and comorbidities suggest that foreign-born patients who might benefit from early treatment for COVID-19 are present in the area. However, emergency rooms remain the first gateway to the health system for the majority of migrant patients, and the lack of contact with primary care doctors delays COVID-19 diagnosis, hampers the administration of early treatments and might worsen outcomes.[1] Therefore, we believe that urgent, proactive actions are needed to improve the access to care for patients belonging to ethnic minorities.

Author statements

Acknowledgments

The authors would like to acknowledge all the physicians and nurses involved in running the outpatient clinic for early treatment of COVID-19 at our institution. The work presented in this article did not receive research funding. All authors have read and approved the article.

https://doi.org/10.1016/j.puhe.2023.01.021

Competing interests

A.B. reports research grants and payment to the institution from MSD, ViiV Healthcare and honoraria from GSK, Gilead. All the other authors have no conflict of interest to disclose.

Author contributions

S.G. and G.F. contributed to data gathering and writing the first draft. T.M. contributed to conceptualization, data curation, analysis, and reviewing and editing the article. M.S. contributed to supervision and reviewing and editing the article. A.B. and L.Z. contributed to conceptualization, supervision, resource availability, and reviewing and editing the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.01.021.

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22 December 2022
Available online 30 January 2023

Public Health 223 (2023) 67–71

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Themed Paper — Original Research

Integration of disease surveillance in the English context: a qualitative study

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ARTICLE INFO

Article history:
Received 20 May 2023
Received in revised form
14 July 2023
Accepted 20 July 2023
Available online 22 August 2023

Keywords:
Surveillance
Integrated disease surveillance
Early warning

ABSTRACT

Objectives: The world is experiencing increasing threats from infectious diseases and environmental hazards. Integration of disease surveillance systems has been put forth as one way to ensure more timely analysis of data and response. This study sought to explore the current context and state of integration of disease surveillance in England, including the barriers and facilitators to integration, as well as opportunities for improvement.

Study design: Qualitative study with focus groups and key informant interviews.

Methods: Focus group discussions (FGDs) and key informant interviews (KIIs) were conducted with key national, regional, and local stakeholders involved in surveillance activities in August and September 2022. These discussions and interviews were recorded, transcribed, and coded using a within-case content and thematic analysis.

Results: In total, five FGDs and 10 KIIs were conducted with 27 participants. Participants had different views on what integration is, though mostly agreed that surveillance systems in England are not integrated. Lack of standardisation, governance and oversight, and structural and financial barriers were hindering the current system from being more integrated. The additional benefits of integration above and beyond the 'status quo' during response activities were questioned by some.

Conclusion: England does not have a single integrated disease surveillance system but has a range of disease-specific surveillance systems that have evolved largely independently to meet operational needs. Greater integration may be desired and to a certain extent is important, but it is essential that it is understood as a means to an end and the overall purpose of surveillance is kept in mind.

Introduction

Infectious disease and environmental hazard reports are increasing globally, as evidenced by the 2014-16 Ebola outbreak that spread to 10 countries and caused 11,325 deaths, an outbreak of Mpox virus in more than 30 countries in 2022, and the COVID-19 pandemic.[1,2] As evidenced increasingly in One Health research, environmental issues and global climate change are contributing to the emergence and re-emergence of infectious diseases.[3] In the UK, the government has ranked pandemics as the threat with the potential for greatest impact in its National Risk Register and sets out in its pandemic preparedness plans the need for robust surveillance.[4,5]

Surveillance is an essential component of any national health protection system, underpinning its ability to detect and assess the impact of hazards to inform a response. In most countries, distinct surveillance systems for a range of health threats often operate independently or are integrated to varying degrees. The integration of disparate surveillance systems should improve information sharing and more accurate and timely analysis of data to inform action.[6] Integration of surveillance is purported to be part of a solution to prevent recurrence of delayed decision-making and deficient responses, such as those seen in many countries during the COVID-19 pandemic.[6,7,8] Much of the published work on integration of surveillance systems has focussed on lower-middle income country settings or on integrated disease surveillance and response (IDSR), which is a specific strategy for implementing surveillance and response systems advocated by the World Health Organization

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https://doi.org/10.1016/j.puhe.2023.07.027

(WHO) African Region.[9] While IDSR is a strategy specific to the WHO African Region, there is little literature on the state of integrated disease surveillance (which includes response as a core component of surveillance) as a concept (referred to in this report as IDS) in other regions of the world.

In England, the UK Health Security Agency (UKHSA) is the government agency responsible for public health protection and infectious disease surveillance. It has a remit to 'develop a robust health intelligence system that is accessible and integrated for the timely identification and prevention of public health threats reaching the UK'.[10] UKHSA took on these responsibilities from, now dissolved, Public Health England in October 2021. It also serves as the International Health Regulations (IHR) National Focal Point for the UK on behalf of the four nations (Scotland, Northern Ireland, Wales, and England). UKHSA has several directorates and teams whose work is important for IDS. These include national, regional, and local field epidemiology service teams, data and analytical sciences, and health protection teams. In addition, certain public health functions relevant to surveillance sit with local authorities, the National Health Service (NHS), and the Office of Health Improvement and Disparities (OHID). However, there is little published information on the state of integration of surveillance systems in England.

The aim of this study was to explore the current context and state of integration of disease surveillance in England, including the barriers and facilitators to integration, as well as opportunities for improvement.

Methods

Study setting

This study is part of a wider multicomponent programme funded by the Bill and Melinda Gates Foundation (BMGF) and delivered by International Association of National Public Health Institutes (IANPHI) of which the UKHSA is a member. This programme seeks to obtain a comprehensive understanding of the current state of IDS implementation globally as well as elucidate the available evidence-base for IDS. The content, methods, and findings of the programme are published fully elsewhere, including summary findings from the individual deep dives.[11,12] This article specifically focuses on one component, the in-depth study of IDS in England, and seeks to provide a more comprehensive overview of the findings from this study that is not published elsewhere.

Study type

The study used qualitative methods to assess and understand the state of integrated disease surveillance in England. Five domains considered necessary for IDS, using a bespoke framework based on the WHO IDS framework and Morgan et al. (2021), were overarching themes for analysis, namely: 1) governance, 2) system and structure, 3) financing, 4) core functions, and 5) resourcing requirements.[8,13]

Qualitative data

Qualitative data were collected through key informant interviews (KIIs) and focus group discussions (FGDs) with stakeholders in human health, animal health, and environmental health disciplines working at national, regional, and local levels of the England administrative system. Invitees to the FGDs and KIIs, included individuals specialising in screening and immunisations, health protection, field services, healthcare public health, environmental hazards, COVID-19, and public health intelligence.

FGDs and KIIs were conducted in English, lasted between 45 and 90 min, and were moderated by trained members of the project team, who were all UKHSA employees or held honorary contracts with UKHSA. In the FGDs, each moderator was assisted by a note-taker. One FGD and one KII were attended by an external observer from the Public Health Agency of Canada. Topic guides for the IANPHI project were adapted to the English context and provided questions and prompts for the semi-structured interviews and discussions (Supplementary File 1). Each moderator and note-taker attended training in qualitative interview and FGD methods. All FGDs and KIIs were conducted online via Microsoft Teams and digitally recorded for transcription and analysis purposes. All identifying information collected during the FGDs and KIIs was kept confidential. Recordings and transcripts were saved in a secure cloud folder accessed only by the project team. Participants were sent information in advance about the study. Participation was voluntary, and participants could decline to participate or leave at any time.

Analysis

A within-case content and thematic analysis was conducted once all KIIs and FGDs were complete. Two analysts (who had facilitated, interviewed, and/or observed the FGD and KIIs) reviewed the summary notes. A deductive-inductive approach was used for the thematic analysis. Responses were compared across different topic areas, health system levels, departments, and organisations to identify patterns that emerged, which were then grouped into five thematic categories based on the framework domains (governance, systems/structures, core functions, finance, and resourcing). The data were also reviewed for new emerging themes. Our results describe the state of integration of surveillance in England according to the framework domains and two novel thematic areas: consensus on integration definition and the need for integration.

Results

Five FGDs were conducted with a total of 17 stakeholders. Ten senior stakeholders from different organisations (including UKHSA, Animal and Plant Health Agency [APHA], and OHID) participated in KIIs. Each of the five FGDs had participants from UKHSA as well as other organisations.

State of surveillance in England

Participants were able to describe details of surveillance systems in England that were not readily available in academic or grey literature. Some explained there was no single overarching surveillance structure that spans across specialists, instead there are multiple separate surveillance systems. These systems use different tools and interfaces, though most are electronic with some manual linkages or data entry required. Many stakeholders were able to describe their specialist area of surveillance, either by topic (e.g., gastrointestinal infections, environmental), discipline (e.g., field epidemiology), or geography (e.g., local authority area), but admitted they did not have a complete understanding of and were unable to describe or list other surveillance systems within England. Most of the surveillance systems were described as highly developed and standardised in terms of topic areas covered and data flows at the regional or national level. However, those seeking information on local occurrences of a disease must go to multiple places to find the information. A participant explained that UKHSA is moving towards a more integrated system in England; there is now a clear technical objective to create systems that do so and new platforms are in development.

The list of [where] integration doesn't happen is a lot longer than the list of [where] integration does happen, but the few instances where it does happen shows that a) [it] is feasible and b) [it] is real. (KII, UKHSA, National)

The findings also corroborate the key domains identified a priori as necessary for integration. These are presented as follows.

Governance domain

Within England, laws and other regulations facilitate surveillance by mandating reporting and providing a legal instrument for sharing of data, e.g., the notification of infectious diseases (NOIDs), IHR, and changes to legislation during the COVID-19 response, which allowed for increased sharing of data. However, not all hazards of public health importance are supported by legislation (including some environmental hazards); there is no law to mandate integration of surveillance, and no requirement to report or record negative test results outside of enhanced investigations and research studies.

The legal duty to spell out [where surveillance] should happen is [in fact] a powerful mechanism by which integration can happen (KII, UKHSA, National)

COVID-19 was a game-changer in terms of data sharing … it made [it] much easier for us to actually share data with other organisations and … quite granular information. (KII, UKHSA, Regional)

Is there a single set of overarching guidance or even a legal instrument?… Not at all (KII, UKHSA, National)

Stakeholders explained that there is no single overarching governance body for human health surveillance across the UK, though activities must occur within the governance controls set out by separate organisations. In contrast, APHA has the UK Surveillance Forum, chaired by the four Chief Veterinary Officers of the four nations in the UK. This group oversees different aspects of surveillance across multiple species.

Participants felt that UKHSA should ideally have influence over the quality of data collection, particularly in terms of how data are collected and standardisation of systems, definitions, and tools. Currently, it lacks the authority to do this since most data are initially collected by the NHS. UKHSA can provide guidance but does not have the authority to mandate a change in the system. Some stakeholders felt that there was a natural separation between which organisations assess risks and those that take decisions to manage public health risk; some felt that UKHSA should not play both roles. Notwithstanding, stakeholders described that UKHSA does have the responsibility for ensuring system governance to effectively detect disease threats and to have intelligence to respond to them effectively.

Key thing is the overall strategic leadership of surveillance with a purpose and therefore some rational priority setting (KII, DHSC, National)

There is a bit of statute on who's allowed to take actions, especially at the national level, and it almost always defaults back to a politician, government, to ministers (KII, UKHSA, National)

I'm not a full advocate… in separating risk assessment from risk management…I personally feel UKHSA provides the expert input…. If something is not feasible to implement, that's for the risk managers, which in my opinion is… government [to deal with]. I feel that when UKHSA slightly puts a foot in both camps, that's where things potentially could go wrong (FGD, National)

Systems and structure domain

In England, many different organisations are involved in surveillance to varying degrees (Supplementary File 2). Organisational boundaries within England and national boundaries within the UK make integration difficult because each one has different access to data assets, IT systems (even within the same organisation), and procedures, and may use different definitions and denominators. Trust, relationships, and goodwill between colleagues help to overcome some of these boundaries by sharing of information, on often an ad hoc basis, via networks and meetings. However, public health system restructuring has redefined organisational remits for disease surveillance and disrupted previous relationships.

What I do think is probably essential is that we have the right people talking to each other and informing each other about what data are available so that they, as the experts, can work together on deciding which data to share (KII, APHA, National)

The constant [public health system] reorganisations … are not helping, changing rules and responsibilities (FGD, Regional)

Part of the difficulty is that half the people [who used to work on surveillance together have] moved out of the agency (KII, UKHSA, National)

When systems do not support access to data across organisations, further delays may be experienced if there is siloed working (within or across organisations) or an unwillingness to share, for example, due to information governance concerns or professional concerns about appropriate use of data sets. Some described a risk that if data are given away too freely, it may be misinterpreted, and wrong decisions or actions may be taken based on those assumptions.

You lose some of the nuance of each of the data sets as they're collected because each individual data set has its own…quirks and foibles that you as an asset owner…as an expert know about….[when] things get shifted and pushed into one big pool of data you lose that nuance and you lose that understanding of what the data can and can't tell you (FGD, National)

Finance and resource requirements domains

Technology to enable integration of surveillance exists, but a lack of funding means activities to make use of this technology and fully realise its benefits cannot be conducted. Budget cycles are usually only a few years long, so long-term sustainability of surveillance funding is not guaranteed. New collaborative surveillance activities may also have the problem of lack of clarity as to which agency will fund which aspects.

One of the big problems is that no one wants to fund surveillance. People will fund research….That's quite an important difference (KII, OHID, National)

We have to stop expecting the highest level of results without funding things (FGD, Regional)

We've never really had the money to do this (KII, UKHSA, National)

Core functions domain

In terms of core functions, the need for standardisation was highlighted by many stakeholders who reported the lack of sufficient standardisation in definitions, units of analysis, denominator populations, reporting styles, testing availability and approaches, geographical boundaries, quality, and other components across the health system are major barriers to integration. In addition, a lack of metadata limits in-depth understanding of exposures and outcomes, which necessitates research. Measures to increase the standardisation of reporting, such as the development of an internationally agreed set of definitions and the provision of Standard Operating Procedures or guidelines, and incentives to improve standardisation of reporting, were suggested by stakeholders.

> *If we are working to be able to integrate our disease surveillance or integrate our disease data…. we have to be collecting it in a consistent and standardised way, using the same definitions (KII, UKHSA, National)*

> *I don't feel like we have enough influence or control over the standardisation of data and tests and reporting of tests… (KII, UKHSA, Regional)*

There were also two emerging themes from the study, namely the lack of consensus as to what integration means in practice, and questions regarding the need for it.

What is integration?

There was no consensus among participants as to what integration means in the English context. The question 'what do we mean by integrated disease surveillance?' was frequently asked at the beginning of the KIIs and FGDs by participants. Some viewed it as the system's ability to converge the most detailed level of data in one place to conduct joint analysis, while others viewed it as the ability of users at the frontline of health care provision to access information in a timely and efficient manner (thereby demonstrating the performance of the entire system), linking with response, or being able to follow a patient's journey throughout the public health system. For all interpretations, stakeholders felt that most systems were not integrated in England. While data are frequently shared with individuals and organisations through networks, forums, or ad hoc communications, stakeholders did not feel this qualified as integration.

> *There is very good synthesis of insight across multiple surveillance systems…But I don't think that they are integrated in the sense that we can present them for interrogation in the same kind of analytical environment. (KII, UKHSA, National)*

> *Just talking to each other, sharing effectively… that is not surveillance integration… that is just using the surveillance information wisely (FGD, Regional)*

Need for integration

While integration was viewed positively by some stakeholders, one interesting finding was that some stakeholders questioned the need or benefit from additional or total integration of surveillance and demonstrated a wariness towards a universal solution. The scope and nature of surveillance integration should be determined by the aim of the disease surveillance system, which is based on individual, organisational, and political priorities, and these may not be aligned. Therefore, questions around 'what and who are we integrating surveillance for?' were raised. The aims of the surveillance system should be borne in mind and some integration may risk losing nuance and compromising aims. Some were concerned about the risks of a single system leading to an 'unwieldy' IT infrastructure that would have a substantial disruptive impact if it were to stop functioning.

> *It would take… lots of time and manpower and resources and money to do [integration]. And what would that enable us to do that we can't at the moment? (FGD, Regional)*

> *We can have an integrated surveillance system, but what is the purpose? What do you need to know? … are we sharing it with you for [a] purpose? (FGD, Regional)*

> *If we have one consolidated set up, we are even more at risk …. when something goes wrong that we would all lose access to the data that we need to enact public health action. (FGD, National)*

It was, however, noted that integration of surveillance systems should not just be for infectious diseases. It is essential to include both environmental hazards and animal health, utilising a One Health approach to effectively manage health threats.

Discussion

To the best of our knowledge, this is the first time the state of disease surveillance integration in England has been assessed. The surveillance system in England is not integrated, but participants felt the existing systems were mostly fit for current purposes. Due to the plurality of surveillance systems, it is uncertain whether a fully integrated disease surveillance system within England can be realised. There was a lack of consensus among stakeholders as to what integration means, as well as a questioning of the additional benefit integration would provide.

Whilst integration can have significant benefit for research purposes, key informants were less sure if there would be an additional benefit to acute service work and response activities. However, this could be due to lack of awareness of the potential benefits integration provides. Enthusiastic advocacy is important for promoting and enabling integration of surveillance systems, including human, animal, and environmental hazards. Surveillance must be an ongoing process, if it is stopped signals are missed, and if restarted, missing data impede trend analysis. Therefore, it is necessary to have the long-term resources to reflect the longitudinal nature of the work and adequate funding to deliver additional beneficial action beyond the current status quo.[6] If pursued, it is clear there needs to be political support and prioritisation, and adequate funding.

While the current remit for UKHSA states that it should 'develop a robust health intelligence system that is accessible and integrated', stakeholders did not seem aware of this, or at least did not mention it.[10] Additionally, most stakeholders directly involved in surveillance activities reported they didn't have much knowledge of the other surveillance activities in England, which implies no single group or person has full understanding of the whole surveillance system. It would be a considerable undertaking to go from the current status quo of iterative surveillance system reform to a 'one size fits all' approach. However, current surveillance systems could be improved to be more automated and agile, with data sharing agreements in place.[6] This requires willingness to fund improvements to these systems during 'down-times', which may not be seen as cost-effective as the impact and value of surveillance system activities changes with context. Further clarity on what is

meant by 'integrated', and the role and responsibility of UKHSA and other stakeholders would be beneficial. This is especially in terms of whether the UKHSA's role is to assess or manage disease risks, or both. Surveillance activities are also undertaken by organisations outside of UKHSA. Should governance of England's surveillance systems be strengthened, those responsible could make use of WHO's TAPIC framework.[14]

It is important to understand where integration adds value and how it achieves intended population health outcomes. Further cost-benefit analysis on the value of integrated disease surveillance in systems with good disease prevention, mitigation, and preparedness measures would inform distribution of resources for action.

The findings of this study must be considered in light of its limitations. Participation rates were low for the FGDs and KIIs due to the limited availability of potential participants. The researchers were UKHSA staff, which may have introduced bias when interviewing other members of the same organisation. Finally, the participants are drawn from England and may therefore not be generalisable to the other UK nations (Wales, Scotland, and Northern Ireland).

While there are mechanisms to enable data-sharing, England does not have a single integrated disease surveillance system. Further integration may be desirable to ensure improved outbreak detection and response but will only be feasible by certain conditions being met: clarity on the scope and nature of integration, political will and support, additional sustained funding, and clarity of organisational governance. Integration to a certain extent is important, but it is essential that it is understood as a means to an end and the overall purpose of surveillance is kept in mind.

Author statements

Acknowledgements

We would also like to acknowledge the generous contribution of Canada as our NPHI twinning partner and Celine Nadon (Public Health Agency Canada) who attended two England FGDs as an external participant.

Ethical approval

This study received organisational approval from UKHSA to be conducted in England. Separately, an ethical waiver was sought and received from the Institutional Ethical Review Board at Emory University, on behalf of IANPHI, on 8 July 2022 that covers the IANPHI global study of which this study is a subcomponent.

Funding

This study was funded by the Bill Melinda Gates Foundation (Grant ID: INV-037877).

Competing interests

AL is the co-editor-in-chief of the journal.

Authorship contribution statement

All authors were involved in data collection, analysis, and interpretation. JW drafted the article and SM, HW, and AL provided revisions. All authors approved the final version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.07.027.

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Public Health 223 (2023) e7–e8

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Letter to the Editor

Is it possible to contain COVID-19 in a female prison in Brazil? A pilot study

Brazilian prisons have some of the worst conditions in the world. These places are known for poorly ventilated structures and overcrowded shared cells, being an environment conducive to the development of respiratory diseases. SARS-CoV-2 is the virus that causes severe acute respiratory syndrome, which is transmitted through aerosols.[1] Thus, how to avoid contamination by COVID-19 in these spaces? In this study, we will answer this question.

The study was developed with the participation of 217 inmates in a female prison in the Northeast of Brazil. To ascertain SARS-CoV-2 contamination, we conducted a questionnaire to obtain data of interest and used a qualitative serological test for IgM and IgG antibodies (Eco Diagnostic, Corinto, Brazil) because studies suggest that antibody seroconversion occurs 7–14 days from the onset of symptoms of infection,[2] as well as immunochromatographic antigen (Wama Diagnostic, São Carlos, Brazil), an excellent method for diagnosing the acute phase of the disease. The principles of the Declaration of Helsinki were followed and approved by the National Bioethics Committee of Brazil under the protocol number CAAE 31018520.0.0000.5546.

Among the 217 inmates, 5.5% (12/217) tested positive for the COVID-19 antigen, 2.3% (5/217) of the participants obtained a reacting result for the IgM antibody, and 94% (204/217) tested positive for the IgG antibody (Table 1). The information obtained was analyzed using analysis of variance and Student's t-test in BioEstat 5.0 software (http://www.mamiraua.org.br/pt-br/downloads/programas/bioestat-versao-50). We related antigen detection to the number of inmates who reported recent contact with other participants who tested positive for infection and the appearance of symptoms in the last 15 days before testing, obtaining results of 0.34 ± 0.16, 4.76 ± 0.46, and 2.85 ± 0.36, with $P \leq 0.01$ and 95% confidence interval [CI], referring to detectable antigen and contact with positive participants, resulted in −0.25 to 0.01 and, relative to detectable antigen with the presence of symptoms, −0.28 to −0.01.

We associated inmates with up-to-date vaccination schedule and the IgG antibody index, resulting in 8.55 ± 0.50 and 1.15 ± 0.17 with $P \leq 0.01$ and 95% CI 0.09–0.34, which indicates the formation of memory antibodies (IgG) in large amount in the studied group, demonstrating that virus circulation occurs among inmates with up-to-date vaccination schedule, but vaccination prevented the development of the disease.[3] We compared the relationship between IgM and the amount of inmates who received visitation in the 1-year period, with results of 0.18 ± 0.11 and 6.07 ± 0.26 with $P \leq 0.01$ and 95% CI −0.18 to 0.09, suggesting that visitation may drive the virus into the prison system, also indicating that contamination among inmates relates directly to contact, as demonstrated in studies of the group.[1] During the study, there were no deaths related to the worsening of COVID-19 in the prison system, suggesting that the presence of estrogen and progesterone confer protection against aggravation of SARS-CoV-2 infection.[4]

Table 1
Analysis of seroprevalence and SARS-CoV-2 infection in a group of 217 participants of a female prison in the northeast of Brazil.

Immunological variables	*n*	%	*P**	95% CI
Antigen	12	5.5		
Symptoms	33	15.2		−0.25 to 0.01
Contact with SARS-CoV-2-positive individuals	51	23.5	<0.01	−0.28 to − 0.001
IgM	5	2.3		
Close visit	16	7.3	<0.01	−0.18 to 0.09
IgG	204	94		
Complete vaccine schedules for COVID-19	120	55.2	<0.01	0.09 to 0.34

P-value for Student's t-test.
*Significant when *P*-value <0.05.

On the other hand, the high levels of antibodies against SARS-CoV-2 found in this target public may represent a lower risk of complications in cases of postacute COVID-19 syndrome. A study by Ayoubkhani et al. suggested that immunity acquired through the vaccination process has a protective role against prolonged symptons of COVID-19, mainly due to administration of the booster dose. Similarly, Azzolini et al.[5] reinforced that two or three doses of vaccine can directly impact on immune response with immediate consequent decrease in hospitalization rates and incidence of long-term COVID-19. Thus, the control of the circulation of the pathogen as well as monitoring of new variants of concern have become one of the main tools in the preservation of public health in several social sectors, including the prison systems.

Through the present study, we show that it is possible to contain SARS-CoV-2 contamination in female prisons. By monitoring cases of COVID-19, through antigenic testing in prisons, we can control the incidence of infection, avoiding aggravations and deaths in the Brazilian prison system.

https://doi.org/10.1016/j.puhe.2023.01.023

Author statements

Funding

There is no funding source.

Competing interests

The authors have no conflicts of interest to declare.

Author contributions

All authors contributed equally to this work.

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4 January 2023
Available online 1 February 2023

Public Health 223 (2023) e9–e11

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Letter to the Editor

Reasons for parental refusal of human papillomavirus vaccine during the COVID-19 pandemic in 2020

The human papillomavirus (HPV) vaccine was first approved in 2006, and more than 135 million doses have been administered ever since.[1] Although the vaccine is safe and effective in preventing anogenital and oropharyngeal cancers, uptake remains suboptimal in the United States, falling short of the *Healthy People 2020* goal of vaccinating 80% of 13- to 15-year-olds.[2] Among the known barriers to HPV vaccine uptake, safety concerns have recently gained more attention during the COVID-19 pandemic, with a recent study reporting increase rate of HPV vaccine refusal due to safety concerns.[3] However, it is unknown whether HPV vaccine refusal is

Table 1
Sociodemographic factors associated with various reasons for HPV vaccine refusal, 2020 NIS-Teen (n = 2,901).

Characteristics	Frequency (unweighted percent)	Adjusted odds ratios (95% confidence interval)				
		Not necessary (n = 421)	Not recommended (n = 285)	Safety/side-effects (n = 731)	Lack of knowledge (n = 223)	Not sexually active (n = 196)
Adolescents						
Age						
13	657 (23.2)	Reference	Reference	Reference	Reference	Reference
14	632 (22.2)	1.13 (0.65, 1.98)	1.28 (0.63, 2.60)	1.42 (0.94, 2.15)	0.92 (0.48, 1.78)	0.85 (0.37, 1.94)
15	573 (17.9)	1.02 (0.57, 1.82)	1.06 (0.52, 2.14)	1.51 (0.99, 2.31)	0.91 (0.45, 1.83)	1.17 (0.49, 2.77)
16	525 (18.5)	1.09 (0.60, 1.99)	0.78 (0.36, 1.68)	1.24 (0.80, 1.92)	0.97 (0.47, 1.99)	1.06 (0.44, 2.58)
17	514 (18.3)	1.87 (0.98, 3.57)	0.75 (0.33, 1.69)	1.62 (0.98, 2.70)	0.91 (0.45, 1.83)	0.86 (0.32, 2.33)
Gender						
Female	1255 (43.2)	Reference	Reference	Reference	Reference	Reference
Male	1646 (56.8)	**0.70 (0.50, 1.00)**	**2.27 (1.37, 3.74)**	**0.69 (0.52, 0.93)**	0.94 (0.60, 1.47)	0.85 (0.52, 1.40)
Race/ethnicity						
Non-Hispanic White	2000 (60.5)	Reference	Reference	Reference	Reference	Reference
Non-Hispanic Black	200 (10.7)	1.31 (0.66, 2.60)	1.50 (0.65, 3.45)	**0.32 (0.17, 0.61)**	**2.59 (1.24, 5.40)**	1.92 (0.86, 4.29)
Hispanic	379 (19.5)	0.67 (0.37, 1.24)	**2.16 (1.29, 3.64)**	0.63 (0.38, 1.02)	1.60 (0.81, 3.17)	2.01 (0.93, 4.33)
Non-Hispanic Other	322 (9.5)	1.22 (0.67, 2.21)	**2.04 (1.01, 4.09)**	**0.59 (0.35, 0.99)**	1.29 (0.64, 2.59)	1.39 (0.67, 2.89)
Poverty						
Above poverty	2465 (85.8)	Reference	Reference	Reference	Reference	Reference
Below poverty	343 (14.2)	1.25 (0.66, 2.39)	1.18 (0.59, 2.37)	**0.52 (0.31, 0.86)**	0.61 (0.32, 1.16)	**2.69 (1.16, 6.22)**
Number of doctor visits						
≥4	509 (13.1)	Reference	Reference	Reference	Reference	Reference
2–3	926 (29.2)	0.89 (0.53, 1.49)	1.29 (0.69, 2.39)	1.12 (0.75, 1.67)	0.78 (0.39, 1.56)	0.94 (0.44, 2.03)
1	879 (33.0)	1.16 (0.72, 1.86)	1.16 (0.62, 2.17)	**0.64 (0.42, 0.96)**	0.59 (0.29, 1.21)	1.39 (0.70, 2.75)
None	568 (24.7)	0.99 (0.56, 1.75)	1.04 (0.51, 2.13)	0.93 (0.57, 1.52)	0.72 (0.33, 1.55)	1.40 (0.62, 3.16)
Mother's						
Children in the house						
1	1040 (31.6)	Reference	Reference	Reference	Reference	Reference
2–3	1463 (55.6)	0.76 (0.51, 1.12)	0.65 (0.38, 1.10)	**1.67 (1.16, 2.39)**	0.93 (0.58, 1.49)	1.19 (0.63, 2.23)
≥4	398 (12.8)	**1.83 (1.03, 3.26)**	**0.29 (0.13, 0.62)**	1.02 (0.61, 1.73)	0.63 (0.27, 1.49)	1.50 (0.69, 3.26)
Mother's age						
≤34	210 (8.0)	Reference	Reference	Reference	Reference	Reference
35–44	1345 (44.3)	0.87 (0.41, 1.88)	0.59 (0.26, 1.36)	0.76 (0.45, 1.30)	1.22 (0.55, 2.70)	0.86 (0.33, 2.23)
≥45	1346 (47.7)	0.98 (0.43, 2.25)	0.70 (0.29, 1.69)	0.75 (0.42, 1.32)	2.07 (0.96, 4.48)	1.17 (0.42, 3.28)
Marital status						
Married	2135 (65.1)	Reference	Reference	Reference	Reference	Reference
Not married	766 (34.9)	1.06 (0.70, 1.61)	0.90 (0.53, 1.53)	1.41 (0.95, 2.09)	0.92 (0.54,1.56)	0.49 (0.24, 1.01)
Education						
College graduate	1385 (42.0)	Reference	Reference	Reference	Reference	Reference
Some college degree	902 (29.2)	1.09 (0.72, 1.66)	1.06 (0.61, 1.86)	0.90 (0.64, 1.28)	0.79 (0.45, 1.38)	0.78 (0.37, 1.63)

(*continued on next page*)

https://doi.org/10.1016/j.puhe.2023.01.025

Table 1 (*continued*)

Characteristics	Frequency (unweighted percent)	Adjusted odds ratios (95% confidence interval)				
		Not necessary ($n = 421$)	Not recommended ($n = 285$)	Safety/side-effects ($n = 731$)	Lack of knowledge ($n = 223$)	Not sexually active ($n = 196$)
High school graduate	428 (21.8)	0.82 (0.49, 1.38)	**2.12 (1.14, 3.94)**	0.85 (0.54, 1.34)	1.37 (0.71, 2.65)	0.62 (0.30, 1.29)
Less than high school	186 (7.0)	0.52 (0.20, 1.37)	2.14 (0.96, 4.74)	1.19 (0.61, 2.31)	**2.45 (1.06, 5.68)**	**0.12 (0.02, 0.76)**
Reasons/barriers (collapsed)						
Not necessary	421 (16.1)					
Not recommended	285 (11.4)					
Safety/side-effects	731 (24.8)					
Lack of knowledge	223 (7.7)					
Not sexually active	196 (7.7)					
COVID/pandemic	19 (0.9)					
Other reasons	876 (31.6)					

HPV, human papillomavirus; NIS-Teen, National Immunization Survey–Teen.
Boldface indicates statistical significance ($P < 0.05$).

specifically associated with COVID-19. We described the reasons for HPV vaccine refusal during COVID-19 pandemic in 2020 in the United States.

We analyzed the 2020 National Immunization Survey–Teen, a deidentified, publicly available, nationally representative, random-dial-digit telephone survey of parents/guardians of 13- to 17-year-olds in the United States. Data have been approved by the National Center for Health Statistics Research Ethics Review Board; hence, our analysis was exempt from institutional review board approval. Analytic data ($n = 2{,}901$) included only unvaccinated adolescents. Outcome of interest was reasons given by parents/guardians for HPV vaccine refusal, derived from unique responses to the survey question, "*What is the main reason teen will not receive HPV shots in the next* 12 months?" Parents/guardians of unvaccinated adolescents identified the primary reason for vaccine refusal from a list of 29 unique predefined reasons. For regression analyses, we only looked at the top five most frequently cited reasons "not needed or not necessary," "safety/side effects concerns," "not recommended," "lack of knowledge," and "child not sexually active." Weighted prevalence rates of reasons for HPV vaccine refusal were estimated for the overall population. Next, five separate weighted multivariable logistic regression models were used to examine the association between adolescent and mother's sociodemographic and healthcare utilization factors, and the five most frequently cited reasons for refusal: "*not needed or not necessary,*" "*safety/side effects concerns*," "*not recommended,*" "*lack of knowledge,*" and "*child not sexually active*." All analyses were performed with SAS 9.4 survey procedures to account for the complex survey design of the NIS-Teens data. Tests were two tailed, and significance was set at $P < 0.05$.

Of the 29 unique reasons cited for HPV vaccine refusal, the five most frequently cited reasons were safety/side-effects concerns (24.8%), not necessary (16.1%), not recommended (11.4%), lack of knowledge (7.7%), and not sexually active (7.7%; Table 1). Less than 1% of parents/guardians cited COVID-19 as reason for HPV vaccine refusal. In the adjusted regression analyses of parents/guardians' main reasons for HPV vaccine refusal, parents/guardians who cited safety/side-effects concerns were less likely to be non-Hispanic Black (adjusted odds ratio [aOR] = 0.32; 95% confidence interval [CI] 0.17, 0.61), or live below poverty line (aOR = 0.52; 95% CI 0.31, 0.86). Those who cited the vaccine was not recommended were more likely to be males (aOR = 2.27; 95% CI 1.37, 3.74), Hispanics (aOR = 2.16; 95% CI 1.29, 3.64), or mothers with high school diploma or less (aOR = 2.12; 95% CI 1.14, 3.94). Parents/guardians citing lack of knowledge as a reason for not vaccinating their adolescent child was associated with being non-Hispanic Black (aOR = 2.59; 95% CI 1.24, 5.40) or mothers with high school diploma or less (aOR = 2.45; 95% CI 1.06, 5.68; Table 1).

The purpose of this study was to describe the main reasons for non-vaccination of HPV vaccine among parents/guardians of unvaccinated adolescents. The five most common reasons for HPV vaccine refusal in the United States in 2020 made up about two-thirds of the reasons given by parents/guardians in this survey. Only 0.9% of parents/guardians cited COVID-19 pandemic as a reason for HPV vaccine refusal. Future research should use data collected after 2020 to evaluate if COVID-19 disinformation is contributing to parents' refusal to get the HPV vaccine. We note with concern that after the demonstrable success of the HPV vaccine as a cancer-preventing vaccine, a proportion of parents/guardians continue to cite lack of knowledge and physician recommendation as primary reasons for vaccine refusal. Physicians should use clinical encounters as opportunities to educate parents and actively recommend the HPV vaccine.[4] Doing so may decrease HPV vaccine misinformation and hesitancy.[5]

Our study is not without limitations. First is the cross-sectional nature of the survey, any change in intention to vaccinate was not recorded. Also, it is unknown whether some of the vaccine safety concerns are COVID related. Finally, there is non-response bias, although the use of weighting reduces this potential bias. In conclusion, our study showed that in 2020, 29 unique reasons were reported for refusing the HPV vaccine, with safety/side-effects concerns being the most cited reason and COVID-19 accounted for <1% of reasons given.

Author statements

Competing interests

N.O.-P. is a scientific advisor to Navigating Cancer. All other co-authors had no conflict to declare.

Funding

N.O.-P. reported receiving grants from the National Institute of Health/National Institute of Dental and Craniofacial Research (K0s1DE030916) outside of the submitted work.

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1 January 2023
Available online 1 February 2023

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Public Health 223 (2023) 209–216

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Self-reported sleep disorders and the risk of all cancer types: evidence from the Kailuan Cohort study

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ARTICLE INFO

Article history:
Received 13 March 2023
Received in revised form
18 June 2023
Accepted 3 August 2023
Available online 5 September 2023

Keywords:
Sleep quality
Cancer
Risk
Prospective
Insomnia
Snoring

ABSTRACT

Objectives: Previous studies that focussed on sleep disturbance have primarily examined specific aspects of sleep disorders rather than considering overall sleep quality. We aimed to investigate different sleep disorders and their combination as risk factors for different types of cancer.
Study design: Prospective cohort study.
Methods: In this prospective cohort study, we included 78,232 participants. A self-reported questionnaire was used to address insomnia, daytime sleepiness, snoring, and sleep duration. Overall sleep quality was evaluated by summarising these four sleep parameters. Cox proportional hazards analysis was used to estimate the hazard ratios and their 95% confidence intervals for determining the effect of the overall sleep-quality score and its components on the risk of incident cancer.
Results: During a median follow-up of 5.67 years, 1266 participants were diagnosed with incident cancer. Compared to participants in the best sleep-quality score group, participants in the worst sleep-quality score group had a higher subsequent risk of overall cancer, and colorectal, breast, uterine or uterine cervical, prostatic, kidney, and bladder cancer. Participants with insomnia and snoring status had an elevated risk of head and neck, breast, uterine or uterine cervical, prostatic, kidney, bladder cancer, and lymphoma.
Conclusions: Poor overall sleep-quality scores as well as poor scores for the scale's components, including insomnia and snoring status, elevated the risk of overall and several specific-site cancers.
Trial registration: Kailuan Study, ChiCTR2000029767. Registered 12 February, 2020-Retrospectively registered, https://www.chictr.org.cn/showprojEN.html?proj=48316.

According to World Health Organization (WHO), cancer ranks as the first or second leading cause of death in 112 of 183 countries, with an estimated 19.3 million new cancer cases and nearly 10.0 million cancer deaths in 2020. Overall, the burden of cancer incidence and death is rapidly increasing, especially in low- and middle-income countries, which already struggle to cope with the current burden, reflecting both population ageing and changes in the prevalence and distribution of the major risk factors for cancer. The established risk factors for the initiation and development of cancer include tobacco use,[1] infectious agents,[2] alcohol consumption,[3] obesity,[4] physical inactivity,[5] and socioeconomic factors. Notably, many cancer cases can be prevented, and it is essential to provide robust, independent scientific evidence on the prevalence, patterns, and causes of cancer, as well as prevention and early detection.

Sleep disorders are frequent in the general population, with nearly 23%–56% of the general population suffering from them.[6] Recently, studies have found that sleep disorders are associated

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https://doi.org/10.1016/j.puhe.2023.08.007

with multiple health consequences, including obesity,[7] metabolism disorders,[8] impaired cognitive performance,[9] cardiovascular disease (CVD),[10] chronic kidney disease,[11] and even cancer.[12] Overall, a bidirectional relationship has developed between sleep disorders and cancer over the last few decades. Sleep disorders can occur as a consequence of cancer treatment and can cause an impaired quality of life. On the other hand, some types of sleep disorders have been classified by the WHO-International Agency for Research on Cancer (IARC) as risk factors for cancers, demonstrating the scientific community's growing interest in the topic.

Previous studies have mainly focussed on patients with sleep disturbances who had received chemoradiotherapy, making the results unsuitable for extrapolation to the general population. Moreover, previous sleep disturbance studies were only focused on one aspect of sleep disorders instead of overall sleep quality. In the current study, we aimed to investigate different sleep disorders and their components, including insomnia, daytime sleepiness, sleep duration, and snoring, as well as their combination as risk factors for different types of cancer by drawing data from the Kailuan cohort study.

Methods

Study Population

The current prospective analysis was based on a subset of the Kailuan Cohort, a multicenter ongoing prospective study based in the Kailuan community in Tangshan, Hebei Province in North China.[13] Briefly, in 2006–2007, 101,510 adults (81,110 men and 20,400 women) aged 18–98 years were included and followed up every 2 years. Each examination included face-to-face questionnaire surveys, body measurements, and clinical and laboratory examinations. In 2014, all individuals were invited to provide information on their sleep parameters. Among the 82,693 participants who completed the sleep questionnaire, 637 individuals with a history of cancer and 3824 participants with missing data on covariates were excluded, leaving 78, 232 participants who were ultimately enrolled in this study (Fig. 1).

Assessment of sleep disorders (exposure)

The participants' overall sleep quality scores (SQSs) were the main exposure in this study. Overall scores were calculated by summing all sleep disorders that were collected through questionnaires by trained field workers. Overall sleep-quality scores (SQS) included insomnia, daytime sleepiness, sleep duration, and snoring, with scores ranging from 0 (best) to 8 (worst), as described in Supplemental Table 1.[14,15] Participants were divided into three groups based on the overall SQS: worst sleep quality (SQS: >5), poor sleep quality (SQS: 3–5), and best sleep quality (SQS: <3).

Insomnia

The Chinese version of the Athens Insomnia Scale (AIS)[16] was used to assess the participants' insomnia status in the past month. The AIS, a self-report questionnaire, includes the following eight items: sleep induction, night awakening, awakening in the early morning, total sleep duration, total quality of sleep, decreased sense of wellbeing, overall functioning, and daytime sleepiness. Scores for each item range from 0 to 3 (0 = no event, 1 = mild, 2 = moderate, and 3 = severe). Insomnia was defined as a total AIS score of ≥6. An AIS validation study in China demonstrated good test–retest reliability (83%), sensitivity (96%), and specificity (76%) compared to physician diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

Daytime sleepiness

As a measure of daytime sleepiness, we used the Chinese version of the Epworth Sleepiness Scale,[17] which includes eight items, each scored from 0 to 3, denoting a greater chance of falling asleep while engaged in certain daily situations. An overall score of ≥10 indicates excessive daytime sleepiness.[18] In Chinese adults, the Chinese version of the Epworth Sleepiness Scale has shown good test–retest reliability (rho = 0.74) and a significant correlation (Spearman rho = 0.75) with the English version.[17]

Sleep duration and snoring

Through a questionnaire, participants were asked to report the usual hours of sleep (in hours) they got in a typical night. We categorised nighttime sleep duration into five groups: <6.0 h, 6.0–6.9 h, 7.0–7.9 h, 8.0–8.9 h, and ≥9 h, and the group with 7–8 h of sleep per night was taken as the reference category for its effectiveness in promoting optimal health. Snoring status was classified into three categories, never or rarely, occasionally, and

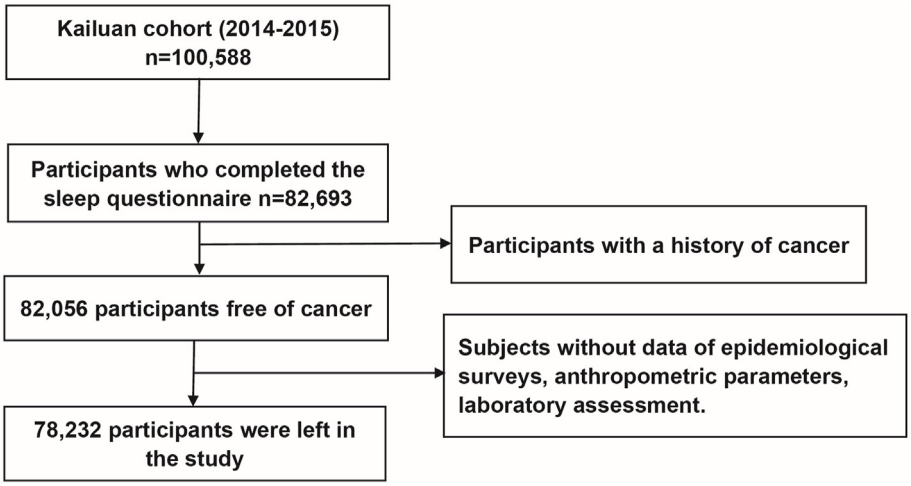

Fig. 1. Flow chart of study participants.

frequent snoring, based on the frequency of self-reported snoring plus breathing stops (approximately 10 s or longer) during usual sleep. Notably, the presence of breathing stops was defined as follows: 1) individuals who reported experiencing choking and waking owing to nocturnal breathing interruptions and 2) bedmates or family members stating that the participants experienced severe breathing stops even when the participants themselves were unconscious of these symptoms.

Outcome ascertainment

Incident cancer cases were identified via 1) biennial self-reports until December 31, 2022; 2) checking medical records linked with the Tangshan Medical Insurance System, the Kailuan Social Security System, and the Provincial Vital Statistics; and 3) examining discharge lists from the 11 affiliated hospitals. Further confirmation of all cases was performed by specialists based on either specific clinical features or histopathological findings from the hospitals where the patients were treated for cancer. Cancer cases were coded using the International Classification of Diseases, Tenth Revision (ICD-10). In addition, death cases were also identified from the Kailuan Social Security System.

Assessment of covariates

Data on covariates, including age, sex, income level (>5000 ¥), educational background (high school or above), rural area residence, physical exercise (≥3 times/week, ≥30 min/time), smoking (≥1 cigarette/d), drinking (≥100 ml of an alcoholic beverage/day), tea consumption (>4 times/w), sedentary lifestyle (>8 h/d), high salt intake (>12 g/d), high-fat diet, sleep medication usage, family history of cancer, history of chronic kidney disease (CKD), and hepatitis C virus (HCV) infection, were collected via questionnaires at the baseline examination (2014–2015). Hypertension was defined as having an systolic blood pressure (SBP) of ≥140 mmHg and/or a diastolic blood pressure (DBP) of ≥90 mmHg and/or a history of diagnosis and/or taking antihypertensive medication.

Levels of serum fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TGs), C-reactive protein (CRP), uric acid (UC), creatinine (Cr), alanine aminotransferase (ALT), total bilirubin (TBIL) and hepatitis B surface antigen (HBsAg) were determined using an autoanalyzer (Hitachi 747; Hitachi) at the central laboratory of Kailuan Hospital. Diabetes was defined as having an FBG level of ≥7 mmol/L and/or having a history of diabetes and/or taking diabetes medication.

The diagnoses of liver cirrhosis, fatty liver, gallstones, and gallbladder polyps were based on the results of abdominal ultrasounds by using real-time ultrasound sonography (PHILIPS HD-15) or medical records from the Tangshan medical insurance system.

Statistical analysis

Continuous variables with normal distribution are described as means ± standard deviations (SDs) and were compared by one-way analysis of variance. Skewed distributed variables are described as the median (interquartile range) and were analysed by nonparametric tests. Categorical variables are represented by absolute values with percentages and were compared by the chi-square test. The person-years were calculated from the date of the baseline examination (2014–2015) until death, cancer diagnosis, or the end of the follow-up (31 December 2020), whichever occurred first. The restricted cubic spline (RCS) plot was used to describe the dose–response association between sleep scores and cancer risk. Cox proportional hazards analysis was used to estimate the hazard ratios (HRs) and their 95% confidence intervals (CIs) for determining the effect of the overall sleep-quality score and its components, including insomnia, daytime sleepiness, sleep duration, and snoring, on the risk of incident cancer.

Only the first reported type of cancer was included in the pooled cancer analyses. Furthermore, for each cancer type, site-specific assessments were performed. Chronic hepatitis B virus (HBV) and HCV infection, fatty liver, and liver cirrhosis were further adjusted in the multivariate model of liver cancer in the site-specific analysis. Gallstones and gallbladder polyps were also adjusted in the gallbladder or extrahepatic bile duct cancer model. Moreover, we adjusted CKD in the kidney cancer model. The analyses of breast, uterine or cervical, ovarian, and prostatic cancers were performed only in men or women as applicable.

Previous studies have observed a two-way connection between sleep disorders and cancer. To eliminate the possibility of reverse causation and potential effects of the use of sleep medications, we separately excluded participants with incident cancer that had occurred within the first year of follow-up or who took sleep medications in the sensitivity analyses. All *P* values were two-tailed with a significance level of <0.05. Statistical analyses were performed using a commercially available software program (SAS software, version 9.4).

Results

Baseline characteristics of the study population stratified by overall SQS

The mean (SD) age of the 78,232 individuals at baseline was 51.55 (15.06) years (range: 18–98 years), including 63,195 (80.78%) men and 15,037 (19.22%) women. Participants in the poor sleep-quality-score group (scores: >5) were younger, more likely to be female, and more likely to take sleep medication. Significant differences were found for age, levels of FBG, TC, body mass index (BMI), SBP, TGs, CRP, Cr, and TBIL, the percentage of family income, educational background, rural area residence, physical exercise, smoking status, drinking status, family history of cancer, diabetes mellitus, hypertension, CKD, tea consumption, sedentary lifestyle, high salt intake, high fat consumption, fatty liver, gallstones, and HCV infection among the three prespecified groups. The levels of DBP and ALT and the percentage of cirrhosis, gallbladder polyps, and HBsAg seropositivity, on the other hand, did not differ significantly among the different sleep-quality-score groups (Table 1).

The association of overall SQS with the risk of combined and site-specific cancers

During a median (interquartile range) follow-up of 5.67 (5.21–6.10) years, 1266 participants were diagnosed with incident cancer, including 58 with head and neck cancer, 48 with oesophageal cancer, 83 with gastric cancer, 174 with colorectal cancer, 96 with liver cancer, 28 with pancreatic cancer, 424 with lung cancer, 98 with breast cancer, 37 with uterine or uterine cervical cancer, 46 with prostatic cancer, 54 with kidney cancer, 49 with bladder cancer, 15 with lymphoma and leukaemia, and 56 with other types of cancer including bone and soft tissue, ovarian, skin, and gallbladder cancer. Compared to participants in the best sleep-quality-score group (scores: <3), participants in the worst sleep-quality-score group (scores: >5) had a higher subsequent risk of combined cancer (adjusted HR = 1.44; 95% CI: 1.12–1.92) after adjustments were made for confounders (Table 2). The results from RCS (Fig. 2) showed a positive dose–response and linear association of the overall sleep-quality scores with overall cancer risk (*P*-overall = 0.001, P-nonlinear = 0.093). The associations of sleep-quality scores with specific-site cancer risk are presented in

Table 1
Baseline characteristics of the participants stratified by overall sleep quality score.

Variables	Overall sleep quality score			
	<3	3–5	>5	*P*-value
n (%)	66,883	7850	3499	
Men (%)	54,382 (81.31)	6168 (78.57)	2645 (75.59)	<0.001
Age (year)	51.73 ± 15.11	52.40 ± 14.64	46.28 ± 14.08	<0.001
FBG (mmol/L)	5.83 ± 1.97	5.84 ± 2.16	5.72 ± 1.78	0.003
TC (mmol/L)	5.19 ± 1.33	5.22 ± 1.73	5.09 ± 1.05	<0.001
BMI (Kg/m^2)	24.86 ± 3.33	25.11 ± 3.47	25.11 ± 3.71	<0.001
SBP (mmHg)	135.86 ± 19.87	134.94 ± 19.54	130.56 ± 18.51	<0.001
DBP (mmHg)	81.83 ± 10.85	82.04 ± 11.17	81.74 ± 11.16	0.238
TG (mmHg)	1.26 (0.87,1.91)	1.28 (0.87,1.94)	1.30 (0.90,2.07)	<0.001
CRP (mg/L)	1.00 (0.50,2.10)	1.05 (0.40,2.30)	1.10 (0.50,2.20)	0.028
SUA (μmol/L)	323 (269,383)	324 (267,384)	323 (265,391)	0.978
Scr (μmol/L)	72.80 (62.00,84.70)	74.00 (63.80,85.40)	74.00 (62.70,86.80)	<0.001
ALT (u/L)	20.00 (15.00,28.00)	20.00 (14.80,28.00)	20.00 (14.00,29.00)	0.532
TBIL (umol/L)	13.00 (10.10,16.70)	13.30 (10.30,17.00)	12.70 (9.90,16.30)	<0.001
Per capita income (>5000 ¥)	13,582 (20.31)	1351 (17.21)	777 (22.21)	<0.001
Educational background (High school or above, %)	18,147 (27.13)	2478 (31.57)	1568 (44.81)	<0.001
Rural area life (%)	23,963 (35.83)	2859 (36.42)	1608 (45.96)	<0.001
Physical exercise (%)	15,573 (23.28)	2131 (27.15)	866 (24.75)	<0.001
Smoking status (%)	26,898 (40.22)	3376 (43.01)	1542 (44.07)	<0.001
Drinking status (%)	21,783 (32.57)	3637 (46.33)	1722 (49.21)	<0.001
Family history of cancer (%)	845 (1.26)	137 (1.75)	80 (2.29)	<0.001
Diabetes mellitus (%)	7780 (11.63)	920 (11.72)	351 (10.03)	0.014
Hypertension (%)	26,825 (40.11)	3163 (40.29)	1114 (31.84)	<0.001
CKD (%)	289 (0.43)	117 (1.49)	84 (2.40)	<0.001
Tea consumption (>4 times/w, %)	2600 (3.89)	378 (4.82)	186 (5.32)	<0.001
Sedentary lifestyle (> 8 h/d, %)	14,776 (22.09)	1958 (24.94)	1047 (29.92)	<0.001
High salt consumption (>12 g/d, %)	3518 (5.26)	462 (5.89)	251 (7.17)	<0.001
High fat diet (regularly, %)	2179 (3.26)	270 (3.44)	143 (4.09)	0.023
Fatty liver (%)	25,810 (42.63)	3654 (46.55)	1309 (37.41)	<0.001
Gallbladder polyp (%)	775 (1.16)	90 (1.15)	36 (1.03)	0.781
HCV infection (%)	51 (0.08)	10 (0.13)	5 (0.14)	<0.001
HBsAg Seropositive (%)	1200 (1.79)	114 (1.45)	68 (1.94)	0.067
Sleep medication (%)	345 (0.52)	255 (3.25)	189 (5.40)	<0.001

Note: FBG: fasting blood glucose; TC: total cholesterol; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; CRP: C-reactive protein; SUA: serum uric acid; Cr: creatinine; ALT: alanine transaminase; TBiL: total bilirubin; CKD: chronic kidney disease.

Table 2
The association of the overall sleep-quality score with the overall cancer risk.

Overall sleep-quality score	Cases/person-years	Crude models		Adjusted models	
		HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
< 3	1041/376,845	Ref.		Ref.	
3–5	142/44,423	1.16 (0.97,1.38)	0.108	1.09 (0.92,1.30)	0.322
> 5	83/20,144	1.44 (1.12,1.92)	0.002	1.28 (1.02,1.69)	0.041
P for trend			0.101		0.141

Note: Adjusted models included age (every 10 years), sex, BMI, TC, TG, Scr, UA, CRP, smoking status, drinking status, physical activity, sedentary lifestyle, family income, tea consumption, rural life, salt intake, high-fat diet, diabetes, and family history of cancer.
HR: hazard ratio; CI: confidence interval.

Table 3. Compared to participants with the best overall SQSs (scores: <3), individuals with the worst overall sleep-quality scores (scores: >5) exhibited an elevated risk of colorectal cancer (adjusted HR = 1.91; 95% CI: 1.05–3.48), breast cancer (adjusted HR = 2.58; 95% CI: 1.38–4.83), uterine or uterine cervical cancer (adjusted HR = 2.82; 95% CI: 1.07–7.43), prostatic cancer (adjusted HR = 3.55; 95% CI: 1.24–10.14), kidney cancer (adjusted HR = 3.81; 95% CI: 1.61–9.03), and bladder cancer (adjusted HR = 5.32; 95% CI: 2.33–12.17). Notably, in the multivariate analyses, participants with SQSs of 3–5 were also associated with an elevated risk of breast cancer incidence (adjusted HR = 2.01; 95% CI: 1.20–3.36) compared to participants with SQSs of <3 (see Fig. 3).

Fig. 3 illustrates the association of the overall sleep-quality score components, including insomnia (no vs. yes), daytime sleepiness (no vs. yes), sleep duration (7–8 h vs. others), and snoring (no vs. occasional and frequent), with site-specific cancer risk. Compared to people who rarely or never had insomnia, participants who suffered from insomnia had an elevated risk of head and neck cancer (adjusted HR = 2.03; 95% CI: 1.04–3.97), breast cancer (adjusted HR = 2.41; 95% CI: 1.50–3.86), uterine or uterine cervical cancer (adjusted HR = 2.39; 95% CI: 1.11–5.16), prostatic cancer (adjusted HR = 2.68; 95% CI: 1.19–6.02), kidney cancer (adjusted HR = 2.77; 95% CI: 1.34–5.70), bladder cancer (adjusted HR = 3.49; 95% CI: 1.73–7.03), and lymphoma (adjusted HR = 7.44; 95% CI: 1.35–41.15). In addition, participants who were likely to snore had an elevated risk of breast cancer (adjusted HR = 2.29; 95% CI: 1.36–3.84), uterine or uterine cervical cancer (adjusted HR = 2.50; 95% CI: 1.06–5.85), prostatic cancer (adjusted HR = 3.08; 95% CI: 1.39–6.80), kidney cancer (adjusted HR = 2.77; 95% CI: 1.34–5.70), and bladder cancer (adjusted HR = 3.68; 95% CI: 1.79–7.56). It is worth noting that borderline significant associations of nonoptimal sleep duration with the risk of breast cancer (adjusted HR = 3.68; 95% CI: 1.79–7.56) and prostatic cancer (adjusted HR = 1.83; 95% CI:

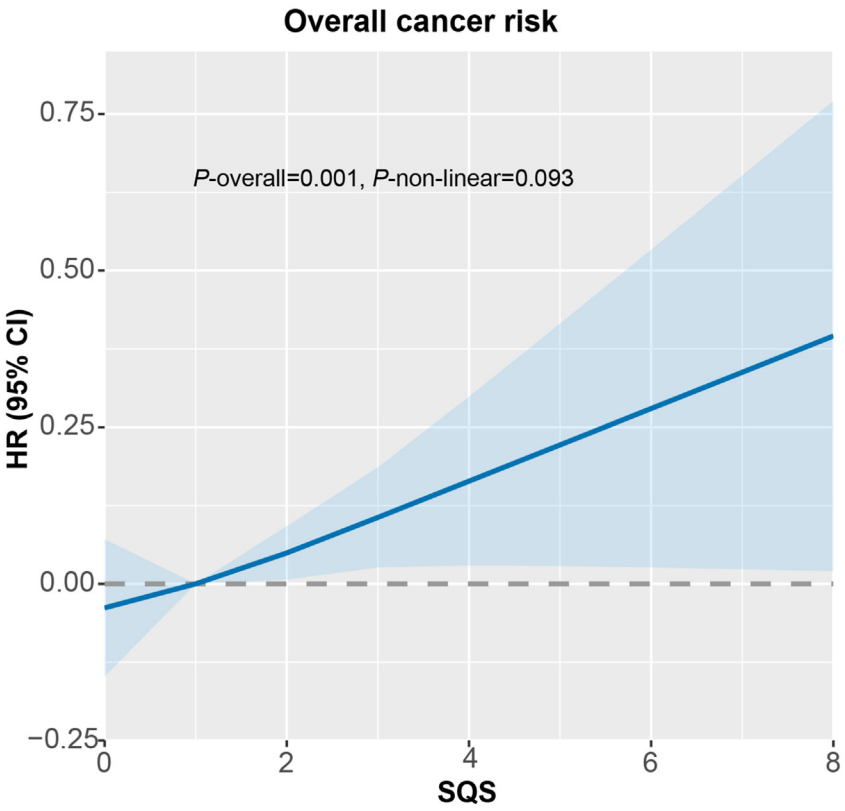

Fig. 2. The dose–response association of overall sleep-quality score with overall cancer risk.

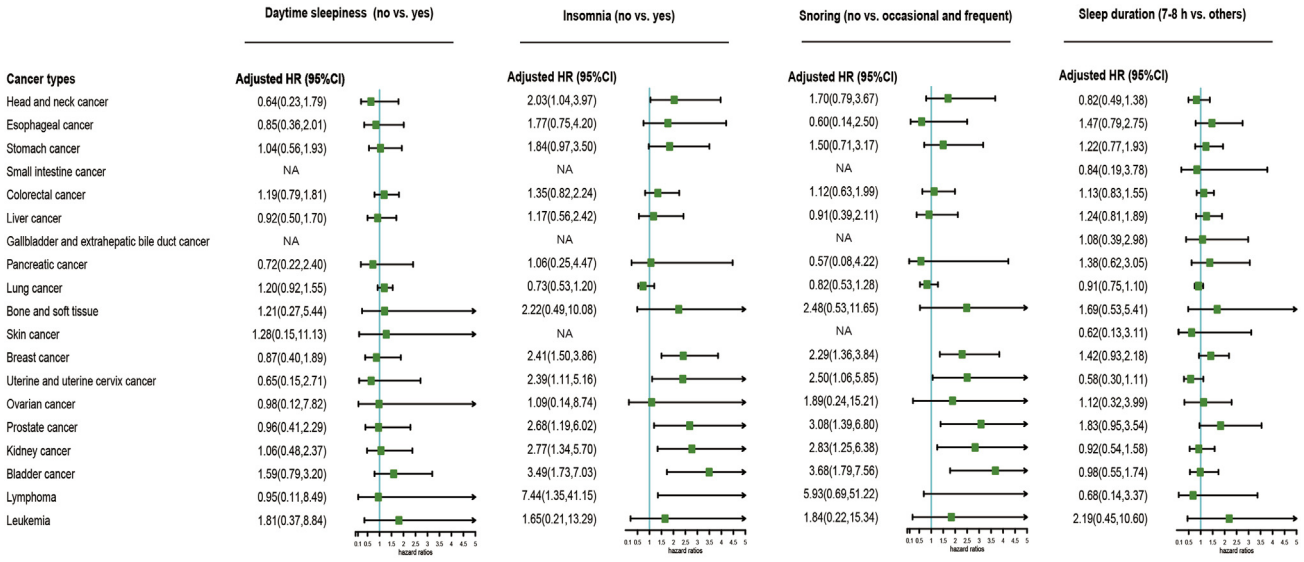

Fig. 3. The association of the overall sleep-quality score components with the risk of specific-site cancer.

0.95–3.54) were observed. However, we failed to find a significant association between daytime sleepiness and site-specific cancer risk.

In the sensitivity analysis, we excluded 164 patients with incident cancer that occurred within the first year of follow-up and 789 individuals who took sleep medications. Significant associations of poor sleep quality (scores: >5) with the risk of colorectal cancer (adjusted HR: 2.05–2.08), breast cancer (adjusted HR: 2.05–2.08), uterine or uterine cervical cancer (adjusted HR: 2.78–2.80), prostatic cancer (adjusted HR: 2.96–3.68), kidney cancer (adjusted HR: 3.90–4.08), and bladder cancer (adjusted HR: 5.17–5.80) were found in the multivariate analyses (Table 4).

Discussion

In this large-scale, community-based study among the Chinese population, we found that 1) participants with poor sleep quality based on the total SQS (scores: >5) had an elevated risk of overall,

Table 3
The association of the overall sleep-quality score with the risk of specific sites of cancers.

	Cancer types		Overall sleep-quality score		
			<3	3–5	>5
Overall	Head and neck cancer	Cases/person-years	46/376,845	7/44,423	5/20,144
		Adjusted HR (95%CI)	Ref.	1.20 (0.54,2.66)	1.72 (0.67,4.39)
	Oesophageal cancer	Cases/person-years	40/376,845	6/44,423	2/20,144
		Adjusted HR (95%CI)	Ref.	1.14 (0.48,2.70)	1.12 (0.27,4.69)
	Stomach cancer	Cases/person-years	66/376,845	12/44,423	5/20,144
		Adjusted HR (95%CI)	Ref.	1.44 (0.77,2.67)	1.64 (0.65,4.13)
	Colorectal cancer	Cases/person-years	146/376,845	16/44,423	12/20,144
		Adjusted HR (95%CI)	Ref.	0.86 (0.51,1.45)	1.91 (1.05,3.48)
	Liver cancer [a]	Cases/person-years	83/376,845	7/44,423	6/20,144
		Adjusted HR (95%CI)	Ref.	0.70 (0.32,1.53)	1.70 (0.73,3.95)
	Pancreatic cancer	Cases/person-years	24/376,845	3/44,423	1/20,144
		Adjusted HR (95%CI)	Ref.	0.99 (0.30,3.30)	1.10 (0.15,8.24)
	Lung cancer	Cases/person-years	370/376,845	43/44,423	11/20,144
		Adjusted HR (95%CI)	Ref.	0.95 (0.69,1.30)	0.77 (0.42,1.40)
	Kidney cancer [b]	Cases/person-years	44/376,845	4/44,423	6/20,144
		Adjusted HR (95%CI)	Ref.	0.85 (0.31,2.39)	3.81(1.61,9.03)
	Bladder cancer	Cases/person-years	35/376,845	7/44,423	7/20,144
		Adjusted HR (95%CI)	Ref.	1.49 (0.66,3.38)	5.32(2.33,12.17)
	Lymphoma or leukaemia	Cases/person-years	11/376,845	2/44,423	2/20,144
		Adjusted HR (95%CI)	Ref.	1.96 (0.21,15.51)	8.03 (0.88,73.24)
Women	Breast cancer [c]	Cases/person-years	67/70,380	19/9520	12/4919
		Adjusted HR (95%CI)	Ref.	2.01 (1.20,3.36)	2.58 (1.38,4.83)
	Uterine or uterine cervix cancer [c]	Cases/person-years	27/70,380	5/9520	5/4919
		Adjusted HR (95%CI)	Ref.	1.45 (0.55,3.77)	2.82 (1.07,7.43)
Men	Prostate cancer [c]	Cases/person-years	35/306,465	7/34,903	4/15,225
		Adjusted HR (95%CI)	Ref.	1.50 (0.66,3.42)	3.55 (1.24,10.14)

Note: Models were adjusted for age (every 10 years), sex, BMI, TC, TG, Scr, UA, CRP, smoking status, drinking status, physical activity, sedentary lifestyle, family income, tea consumption, rural life, salt intake, high-fat diet, diabetes, and family history of cancer.
[a] Further adjusted for ALT, TBIL, HBV and HCV infection, liver cirrhosis and fatty liver disease.
[b] Further adjusted for CKD.
[c] Conducted only among men or women.

Table 4
Sensitivity analyses of the association of the overall sleep-quality score with the risk of specific sites of cancers.

	Overall sleep-quality score		
	<3	3–5	>5
Excluding cancer occurred within 1st year of follow-up (n = 78,068)			
Colorectal cancer	Ref.	0.71 (0.39,1.28)	2.05 (1.12,3.73)
Breast cancer	Ref.	1.98 (1.15,3.42)	2.81 (1.49,5.30)
Uterine or uterine cervix cancer	Ref.	1.54 (0.59,4.05)	2.78 (1.04,7.22)
Prostate cancer	Ref.	1.57 (0.69,3.58)	3.68 (1.28,10.56)
Kidney cancer	Ref.	0.87 (0.31,2.44)	3.90 (1.64,9.27)
Bladder cancer	Ref.	1.74 (0.76,3.99)	5.17 (2.11,12.65)
Excluding participants who took sleep medication (n = 77,443)			
Colorectal cancer	Ref.	0.84 (0.49,1.44)	2.08 (1.14,3.78)
Breast cancer	Ref.	1.88 (1.09,3.21)	2.49 (1.30,4.76)
Uterine or uterine cervix cancer	Ref.	1.56 (0.59,4.08)	2.80 (1.05,7.39)
Prostate cancer	Ref.	1.56 (0.69,3.55)	2.96 (1.03,9.23)
Kidney cancer	Ref.	0.66 (0.20,2.12)	4.08 (1.71,9.70)
Bladder cancer	Ref.	1.53 (0.68,3.48)	5.80 (2.53,13.32)

Note: Models were adjusted for age (every 10 years), sex, BMI, TC, TG, Scr, UA, CRP, smoking status, drinking status, physical activity, sedentary lifestyle, family income, tea consumption, rural life, salt intake, high-fat diet, diabetes, and family history of cancer.
[a] Further adjusted for ALT, TBIL, HBV and HCV infection, liver cirrhosis and fatty liver disease.
[b] Further adjusted for gallstone disease and gallbladder polyp.
[c] Further adjusted for CKD.

colorectal, breast, uterine or uterine cervical, prostatic, kidney and bladder cancer and 2) SQS components, including insomnia and snoring, may serve as the driving force in the association of SQS with cancer risk and elevated the risk of head and neck, breast, uterine or uterine cervical, prostatic, kidney, bladder cancer, and lymphoma.

The main exposure, the overall sleep-quality score, included four sleep disorder parameters. No previous studies have been conducted to explore the association of overall sleep quality with the risk of cancer incidence. However, the findings of the current study are partially supported by several previous studies that focussed on one specific sleep disorder parameter, as described in the following.

Studies conducted to assess the effect of insomnia on the occurrence of cancer have provided conflicting conclusions. A recent review including eight studies with 578,809 participants demonstrated a 24% elevated risk of incident cancer for individuals with insomnia, especially for participants who had the disorder for longer than 10 years.[19] A prospective cohort study conducted in the Norway population suggested that women who had all aspects of insomnia simultaneously had a 2.38-fold risk of breast cancer; however, no significant association was found between individual insomnia symptoms and breast cancer risk.[20] By analysing 2102 men from the AGES-Reykjavik cohort study, Sigurdardottir LG et al. found that men who had problems falling asleep and staying asleep had an elevated risk of prostatic cancer, with corresponding HRs (95% CI) of 1.7 (1.0, 2.9) and 2.1 (1.2–3.7), respectively. The results from a nationwide nested case–control study found that patients with insomnia had an increased risk of all types of cancer, including tracheal, nasal, liver, cervical, oral, colon, lymphatic, thyroid, myeloma, prostatic, bladder, and kidney cancers. However, a statistically insignificant association between insomnia and the onset of cancer was also reported in previous studies.[21,22]

The close association between sleep-disordered breathing and cancer risk has been explored in several epidemiological studies. By analysing over 5000 concurrent patients with suspected obstructive sleep apnoea (OSA), Brenner R et al. found that patients (aged <45 years) with OSA exhibited a much higher risk of total cancer

incidence than the general population.[23] A population-based cohort study including a sample of 34,402 individuals with a follow-up of approximately 5 years evaluated the anatomical site-specific tumour risk in patients with OSA and reported a significant increase in the incidence of breast cancer, renal cancer, uterine cancer, and melanoma, as well as a significant decrease in the incidence of lung and colorectal cancers, when compared to the general population.[24] In addition, studies focussed on one specific cancer site showed the causality between OSA and the risk of breast cancer,[25,26] colorectal cancer,[27,28] head and neck cancer,[29] and bladder cancer.[30]

We observed a borderline significant association of sleep duration (7–8 h vs. others) with breast cancer and prostatic cancer risk. Numerous studies have also investigated sleep duration and the risk of carcinogenesis, particularly by self-administered questionnaires, based on subjective assessments and the number of self-reported sleep hours. By analysing 2833 narcoleptic patients (a rare type of hypersomnia) from 2000 to 2009, Tseng CM et al. found that narcolepsy elevated the risk of head and neck cancer and gastric cancer among female patients.[31] A prospective cohort study found that both extremely short (<5 h) and long sleep durations (≥9 h) increased the risk of colorectal cancer among 75,828 postmenopausal women with an average of 11 years of follow-up.[32] A meta-analysis including 12 prospective studies highlighted a positive association between long sleep duration and colorectal cancer risk.[33] In addition, significant associations between hypersomnia and the risk of liver cancer, breast cancer, and lung cancer have also been reported in several studies.[34–36]

Sleep disorders, including insomnia, hypersomnia, and OSA, can occur as a consequence of the occurrence of cancer or its related treatment, especially radiochemotherapy.[37–39] In the sensitivity analysis, we excluded patients with incident cancer that occurred within the first year of follow-up, and the significant association remained in the multivariate analysis to prevent reverse causation. Although the purpose of the current study was to explore the association between sleep disorders and the occurrence of cancer, studies have agreed on the necessity of effective and timely management of sleep disorders, which can enhance cancer patients' therapeutic responses in terms of survival, quality of life, and comorbidity reduction.[12]

The mechanisms underlying the close association of sleep disorders and cancer risk have been evaluated in several studies. First, the hypothalamus and brain stem regulate the transition between wakefulness and sleep. Hypothalamic orexin neurons cause an alteration in circadian rhythms and are sensitive to a series of signals, including ghrelin, leptin, cytokines, glucose, amino acids, and extracellular changes in pH and pCO2.[40] These signals play critical roles in cancer pathogenesis, including tumour progression, increased cancer cell proliferation, angiogenesis, increased tumour volume, and increased invasiveness.[40] Second, melatonin, a fundamental factor in regulating the sleep–wake rhythm, plays a fundamental role in metabolic, neoplastic, and inflammatory processes. The antitumour effects of melatonin include protection from DNA damage, the stimulation of DNA repair mechanisms, the improvement of mitochondrial respiratory chain function, the inhibition of mitophagy, and telomerase activity.[41] It also affects oestrogen metabolism (i.e., breast cancer) by binding to the oestrogen receptor and reducing its stimulatory actions, hence decreasing steroid production in the gonads. Moreover, melatonin enhances p53 protein expression, stimulates phosphorylation, inhibits cell proliferation, promotes apoptosis, and decreases levels of vascular endothelial growth factor and endothelin-1, which are the foundations of tumour development and metastasis.[42]

The current study's strengths are the prospective study design, large sample size, and wide assessment of confounders, which allowed enough power to investigate a time-to-event association. In addition, the primary exposure, the overall sleep quality score, which includes the four dimensions of sleep disturbance, is more suitable for detailing the association between sleep disturbance and cancer risk. However, limitations of the study merit discussion when interpreting the results. First, the follow-up was relatively short and may not be powerful enough to explore the long-term association between sleep quality and the risk of cancer incidence. Second, this study's sample comprised more males than females, which may impair the generalisability of its findings. However, analyses of breast, uterine or cervical, ovarian, and prostatic cancer were performed only in men or women, which somewhat reduced the effect of sex imbalance. Furthermore, all participants in this study were members of the Kailuan community in Tangshan City, China, and were primarily of northern Han ethnicity. More studies are required to replicate our findings in different ethnic groups. Third, objective measurements of sleep quality were not available in the study, and all data on sleep were gathered by self-reporting. Particularly when collecting data on snoring and sleep duration, recall bias and misclassification may occur. Forth, due to the lack of a professional diagnosis of hypersomnia and OSA in this study, as well as our reliance on extrapolation from sleep duration and self-reported snoring, our ability to make accurate speculations about the precise impact of hypersomnia or OSA on tumorigenesis is limited. Fifth, this study lacks data on circadian rhythm alterations, specifically night-shift work, which has been proposed by WHO-IARC as a possible carcinogen for humans. Future studies should be conducted to assess the precise impact of circadian rhythm alterations on cancer.

Conclusions

In this large-scale prospective study, we found that poor overall sleep quality scores as well as poor scores for the scale's components, including insomnia and snoring status, elevated the risk of overall cancer, head and neck, colorectal, breast, uterine or uterine cervical, prostatic, kidney, and bladder cancer. Sleep disorders may be an early signal of carcinogenesis, and early screening and intervention should be applied for people with sleep disorders. Importantly, sleep problems, as modifiable lifestyle factors, may provide a unique intervention target for cancer prevention.

Author statements

Author contributions

All authors have read and approved the manuscript. Wenqiang Li: Methodology, Software, Writing—Original draft preparation; Chong Li: Writing-Original draft preparation; Tong Liu: Visualization. Yiming Wang: Methodology, Software. Xiangming Ma: Resources. Xiaoli Xiao: Software. Qingsong Zhang: Conceptualisation. Jun Qu: Conceptualisation, Supervision, Validation, Resources.

Ethical approval

This study was approved by the ethics committee of Aerospace center Hospital and Kailuan General Hospital and adhered to the Declaration of Helsinki. Informed consent forms were signed by the participants.

Consent for publication

Obtained.

Availability of data and material

Data will be made available upon reasonable request.

Funding

Not available.

Competing interests

None declared.

Acknowledgments

We thank all the staff and participants of the Kailuan study for their important contributions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.08.007.

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Public Health 223 (2023) 240–248

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/puhe

Original Research

Sex differences in acute health service contact after release from prison in Australia: a data linkage study

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ARTICLE INFO

Article history:
Received 21 January 2023
Received in revised form
18 July 2023
Accepted 4 August 2023
Available online 8 September 2023

Keywords:
Sex differences
Incarceration
Acute health service use
Emergency department
Ambulance

ABSTRACT

Objectives: Women released from prison typically experience worse health outcomes than their male counterparts. We examined sex differences in the patterns, characteristics, and predictors of acute health service contact (AHSC) (i.e. ambulance and/or emergency department use) after release from prison.
Study design: Data linkage study.
Methods: Baseline survey data from 1307 adults (21% women) within six weeks of expected release from prisons in Queensland, Australia (2008–2010) were linked prospectively with state-wide ambulance and emergency department, correctional, mental health, and death records. Crude and adjusted incidence rates and incidence rate ratios of AHSC were calculated overall and by sex. An Andersen–Gill model was fit to examine whether sex predicted AHSC. The interaction effect between sex and each model covariate was tested.
Results: The crude incidence rates of AHSC after release from prison were 1.4 (95% confidence interval [CI]: 1.3–1.5) and 1·1 (95%CI: 1.1–1.2) per person-year for women and men, respectively. The relationship between perceived physical health–related functioning at the baseline and AHSC was modified by sex ($P = 0·039$). The relationship between perceived health-related functioning and AHSC also differed among women. Compared to women who perceived their physical health as fair or good at the baseline, women who perceived their physical health as poor were at greater risk of AHSC (hazard ratio = 2.4, 95% CI: 1.4–3·9, $P = 0.001$) after release from prison.
Conclusions: Among people released from prison, women's and men's AHSC differs depending on how they perceive their own physical health. The specific needs of women and men must be considered in transitional support policy and planning to improve their health outcomes.

Introduction

Women comprise a small proportion of people in prison globally (7%), but their number is growing at a rate in excess of the overall prison population.[1] Women released from prison typically experience a higher burden of morbidity and mortality than both men released from prison and women in the general population, including higher rates of physical and mental disorders.[2–4] Further, women released from prison experience high rates of overdose, self-harm, and other injury,[5] which are often treated in acute health services.[6]

Developing targeted interventions to address poor health outcomes experienced by women and men released from prison requires an understanding of their health service contacts after incarceration. People who face barriers to primary and preventive care, including those released from prison, are more likely to present to acute health services.[7] As such, examining acute health service contacts (AHSCs) (i.e. ambulance attendances and/or emergency department [ED] presentations) can provide insights into the health status and needs of these individuals. People released from prison have higher rates of AHSC than the general population, often for preventable causes such as injury, mental health problems, and substance use.[8,9] Studies of people who

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https://doi.org/10.1016/j.puhe.2023.08.011

frequently use the ED,[10] people living with hepatitis C,[11] people who use drugs,[12] and people who are homeless[13] have observed higher rates of AHSC among those with a history of incarceration. Higher rates of AHSC among people released from prison, particularly for preventable conditions, can be an indicator of unmet health needs in the community and/or poor continuity of care after release from prison.[14] Preventing avoidable AHSC may reduce the burden on acute health services, which are high-cost, resource-constrained healthcare settings.[15]

Research on sex differences in AHSC among people released from prison is limited. There is some evidence that women released from prisons in the United States have higher rates of ED presentation,[8,16] use the ED sooner after release,[9] and present more frequently to the ED than do men released from prison.[8] However, very few studies have examined ambulance attendances after release from prison, whether in isolation or in combination with ED contacts, and almost nothing is known about potential differences in the predictors or clinical characteristics of AHSCs between women and men released from prison. Therefore, we aimed to (1) compare socio-demographic and health-related characteristics of women and men released from prison and (2) compare the incidence, clinical characteristics, and predictors of AHSCs after release from prison between women and men.

Methods

Our study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology checklist for cohort studies (Supplementary Table 1).

Study design and participants

We used data from a previously conducted randomised controlled trial (RCT) of a case-management intervention for adults released from prison.[17] Briefly, 1325 women and men (≥18 years) recruited from prisons in Queensland, Australia between 1 August 2008 and 31 July 2010 completed a baseline interview within six weeks of expected release from custody (herein referred to as the index release). Other than the intentional over-representation of women, the cohort was representative of people released from Queensland prisons during the study period, on assessed demographic and criminal justice variables.[17]

Linked administrative data

Baseline survey data were probabilistically linked to state-wide ambulance (1 January 2007–1 January 2014), ED (1 June 2002–31 July 2012), hospital (1 July 1999–31 July 2012), and community mental health records (1 August 2008–31 May 2013) and to national death records (1 September 2008–31 December 2013). National death records were used to censor follow-up time upon death. Using a unique identifier, survey data were also deterministically linked to state-wide correctional records (1 July 2006–31 December 2013). Follow-up was censored at 31 July 2012 to ensure complete coverage across all data sources.

Measures

Definitions of all variables are presented in Supplementary Table 2. Socio-demographic and health-related characteristics ascertained from the baseline survey included age at index release, indigenous status, relationship status, gender and sexuality (i.e. lesbian, gay, bisexual, transgender [LGBT]), level of education, employment status prior to index incarceration, accommodation prior to index incarceration, lifetime injection drug use, lifetime suicide attempts, lifetime diagnosis of a mental disorder, removal from family as a child, and prior youth justice detention. Validated screening tools administered at baseline included the Enriched Social Support Inventory (for assessing perceived social support),[18] Fagerström Test for Nicotine Dependence (for tobacco dependence),[19] Alcohol Use Disorders Identification Test (for risky alcohol use),[20] Kessler 10 (K10 – for measuring psychological distress),[21] and the Short Form 36 Physical Component Summary score (SF36-PCS – for measuring perceived physical health-related functioning).[22] All validated measures were categorised using previously established cutoffs.[18–20,23]

Variables ascertained from correctional records included sex, duration of index incarceration, number of previous incarcerations, and parole status after the index release. Hepatitis C virus exposure status was ascertained through correctional medical records reviewed at the time of baseline survey.

Measures ascertained from ambulance records included clinical characteristics of ambulance attendance, location of ambulance attendance, date and time of attendance and discharge, previous ambulance attendance (in the past 12 months), police co-attendance, administration of naloxone, initial Glasgow Coma Scale score, transport to further care, and patient continuation to the ED.

Measures ascertained from ED records included mode of arrival, triage category, date and time of presentation and discharge, previous ED presentation (in the past 12 months), length of ED stay, departure destination, any referral to mental healthcare by ED, continuation to hospital, and primary International Classification of Diseases (ICD)-10-Australian Modification (AM) diagnosis by key ICD-10-AM chapters.[24] Contact with community mental health services following ED departure was ascertained from community mental health records.

Previous diagnosis of a mental illness or substance use disorder, or a dual diagnosis of these conditions, was ascertained at the baseline using ICD-10-AM[25] codes for mental health and substance use disorders from ED and hospital inpatient records before index incarceration and International Classification of Primary Care 2nd edition (ICPC-2)[26] codes derived from correctional medical records.

Outcomes

The primary outcome was AHSC episodes that occurred in the community after release from prison. Adapted from previous studies,[27,28] one AHSC episode was defined as all ambulance and/or ED events occurring ≤24 h apart. For example, if an ambulance attended and the person presented to the ED ≤24 h later, this was considered a single AHSC episode. An ED presentation occurring >24 h after a previous ambulance or ED event was considered a separate AHSC episode. This definition included any combination or number of ED and/or ambulance events, and we placed no limit on how many events comprised an episode.

Statistical analysis

Descriptive statistics were calculated for all measures, overall and stratified by sex. Chi-squared tests were used to test differences between women and men for categorical variables. We conducted a complete case analysis, including only participants with no missing data on any variable of interest.[29]

Time at risk of AHSC was calculated as time spent in the community after index release, excluding time during subsequent periods of incarceration, until death or the end of follow-up,

whichever occurred first. Crude incidence rates (IRs) per person-year were calculated for ambulance attendances, ED presentations, and AHSC episodes for women and men separately, assuming a Poisson distribution. Incidence rate ratios (IRRs) were calculated comparing IRs for women to those for men. Consistent with previous research in this area,[23] to examine time-dependent patterns of AHSC, we calculated piecewise IRs for the following time intervals after any release from prison: 0–14, 15–28, 29–84, 85–180, and 181–365 days, overall and by sex.

To compare predictors of AHSCs between women and men released from prison, we estimated the association between sex and AHSC after release from prison by fitting univariable and multivariable Andersen–Gill models.[30]

We fit an interaction term in our multivariable models to test for effect modification by sex on the association between each model covariate and AHSC. All variables included in the multivariable Andersen–Gill models were tested for effect modification, based on previous research in the general population[31] and in people released from prison.[32] In each model, the impact of another variable (e.g. perceived physical health–related functioning) on the association between sex and AHSC was tested. A Wald test of global significance was used to assess whether effect modification was present (i.e. $P < 0.05$). Where there was evidence of effect modification, hazard ratios (HRs) are reported using a single reference group (i.e. non-exposed males), and also by sex, as recommended previously.[33,34]

In sensitivity analyses, we tested the following alternative definitions of AHSC: (1) adopting a 12-h cut-off instead of a 24-h cut-off (i.e. a less conservative definition), (2) treating all ED and ambulance events as unique episodes (i.e. assuming no interdependence of events), and (3) excluding pregnancy-related episodes and events, given that only women can have pregnancy-related events and that pregnancy-related events may therefore affect estimates of the incidence and predictors between sexes. All analyses were conducted using Stata version 15·1.[35]

Ethics approvals

This study was approved by the University of Queensland Behavioural and Social Sciences Ethical Review Committee (#2007000607), the Queensland Health Human Research Ethics Committee (HREC/11/QHC/40), the Queensland Corrective Services Research Committee, and the Australian Institute of Health and Welfare Ethics Committee (EC2012/4/58). All participants gave informed consent.

Results

We excluded ten participants whose health records were not linked and eight who were not released from prison during follow-up. The remaining 1307 (98·7%) participants were included in analyses. Approximately one-fifth of these participants were women ($n = 277$, 21%). There were 3243 person-years of follow-up in the community, with a median of 2·6 years (interquartile range [IQR]: 0.3–3.2 years) per person.

Women were more likely than men to serve short prison sentences ($P < 0.001$) and to identify as Indigenous ($P < 0.001$) or as LGBT ($P < 0.001$; Table 1). Women were also more likely than men to have a lifetime history of mental illness and/or dual diagnosis ($P < 0.001$), or suicide attempt ($P = 0.001$). Women reported higher education levels than men ($P = 0.007$) but were more likely than men to report unemployment prior to their index incarceration ($P < 0.001$).

Table 1
Baseline characteristics for total sample and stratified by sex.

Variable	Women ($n = 277$)	Men ($n = 1030$)	Total ($N = 1307$)	*P*-value
	n (%)	*n* (%)	*n* (%)	
Demographic				
Age at release (years)				
Valid $n = 1307$				
<25	68 (25)	266 (26)	334 (26)	0.665
≥25	209 (76)	764 (74)	973 (75)	
Indigenous status				
Valid $n = 1307$				
Non-Indigenous	182 (66)	794 (77)	976 (75)	<0.001
Indigenous	95 (34)	236 (23)	331 (25)	
Relationship status				
Valid $n = 1296$				
Married or in stable relationship	127 (46)	412 (40)	539 (42)	0.072
Not in stable relationship	147 (54)	610 (60)	757 (58)	
LGBT[a]				
Valid $n = 1306$				
No	228 (82)	1000 (97)	1228 (94)	<0.001
Yes	49 (18)	29 (3)	78 (6)	
Education				
Valid $n = 1303$				
≥10 years of schooling	176 (64)	564 (55)	740 (57)	0.007
<10 years of schooling	99 (36)	464 (45)	563 (43)	
Employment status[b]				
Valid $n = 1297$				
Employed	112 (41)	546 (53)	658 (51)	<0.001
Unemployed	163 (59)	476 (47)	639 (49)	
Accommodation[b]				
Valid $n = 1301$				
Stable housing	231 (83)	850 (83)	1081 (83)	0.879
Unstable housing	46 (17)	174 (17)	220 (17)	
Perceived social support				
Valid $n = 1307$				
Moderate-high	230 (83)	828 (80)	1058 (81)	0.320
Low	47 (17)	202 (20)	249 (19)	
Removed from family as a child				
Valid $n = 1307$				
No	208 (75)	837 (81)	1045 (80)	0.023
Yes	69 (25)	193 (19)	262 (20)	
Criminal justice				
Duration of index incarceration[c]				
Valid $n = 1300$				
>365 days	16 (6)	249 (24)	265 (20)	<0.001
91–365 days	107 (39)	560 (55)	667 (51)	
≤90 days	151 (55)	217 (21)	368 (28)	
Released on parole[b]				
Valid $n = 1299$				
No	232 (84)	865 (85)	1097 (85)	0.965
Yes	43 (16)	159 (16)	202 (16)	
Previous incarceration				
Valid $n = 1299$				
None	104 (38)	334 (33)	438 (34)	0.105
One or more	171 (62)	690 (67)	861 (66)	
Prior youth justice detention				
Valid $n = 1307$				
No	224 (81)	722 (70)	946 (72)	<0.001
Yes	53 (19)	308 (30)	361 (28)	
General health				
Perceived physical health-related functioning (SF36 PCS[d])				
Valid $n = 1288$				
Fair or good	227 (84)	887 (87)	1114 (87)	0.139
Poor	44 (16)	130 (13)	174 (14)	
Hepatitis C exposure status				
Valid $n = 1307$				
Unknown	132 (48)	517 (50)	649 (50)	
Negative	90 (33)	372 (36)	462 (35)	0.036
Positive	55 (20)	141 (14)	196 (15)	
Mental health				
Past suicide attempt				
Valid $n = 1307$				
None	198 (72)	832 (81)	1030 (79)	0.001
At least once	79 (29)	198 (19)	277 (21)	

Table 1 (*continued*)

Variable	Women ($n = 277$)	Men ($n = 1030$)	Total ($N = 1307$)	*P*-value
	n (%)	*n* (%)	*n* (%)	
Mental disorder status				
Valid $n = 1307$				
No diagnosis	92 (33)	525 (51)	617 (47)	<0.001
Mental illness only	30 (11)	69 (7)	99 (8)	
Substance use only	78 (28)	236 (23)	314 (24)	
Dual diagnosis	77 (28)	200 (19)	277 (21)	
Psychological distress[e]				
Valid $n = 1302$				
Low-moderate	237 (86)	943 (92)	1180 (91)	0.001
Severe-very severe	40 (14)	82 (8)	122 (9)	
Substance use				
Lifetime injection drug use				
Valid $n = 1304$				
No	108 (39)	468 (46)	576 (44)	0.050
Yes	169 (61)	559 (54)	728 (56)	
Tobacco dependence				
Valid $n = 1304$				
None-moderate	208 (75)	813 (79)	1021 (78)	0.150
High	69 (25)	214 (21)	283 (22)	
Risky alcohol use				
Valid $n = 1304$				
Low-moderate	234 (85)	882 (86)	1116 (86)	0.794
High	41 (15)	147 (14)	188 (14)	
Health service use				
ED presentation(s) in 12 months prior to incarceration				
Valid $n = 1307$				
None	229 (83)	867 (84)	1096 (84)	0.546
One or more	48 (17)	163 (16)	211 (16)	
Ambulance attendance(s) in 12 months prior to incarceration				
Valid $n = 1307$				
None	230 (83)	849 (82)	1079 (83)	0.824
One or more	47 (17)	181 (18)	228 (17)	
Randomisation				
Valid $n = 1307$				
Control	516 (50)	137 (50)	653 (50)	0.850
Intervention	514 (50)	140 (51)	654 (50)	

Removed from family as a child – three participants answered, 'don't know'. Prior youth justice detention – thirteen participants answered, 'don't know'. These answers were coded as 'no' to generate a conservative estimate. Due to rounding, some percentages sum to more than 100.
Abbreviation: ED = emergency department.
[a] Lesbian, gay, bisexual, or transgender.
[b] Prior to index incarceration.
[c] Index incarceration.
[d] SF36 PCS: Short form 36 physical component summary score (SF36 PCS). Categorised at one standard deviation below the sample mean.
[e] In the four weeks before baseline.

Incidence of AHSC

Of the 1307 individuals included in the analysis, 915 (70%) accrued 3845 community AHSC episodes (median: 2; IQR: 0–4). Seventy-five percent of women ($n = 209/277$) had one or more AHSC during the study period, compared to 69% of men ($n = 706/1030$) ($P = 0.020$). Women had a similar crude rate of AHSC to men (Table 2). The incidence of AHSC differed between women and men between 85 and 180 days after release from prison ([IRR: 1.4, 95%CI: 1.1–1.7, $P = 0.002$]; Fig. 1) but not in any other time period.

Sex differences in predictors of AHSC

In the unadjusted model, women had a 1.2-times higher risk of AHSC than men (95%CI: 1.1, 1.3, $P < 0.001$). However, this sex difference attenuated to the null in the multivariable model (Table 3). Sex modified the association between perceived physical health–related functioning at the baseline and AHSC ($P = 0.039$). Among people with fair or good perceived physical health–related functioning, women had a lower risk of AHSC than men (HR: 0.8, 95%CI: 0.6–1·0, $P = 0.018$). We also found that the relationship between perceived health-related functioning and AHSC differed among women. Women with poor perceived physical health–related functioning had an increased risk of AHSC compared to women with fair or good perceived physical health–related functioning (HR: 2.4, 95%CI: 1.4–3.9, $P = 0.001$). We did not find a difference in AHSC and perceived physical health–related functioning among men (see Table 4).

Sex differences in characteristics of ambulance attendances and ED presentations

ED presentations made by women were significantly more likely than those by men to be brought in by police (14% of contacts by women vs. 8% of contacts by men; $P < 0.001$; Supplementary Tables 3 and 4). Significantly more ED presentations for women were followed by contact with community mental health services within 48 h following discharge from the ED than those for men (18% vs. 1%; $P < 0.001$; Supplementary Table 4).

Sensitivity analyses

Sensitivity analyses, excluding pregnancy-related presentations and using alternative definitions of AHSC, supported our primary analyses (Supplementary Tables 5–6).

Discussion

In this large, representative cohort study of adults released from prison, we found that the average person released from prison had contact with acute health services approximately 1.2 times per year and that this rate of contact was fairly consistent over time after release. Consistent with general population trends in Australia,[6] rates and predictors of AHSC were similar between women and men released from prison. While not directly comparable, we found that the rates of AHSC were higher for women and men in the study cohort than the sex-specific rates of ED use in the Australian general population (i.e. 1370 for women and 1130 for men per 1000 person-years in the study cohort vs. 327.5 for women and 334.7 for men per 1000 population).[6] Therefore, although we observed no sex difference in the rate of AHSC in the study cohort, both women and men released from prison contact acute health services more often than women and men in the general population.[6] These increased rates of AHSC among women and men released from prison indicate significant health needs among both groups.[36] Furthermore, increased AHSC may be an indicator that the primary healthcare needs of people released from prison are not being met in the community.[37] As such, our findings raise questions about whether women and men released from prison are receiving appropriate, timely healthcare in the community. Consistent with this, the available evidence suggests that existing models of primary care for people released from prison may be insufficient to meet their health needs and that the quality, continuity, and cultural appropriateness of this care is often suboptimal.[38] Taken together, these findings suggest that the design and delivery of evidence-based transitional support services for both women and men is urgently needed.

Women who perceived their physical health-related functioning to be poor at the baseline were more likely to have contact with acute health services than women who perceived their physical health–related functioning to be fair or good at the baseline. Given that this difference in AHSC by perceived physical health–related functioning was not seen among men, the increased risk of AHSC

Table 2
Incidence rates and descriptive statistics of acute health service contact, overall and stratified by sex.

	Number (%) of AHSC	Number (%) of person-years	IR per person-year (95%CI)	IRR (95%CI)	*P*-value for IRR	Median AHSC (IQR)	Range of AHSC
Total	3845 (100)	3243 (100)	1.19 (1.15–1.22)	–	–	2 (0–4)	0–72
Females	980 (26)	713 (22)	1.37 (1.29–1.46)	1.21 (1.13–1.30)	<0.001	2 (1–4)	0–72
Males	2865 (74)	2530 (78)	1.13 (1.09–1.17)	Ref	–	1 (0–4)	0–54

Note: CI = confidence Interval; IR = incidence rate; IQR = iInterquartile range; IRR = incidence rate ratio; AHSC = acute health service contact.

among women released from prison with poor perceived health may reflect differences in help-seeking behaviours between women and men.[39] Among people released from prison, women may have greater awareness of their poor health status than men; it's a finding that has also been observed consistently in general population studies.[40] Additionally, consistent with findings from the general population,[41] there is evidence that women released from prison have better health literacy than men released from prison.[42] As such, women may more accurately assess their health status and subsequently make a decision to present to acute health services. Improved help-seeking behaviour and more accurate self-assessment of health status among people released from prison may result in acute healthcare contacts that are appropriate to prevent even poorer health outcomes among people released from prison. Alternatively, it might also be that help-seeking behaviour and more accurate self-assessment of health status among people released from prison would instead result in fewer AHSCs, as these people might be more likely to visit a General Practitioner (GP) or other specialist services (e.g. mental health, alcohol, and other drug services) before their health deteriorates. Regardless, improved health status and access of primary, preventative, and specialist care (as required) would be of considerable benefit to women and men released from prison and would likely reduce preventable contact with acute healthcare services.

We found that a larger proportion of ED presentations made by women in the study cohort were brought in by police than ED presentations made by men in the study cohort. This contrasts with what is known about ED presentations in the general population, with one recent study reporting that men in the general population were more likely than women in the general population to be brought in to the ED by police.[43] The mechanisms behind police transfer into the ED may differ between women released from prison and women in the general population. Police are frequently first responders to mental health–related issues,[44] and research has found that police co-attendance in ED presentations is frequently in response to mental health crises.[43] As such, the higher prevalence of mental health disorders among women released from prison may account for the higher proportion of police co-attendance among women observed in our study. Furthermore, we found that almost one-fifth of ED presentations made by women in the study cohort resulted in community mental health service contact following discharge from the ED, compared to one percent of ED presentations made by men. This is consistent with patterns in community mental healthcare use in the general population. Women in the general population with mental health needs are more likely than their male counterparts to seek out community mental health care.[45] However, the larger proportion of ED presentations made by women in the study cohort than their male counterparts resulting from being brought in by police suggests that women may not be making the decision to present to acute health services for themselves. It may also be that police are more likely to assess women with acute mental health problems as in need of care and assess men's acute mental health needs from a criminal justice perspective.[46] In any case, the low rates of community mental health contact among men discharged from the ED in our study is a cause for concern, particularly given the high rates of suicide and self-harm among men released from prison.[47,48] Greater investment in mental healthcare for both women and

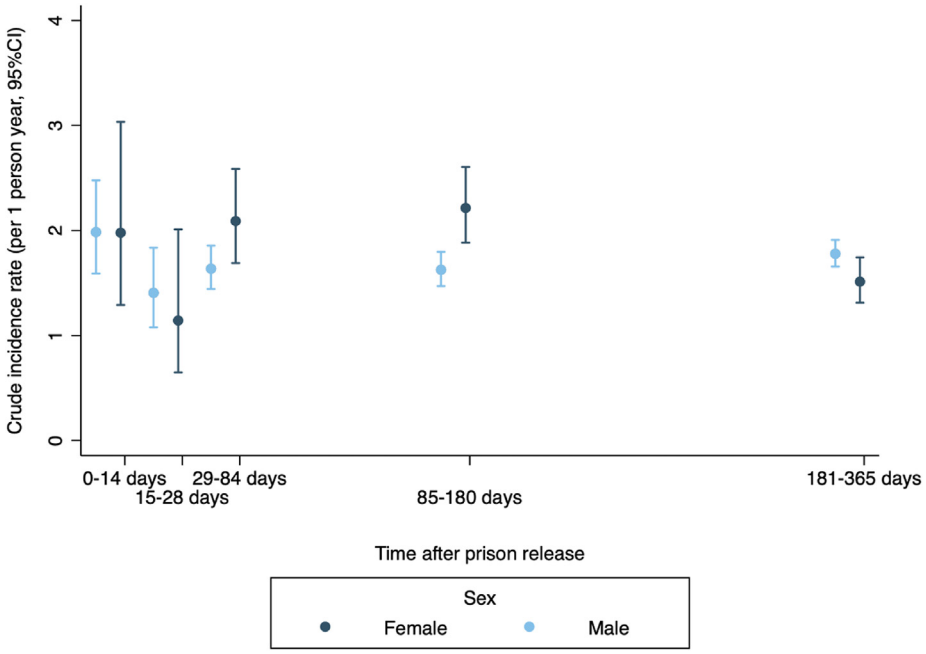

Fig. 1. Piecewise incidence of acute health service contact in the year after release from prison, by sex.

Table 3
Association between baseline characteristics and ambulance attendances, ED presentations, and acute health service contact events.

Variable	AHSC primary definition univariable		AHSC primary definition multivariable[f]	
	Hazard ratio (95%CI)	*P*-value	Adjusted hazard ratio (95%CI)	*P*-value
Demographic				
Sex				
Male	*Ref*	*Ref*	*Ref*	*Ref*
Female	1.2 (1.1–1.3)	<0.001	0.9 (0.7–1.1)	0.354
Age at release (years)				
<25	*Ref*	*Ref*	*Ref*	*Ref*
≥25	1.0 (0.9–1.1)	0.684	0.9 (0.8–1.1)	0.490
Indigenous status				
Non-Indigenous	*Ref*	*Ref*	*Ref*	*Ref*
Indigenous	1.6 (1.5–1.7)	<0.001	1.3 (1.0–1.6)	0.046
Relationship status				
Married or in stable relationship	*Ref*	*Ref*	*Ref*	*Ref*
Not in stable relationship	1.1 (1.0–1.2)	0.001	1.1 (0.9–1.3)	0.537
LGBT[a]				
No	*Ref*	*Ref*	*Ref*	*Ref*
Yes	1.5 (1.3–1.7)	<0.001	1.2 (0.8–1.6)	0.345
Education				
≥10 years of schooling	*Ref*	*Ref*	*Ref*	*Ref*
<10 years of schooling	1.2 (1.1–1.3)	<0.001	1.0 (0.8–1.2)	0.890
Employment status[b]				
Employed	*Ref*	*Ref*	*Ref*	*Ref*
Unemployed	1.6 (1.5–1.7)	<0.001	1.2 (1.0–1.4)	0.010
Accommodation[b]				
Stable housing	*Ref*	*Ref*	*Ref*	*Ref*
Unstable housing	1.6 (1.5–1.7)	<0.001	1.2 (1.0–1.6)	0.071
Perceived social support				
Moderate-high	*Ref*	*Ref*	*Ref*	*Ref*
Low	1.5 (1.4–1.6)	<0.001	1.2 (1.0–1.5)	0.092
Removed from family as a child				
No	*Ref*	*Ref*	*Ref*	*Ref*
Yes	1.4 (1.3–1.5)	<0.001	1.0 (0.8–1.2)	0.692
Criminal justice				
Duration of incarceration[c]				
>365 days	*Ref*	*Ref*	*Ref*	*Ref*
90–365 days	1.2 (1.0–1.3)	0.003	1.1 (0.9–1.3)	0.629
≤90 days	1.6 (1.4–1.7)	<0.001	1.4 (1.1–1.7)	0.007
Released on parole[b]				
No	*Ref*	*Ref*	*Ref*	*Ref*
Yes	1.0 (0.9–1.1)	0.876	1.0 (0.8–1.3)	0.679
Previous incarceration				
None	*Ref*	*Ref*	*Ref*	*Ref*
One or more	2.0 (1.9–2.2)	<0.001	1.4 (1.2–1.7)	<0.001
Prior youth justice detention				
None	*Ref*	*Ref*	*Ref*	*Ref*
One or more	1.5 (1.4–1.6)	<0.001	1.2 (1.0–1.5)	0.047
General health				
Perceived physical health-related functioning (SF36 PCS score[d])				
Fair or good	*Ref*	*Ref*	*Ref*	*Ref*
Poor	1.4 (1.3–1.6)	<0.001	1.5 (1.1–2.0)	0.006
Hepatitis C exposure status				
Unknown	*Ref*	*Ref*	*Ref*	*Ref*
Negative	1.0 (1.0–1.1)	0.510	1.1 (0.9–1.3)	0.648
Positive	1.2 (1.1–1.3)	<0.001	0.8 (0.7–1.1)	0.120
Mental health				
Past suicide attempt				
None	*Ref*	*Ref*	*Ref*	*Ref*
At least once	1.4 (1.3–1.5)	<0.001	0.9 (0.7–1.1)	0.392
Mental disorder status				
No diagnosis	*Ref*	*Ref*	*Ref*	*Ref*
Mental illness only	1.8 (1.6–2.0)	<0.001	1.8 (1.3–2.4)	<0.001
Substance use only	1.9 (1.8–2.1)	<0.001	1.4 (1.2–1.8)	0.001
Dual diagnosis	3.6 (3.3–3.9)	<0.001	2.8 (2.3–3.5)	<0.001
Psychological distress[e]				
Low-moderate	*Ref*	*Ref*	*Ref*	*Ref*
Severe-very severe	1.6 (1.4–1.7)	<0.001	1.1 (0.9–1.5)	0.314
Substance use				
Lifetime injection drug use				
No	*Ref*	*Ref*	*Ref*	*Ref*
Yes	1.7 (1.6–1.8)	<0.001	1.2 (1.0–1.5)	0.059
Tobacco dependence				
None-moderate	*Ref*	*Ref*	*Ref*	*Ref*
High	1.2 (1.2–1.3)	<0.001	0.9 (0.7–1.0)	0.143

(*continued on next page*)

Table 3 (*continued*)

Variable	AHSC primary definition univariable		AHSC primary definition multivariable[f]	
	Hazard ratio (95%CI)	*P*-value	Adjusted hazard ratio (95%CI)	*P*-value
Risky alcohol use				
Low-moderate	*Ref*	*Ref*	*Ref*	*Ref*
Moderate-high	1.6 (1.5–1.7)	<0.001	1.2 (1.0–1.5)	0.108
Health service use				
ED presentation(s) in 12 months prior to incarceration				
None	*Ref*	*Ref*	*Ref*	*Ref*
One or more	1.2 (1.1–1.3)	<0.001	1.1 (0.9–1.3)	0.457
Ambulance attendance(s) in the 12 months prior to incarceration				
None	*Ref*	*Ref*	*Ref*	*Ref*
One or more	1.2 (1.1–1.3)	<0.001	1.0 (0.8–1.3)	0.950

Removed from family as a child – three participants answered, 'don't know'. Prior youth justice detention – thirteen participants answered, 'don't know'. These answers were coded as 'no' to generate a conservative estimate.Due to rounding, some percentages sum to more than 100.
Abbreviations: AHSC = acute health service contact; CI = confidence interval; ED = emergency department.
[a] Lesbian, gay, bisexual, or transgender.
[b] Prior to index incarceration.
[c] Index incarceration.
[d] SF36 PCS: Short form 36 physical component summary score (SF36 PCS). Categorised at one standard deviation below the sample mean, such that poor perceived health status denotes a score of <45, and fair or good perceived health status denotes a score of ≥45.
[e] In the four weeks before baseline.
[f] Multivariable models were adjusted for age at index release, Indigenous status, relationship status, gender and sexuality (i.e. LGBT), level of education, employment status prior to index incarceration, accommodation prior to index incarceration, removal from family as a child, lifetime injection drug use, lifetime suicide attempts, prior youth justice detention, perceived social support, tobacco dependence, risky alcohol use, psychological distress, mental disorder, perceived physical health-related functioning, duration of index incarceration, previous incarceration, parole status after index release, hepatitis C exposure status, prior ED presentation(s) (in the 12 months before index incarceration), and prior ambulance attendance(s) (in the 12 months before index incarceration).

Table 4
Multivariable analysis of interaction between sex and perceived physical health–related functioning.

Sex	Fair or good perceived physical health-related functioning		Poor perceived physical health-related functioning		Poor perceived physical health-related functioning vs. fair or good perceived health-related functioning within sex	
	Adjusted HR (95%CI)	*P*-value	Adjusted HR (95%CI)	*P*-value	Adjusted HR (95%CI)	*P*-value
Male	*Ref*	*Ref*	1.2 (0.9–1.7)	0.159	1.2 (0.9–1.7)	0.159
Female	0.8 (0.6–1.0)	0.018	1.5 (0.8–2.6)	0.209	2.4 (1.4–3.9)	0.001

Interaction term = 1.9, 95%CI: 1.0, 3.4, $P = 0.039$.
Adjusted for age at index release, Indigenous status, relationship status, gender and sexuality (i.e. LGBT), level of education, employment status prior to index incarceration, accommodation prior to index incarceration, removal from family as a child, lifetime injection drug use, lifetime suicide attempts, prior youth justice detention, perceived social support, tobacco dependence, risky alcohol use, psychological distress, mental disorder, duration of index incarceration, previous incarceration, parole status after index release, hepatitis C exposure status, prior ED presentation(s) (in the 12 months before index incarceration), and prior ambulance attendance(s) (in the 12 months before index incarceration).
Abbreviations: HR = hazard ratio; CI = confidence interval.

men released from prison is urgently needed, including targeted strategies for engaging men with mental health issues in community mental health services.

To our knowledge, this is the first study conducted internationally to focus on differences in AHSC between women and men released from prison. Our study used a broadly representative sample of people recruited prior to release from prison. However, our study was subject to some limitations. Data were not available for gender identity, which meant that we were limited to investigating biological sex differences only. However, our approach aligns with Australian prison policies, which generally incarcerate people based on biological sex and not gender identity. The relatively small number of women in our study meant that we may not have had adequate statistical power to detect differences when examining effect modification of the variables investigated on the association between sex and AHSC. However, power calculations from the original RCT[17] indicated that the study population was large enough to detect differences between the original intervention and control groups, and women were intentionally oversampled to permit sex-stratified analyses. Although our findings require replication as the data comprised health records until July 2012, there have been minimal substantive changes in prison release policies in Queensland since 2012 that would suggest that the rates and predictors of ASHC among people released from prison would have changed significantly over time.

Future research exploring differences between women and men released from prison should consider intersectional approaches to consider the role of different social factors (including those not examined by this study, such as disability or having a culturally or linguistically diverse background) that shape the health needs and experiences of these women and men. Additionally, future studies should examine the relationship between incarceration history and health service use by comparing people released from prison to those without incarceration histories, ideally using whole of population cohorts. This would allow examination of whether those who are incarcerated are more likely to have ambulance attendances and/or ED presentations prior to incarceration than the general population. Furthermore, future research could also explore the impact of pre-incarceration health service use on post-incarceration outcomes.

Conclusion

In Australia, women and men released from prison use acute health services at a considerably higher rate than their respective counterparts in the general population. Women released from

prison who perceive their physical health as poor have an elevated risk of acute health service contact compared to women who perceive their health as fair or good. Our findings suggest that both women and men released from prison are not receiving appropriate health care in the community. Women in particular may experience significant barriers in accessing appropriate care following release from prison, which might further compound pre-existing poor health and disadvantage. Strategies for engaging men released from prison with mental health issues in community mental health services are also needed. Improving continuity of care among people released from prison may reduce the burden on acute health services (which are high-cost, resource-constrained health settings), and most importantly, improve the health and wellbeing of these women and men. Evidence-based and culturally appropriate transitional planning is required to address the unique needs of both women and men released from prison.

Author statements

Acknowledgements

The authors would like to acknowledge the Passports project team and the late Professor Konrad Jamrozik for his pivotal role in conceiving and designing the Passports study. The authors also wish to acknowledge the Passports study participants for sharing their stories with us. The authors would like to acknowledge the assistance provided by Queensland Corrective Services to the Passports study. The views expressed herein are solely those of the authors and in no way reflect the views or policies of Queensland Corrective Services.

Ethical approval

This study was approved by the University of Queensland Behavioural and Social Sciences Ethical Review Committee (#2007000607), the Queensland Health Human Research Ethics Committee (HREC/11/QHC/40), the Queensland Corrective Services Research Committee, and the Australian Institute of Health and Welfare Ethics Committee (EC2012/4/58). All participants gave informed consent.

Funding

The Passports study was funded by the National Health and Medical Research Council (NHMRC; GNT409966, GNT1002463). JY receives salary and research support from a NHMRC Investigator Grant (GNT1178027). MW is supported by an NHMRC Postgraduate Scholarship (GNT1151103). MW, JY and SK are researchers in the NHMRC-funded Centre of Research Excellence in Driving Global Investment in Adolescent Health (GNT 1171981).

Competing interests

None declared.

Contributors

EJ, SK, and JY conceived the idea for the study. EJ conducted the analysis, produced the tables and figures, and wrote the first draft. All authors contributed to interpretation of data and critical revision of the article. All authors had access to the data, approved the final version of the manuscript, and had the final responsibility of the decision to submit for publication.

Data sharing

The data used in this study are not publicly available due to privacy considerations. The protocol for the Passports study has been published and is openly available.[17]

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.08.011.

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Public Health 223 (2023) e5–e6

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Letter to the Editor

The cost of climate disasters: an additional call for health emergency preparedness

The last biennium has shown that no country was fully prepared to deal with the COVID-19 pandemic, especially in terms of impact, scale, severity, and speed. The same biennium was particularly costly for several countries in the world because of the consequences of climate disasters. Specifically, the annual analysis carried out by Christian Aid showed that the 10 major climate events caused massive human and environmental damage worth around 170 billion US dollars in 2021 and in 2022 (around 350 billion US dollars during the 2 years when considering additional minor events).[1,2]

There is an upward trend of the costs for such disasters: the total annual cost of the 10 major climate events amounted to a total of 96.7 billion US dollars in 2018,[3] to 129.3 billion US dollars in 2019,[4] and to 145.4 billion US dollars in 2020 (see Supplementary materials).[5] The analysis of the 5 years reveals additional insights, such as the fact that all the regions of the world are affected each year, from the floods in Pakistan in 2022 to droughts in China and Brazil during the same year, up to the cold wave in France in 2021 and fires in the United States in 2019 (see Supplementary materials). Data show that climate events occur all year long, like the locust swarm in East Africa during the first semester in 2020 and the devastating floods in different parts of the world (February to March in Australia during 2022, July in Europe during 2021, June to October in China during 2020, March to June in the United States during 2019).

In spite of the fact that the great majority of events are similar (floods and cyclones/typhoons represented 40% and 30%, respectively, of the major climate events per year during the last 5 years), although of different scale, the cost and consequences may be greatly different according to the context: the floods that submerged parts of Pakistan in June 2022 displaced 7 million people and caused more than 30 billion US dollars in estimated damages, with only 5.6 billion US dollars covered by insurance,[2] which is much more problematic than in other countries like in Europe where coverage would be more extensive. To mention that Pakistan is the eighth most vulnerable country due to climate change, according to the 2021 Global Climate Risk Index,[6] the World Bank estimated that the floods could drive up to 15 million people into poverty.[7] Although hurricane Fiona was the most intense tropical cyclone ever to hit Canada, with winds of over 187 km per hour, no casualties were reported; on the other hand, the same hurricane killed eight people in Puerto Rico and impacted the Dominican Republic with 13,000 people displaced and nearly 1.2 million people experiencing water supply issues.[2] Similarly, the typhoon Mangkhut killed 127 people in the Philippines and six people in China in 2018[8] and destroyed 10,000 homes.[3]

It is important to emphasize that the impacts and costs of climate events fall disproportionately on the poorest and most vulnerable in lower income countries because of aspects such as fewer assets, less insurance, and generally poorer access to comprehensive public health services.[9–12] The situation will be even more problematic, as there will be more intense and frequent weather events in coming years and decades, even with more ambitious environmental mitigation actions.

In light of the above, the reinforcement of broad-based, whole-of-government, and whole-of-society approaches, with the involvement of relevant stakeholders beyond the health sector, to build and maintain effective capacities and systems for the preparedness and response to public health emergencies remains critical. These approaches require concerted actions, collaboration, and mutual accountability between policy-makers, intergovernmental organizations, and global initiatives.

A new Member State–led voluntary and transparent mechanism has been proposed to increase accountability for better health emergency preparedness. The peer-review nature of the Universal Health and Preparedness Review specifically aims to establish a regular intergovernmental dialog between Member States on their respective national capacities for health emergency preparedness.[13]

Climate disasters clearly reveal the interconnection between public health, extreme weather events due to climate change, and societal-financial aftermath. Very few countries have sufficiently ambitious plans on greenhouse gas emissions, and even fewer are on track to meet their goals. At the same time, key strategic context-related actions should be reflected, and tested, in national public health emergency preparedness and response plans. Urgent implementation must be a top political priority.

Author statements

Funding

None reported.

Competing interests

The authors disclose no competing interests.

Author contributions

All authors equally contributed to conceiving, preparing, and finalizing the article.

https://doi.org/10.1016/j.puhe.2023.01.022

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.01.022.

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6 January 2023
Available online 28 February 2023

Public Health 223 (2023) 33–41

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

The journey of cancer patients and the quest to equity: findings from Morocco

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ARTICLE INFO

Article history:
Received 18 January 2023
Received in revised form
26 June 2023
Accepted 11 July 2023
Available online 17 August 2023

Keywords:
Health system
Cancer
Time intervals
Determinants
Morocco

ABSTRACT

Objectives: Rapid diagnostic and assessment pathways for cancer patients provide timely and effective care. This study took place in Morocco, where the majority of patients treated in the public sector are diagnosed at an advanced stage. The aim of this study was to determine the duration of different time intervals along the cancer patient pathway and to highlight problem areas so that strategies can be implemented to make the process more equitable and effective.

Study design: Cross-sectional study.

Methods: Recently diagnosed cancer patients were recruited from four major oncology centres in Morocco; namely, Marrakech, Casablanca, Rabat, and Fez. A questionnaire survey was administered, including sociodemographic and medical information and questions on access to the oncology centre, beliefs, and opinions on the medical staff. The dates of symptom recognition, assessment, diagnosis referral, biopsy, and treatment initiation were collected. Different time intervals (patient, diagnosis, biopsy, and treatment) were estimated and their determinants were investigated.

Results: A total of 812 patients were interviewed. The majority of participants were breast cancer patients. In total, 60% of participants were at stage III–IV. The main facilitators of cancer diagnosis confirmation and treatment initiation were easy access to diagnosis and treatment facilities, financial resources, personal history of cancer, time availability, late stage at diagnosis, advanced age, and private health insurance. The patient interval (i.e., time from symptom recognition to initial healthcare assessment) had a median duration of 30 days. The biopsy and treatment intervals were within the current international recommendations (7 and 28 days, respectively). However, the diagnosis interval (52 days) was twice as long as the recommended timeframes from the UK, Australia, and the World Health Organization (<28 days).

Conclusions: Interval targets should be defined to encourage health systems to be more equitable and effective and to ensure that cancer patients are treated within a defined timeframe.

Introduction

The journey of a cancer patient through the health system is marked by a series of interactions leading to cancer diagnosis and treatment. Depending on the setting, various obstacles may exist at different stages, from seeking initial healthcare advice, to receiving a diagnosis (after a series of referrals to specialists, imaging and

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https://doi.org/10.1016/j.puhe.2023.07.015

biological tests), to eventually attending an oncology centre to start treatment. The four major steps of this journey (i.e., 'appraisal', 'help-seeking', 'diagnostic', and 'treatment')[1] enable the healthcare pathway to be defined into specific intervals. Duration of these intervals vary according to patient characteristics, disease features, and performances of both the providers and the health system.

Several systematic reviews have reported on the duration of diagnosis and treatment intervals and on their determinants.[1–3] Another comprehensive systematic review confirmed that short diagnosis and treatment intervals had beneficial clinical outcomes in breast and colorectal cancer patients.[4] Indeed, it seems fair to presume that efforts to speed up the diagnosis of symptomatic patients are likely to have benefits in terms of earlier stage at diagnosis, improved survival, and improved quality of life.[4] Rapid diagnostic and assessment pathways illustrate how timely and effective care can be provided to patients presenting with cancer symptoms.[5,6] Moreover, several countries put interval targets in place to encourage the health system to be more equitable[7]; however, these targets are mainly related to diagnosis and treatment intervals only.

The Moroccan Ministry of Health, in close collaboration with the Lalla Salma Foundation, has put effort in to the different aspects of cancer control.[8,9] Despite these efforts, the majority of patients hospitalised in public oncology centres in Morocco present with an advanced stage at diagnosis. This study investigated the pathway from symptom recognition to treatment initiation, including the duration of the main intervals and the determinants of these intervals. The interval duration results from this study, when compared with international standards, provide evidence on how to improve and speed up the referral for treatment of cancer patients in Morocco.

Methods

This multicentre, cross-sectional study used a face-to-face questionnaire. Study participants were cancer patients being hospitalised for treatment in one of the four main oncology centres in Morocco (Marrakech, Casablanca, Rabat and Fez).

Participant inclusion criteria were as follows: (1) adult patients with histologically confirmed cancer of any anatomical site; (2) able to answer questions in Arabic or French; (3) provided informed consent. Paediatric cancer cases were excluded (aged 0–14 years).

The interviewers and the principal investigator (PI) of each oncology centre were trained at the same time during a 2-day session by the Casablanca PI (KB). The objective of the training was to standardise the administration of the questionnaire and to define the information to be collected for each item, especially the dates. Data entry via the study portal was also demonstrated.

All newly registered patients were approached and invited to take part in the research project. Consenting study participants were recruited during a 1-month period. The Casablanca centre recruited participants from 1 to 28 February 2018, and the Marrakech, Rabat and Fez centres recruited eligible patients from 1 to 31 May 2018.

Interviews took place inside the oncology centre and lasted 20–30 min. The questionnaire included items on patient identification; sociodemographic information (education level, occupation, marital status, number of children, usual place of residence, place of living during the cancer treatment); medical information (personal history of cancer, direct family history of cancer [parents/children/siblings], cancer stage, cancer site, symptoms duration before visiting a primary health facility); duration to reach a primary health centre, a diagnostic centre, and the oncology centre; information on access to the oncology centre (transportation means, opinion on access using the 5-point Likert scale [1 = strongly agree, 2 = agree, 3 = do not agree nor disagree; 4 = disagree, 5 = strongly disagree]); financial information (health insurance, monthly income, family dependence status, household belongings, global cost of cancer, opinion on the economical aspect of the cancer management); beliefs; and opinions on the attitude of the medical staff before referral to the oncology centre. Study data were collected and were managed using Research Electronic Data Capture hosted at the International Agency for Research on Cancer (IARC).[10,11]

The following key dates were requested in order to allow interval duration estimates: date of symptom recognition, date of biopsy prescription, date of biopsy, date of biopsy result, and date of admission to the oncology centre (representing the date of treatment initiation). The date of symptom recognition was based on information from the referral letter to the oncology centre, or it was recollected in relation to familial, secular, or religious celebrations (e.g., the Ramadan or the Eid Festival). Other dates were collected from the oncology centre patient file or from the electronic medical record.

The main analyses included the determinants of four major intervals. The 'patient interval' was defined as the duration between symptom recognition and first presentation to a healthcare professional to seek evaluation. Symptom duration was requested only at the Casablanca centre. Since the date of symptom recognition was available, the date of the first presentation to a medical provider was estimated by adding the symptom duration date to the date of symptom recognition. Indeed, this date of first presentation could only be extrapolated because patients rarely remember the exact date when they visited a primary healthcare centre to discuss the related symptoms. The 'diagnosis interval' was defined as the duration between the estimated date of first consultation and the date of cancer diagnosis (i.e., date of the histology report with a cancer diagnosis). This diagnosis interval was available only from the Casablanca centre. The 'treatment interval' was defined as the time between the cancer diagnosis and hospitalisation for treatment at the oncology centre. This interval was estimated for the four oncology centres.

Median durations of other intervals were also computed. They included median duration between biopsy prescription and biopsy sampling, median time between biopsy sampling and histopathology result, and median interval between first consultation and hospitalisation for treatment (or 'health system interval'). Durations are presented as medians with interquartile ranges (IQRs). All intervals can be found in Fig. 1.

Statistical analyses

Patient sociodemographic characteristics are presented as proportions. Median duration in days was estimated for the different intervals. The effects of potential determinants on the patient interval, diagnosis interval and treatment interval were estimated by obtaining relative risks (RRs) and their 95% credible intervals (CIs) using Bayesian exponential regression models. Multivariate analysis was performed by including the patient sociodemographic characteristics in the same regression model. Due to the large number of variables on the opinions about oncology hospital access, economical aspects of cancer, beliefs, and attitudes of medical staff, the results would be difficult to interpret; thus, principle component analysis (PCA) was used to create interrelationships and provide fewer continuous variables (components) that were assigned meaningful descriptive statements and stored as component scores.

For easy interpretation of the component scores, the Likert scale of the variables on opinion included in the PCA was recategorised as follows: 1 = strongly disagree; 2 = disagree; 3 = undecided; 4 = agree; and 5 = strongly agree. High-positive patient-component

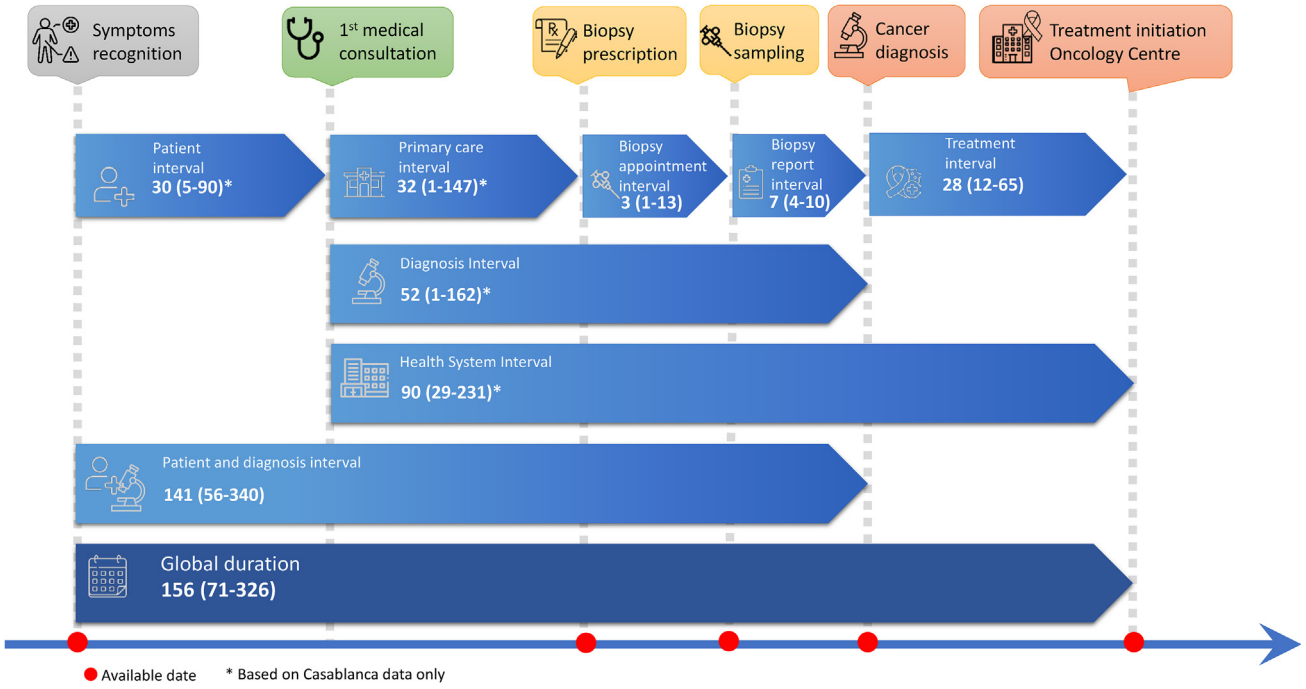

Fig. 1. Median duration and interquartile range (in days) of the different intervals of cancer patients' journey.

scores signified patient agreement with the described component and high-negative scores signified disagreement. To avoid the problem of collinearity when many highly correlated independent variables are in the regression model, the few uncorrelated computed components were included, and these were additionally adjusted for in the multivariate regression models. Significant differences were inferred at a 5% level of significance. Statistical analyses were carried out in Stata 17.0 (Stata Corp LP, Texas, USA) and the Just Another Gibbs Sampler software.

Results

A total of 812 patients were recruited for this study, mainly from Casablanca (n = 234; 29%) and Rabat (n = 229; 28%), followed by Fez (n = 195; 24%) and Marrakech (n = 154; 19%). The majority of patients were women (66%), and the main cancer sites were breast (29%), cervical and colorectal (9% each), and lung (8%). Among the 672 patients with stage information, 60% were at Stage III or IV (see Supplement Table S1).

Fig. 1 shows the median duration and interquartile range of the different intervals. The median durations were as follows: 30 days to first seek medical advice after symptom recognition; 32 days for healthcare providers to prescribe a biopsy; 3 days to have a biopsy appointment; and 7 days to receive the histopathology results. The overall diagnosis interval was 52 days from the date of the first presentation to a healthcare provider, and the median duration between symptom recognition and cancer diagnosis was 141 days. The treatment interval (i.e., time between histological confirmation of cancer and treatment initiation at the oncology centre) was 28 days (range: 12–65 days), and the health system interval (representing the duration from the first consultation to initiate treatment after the mandatory histological confirmation) was 90 days. Median durations of each interval according to major determinants can be found in the Supplement Table S2.

Table 1 presents the determinants of the patient interval duration. A shorter patient interval was statistically significantly associated with older age, being currently married, being in the highest household income category, living in a suburban area, and being covered by private or civil servant health insurance. Having five or more children, compared to none or one child, increased the patient interval duration by 3-fold. Similarly, individuals with a personal history of cancer had a patient interval that was twice as long as individuals without a cancer history. This study did not find any differences in patient interval duration related to gender or education. Belief that "if an abnormality is not disturbing, there is no need to consult a doctor" or "the symptoms are benign and will clear" were not associated with patient interval (adjusted RR for duration as continuous variable: 1.01 [95% CI: 0.92–1.09]).

The determinants of diagnosis interval duration are presented in Table 2. Compared to men, women had a 3-fold longer duration to receive a cancer diagnosis. Patients covered by private or civil servant health insurance also had a longer diagnosis time than deprived and vulnerable patients covered with the RAMED (or basic health insurance). On the other hand, being aged ≥70 years, having been to school (compared to no education), having a caregiver to coordinate the diagnosis period (i.e., a navigator), and being in the highest household income categories (compared to households with no income) reduced the diagnosis interval. Patients who felt that they had been blocked from getting an imaging appointment, compared to those who did not have this feeling, were associated with a 2-fold longer diagnosis interval. However, no significant association was observed with the feeling of being blocked for appointments with doctors or for a biopsy. Patients who generally agreed with the statements that "if an abnormality is not disturbing, there is no need to consult a doctor" or "the symptoms are benign and will clear" had a shorter diagnosis interval (RR = 0.81; 95% CI = 0.73–0.90). However, the more they agreed that "cancer is a punishment", "cancer patients will be rejected by people around them", or "cancer can be treated by healers or marabouts", the longer was the diagnosis interval (RR = 1.43; 95% CI = 1.20–1.70). Factors related to the financial impact (i.e., opinion on the cost of exams, transportation, need of financial support from donors or relatives), the health providers behaviour (i.e., not enough explanation, delayed referral, malpractice), and access to

Table 1
Determinants of patient interval[a] (Casablanca centre data only).

Characteristics	Patients assessed (n = 230)	Crude relative risk (95% CI)		Adjusted relative risk (95% CI)	
Gender					
Men	68	1.00	(Reference)	1.00	(Reference)
Women	162	0.81	(0.60–1.06)	0.75	(0.47–1.08)
Age group (yrs)					
16–49	76	1.00	(Reference)	1.00	(Reference)
50–69	113	0.84	(0.61–1.10)	0.67	(0.44–0.94)
70+	38	0.67	(0.43–0.97)	0.40	(0.20–0.69)
Education					
No	141	1.00	(Reference)	1.00	(Reference)
Yes (primary, secondary, college)	89	1.24	(0.93–1.59)	1.43	(0.95–1.99)
Currently married					
No	83	1.00	(Reference)	1.00	(Reference)
Yes	141	1.08	(0.79–1.38)	0.71	(0.47–1.01)
Total no. of children					
0–1	50	1.00	(Reference)	1.00	(Reference)
2–4	92	0.88	(0.57–1.22)	1.24	(0.72–1.87)
≥5	75	1.29	(0.85–1.83)	3.09	(1.54–5.15)
Currently employed					
No	196	1.00	(Reference)	1.00	(Reference)
Yes	33	0.80	(0.53–1.14)	0.92	(0.50–1.46)
Monthly household income (MAD)					
None	75	1.00	(Reference)	1.00	(Reference)
<2000	107	1.46	(1.06–1.90)	1.48	(1.00–2.12)
2000–4000	36	1.48	(0.95–2.13)	1.14	(0.64–1.80)
>4000	8	0.39	(0.16–0.77)	0.38	(0.12–0.83)
Place of residence					
Urban	139	1.00	(Reference)	1.00	(Reference)
Suburban	41	0.67	(0.46–0.93)	0.43	(0.24–0.68)
Rural	49	1.52	(1.06–2.06)	0.91	(0.53–1.43)
Type of health insurance					
Basic health insurance (RAMED)	191	1.00	(Reference)	1.00	(Reference)
Civil servants and private insurance	27	0.58	(0.37–0.84)	0.52	(0.31–0.82)
None	8	1.79	(0.74–3.45)	2.33	(0.83–4.97)
Personal history of cancer					
No	212	1.00	(Reference)	1.00	(Reference)
Yes	14	2.63	(1.44–4.41)	2.53	(1.14–4.49)
Direct family history of cancer					
No	197	1.00	(Reference)	1.00	(Reference)
Yes	31	0.66	(0.43–0.94)	0.57	(0.36–0.85)
Belief that the disease can be cured by a healer or marabout[b]	223	1.16	(1.01–1.31)	1.09	(0.90–1.31)
Anomaly or symptoms are minor, hence no need for medical consultation[b]	223	1.02	(0.95–1.09)	1.01	(0.92–1.09)

CI: confidence interval; MAD, Moroccan dirham.
[a] Patient interval is defined as the time from symptom recognition to presentation at clinic/health professional.
[b] Component scores created using principle component analysis with low scores indicating strongly agree and high scores strongly disagree.

healthcare facilities were not significantly associated with the duration to receive a cancer diagnosis.

Table 3 shows the factors associated with the time to initiate treatment following cancer diagnosis. The older age group had a treatment duration 2-fold longer than the younger age group, and patients who were currently married had a treatment initiation duration that was 21% longer. In contrast, patients with advanced stage cancer at diagnosis started treatment sooner than those with localised stage cancer, and those with a personal history of cancer started treatment sooner than those with no history. Patients in the highest household income category and those with easy access to the oncology centre (availability of public transportation or other means of transportation) also received treatment more rapidly than patients in other income and transportation categories. This study did not find any association between time to initiate treatment and gender, education level, health insurance coverage status, or place of stay during the ambulatory treatment. Again, the more a patient agreed with the statement “if an abnormality is not disturbing, there is no need to consult a doctor” or “the symptoms are benign and will clear”, the shorter was duration to start treatment (RR = 0.95; 95% CI = 0.91–1.00). The other financial, healthcare providers’ behaviours, and access to medical facilities factors were not associated with the duration of treatment interval.

Discussion

The main determinants of the cancer patient pathway until treatment initiation were as follows: (1) access to diagnosis and medical facilities, thanks to public transportation or own transport means; (2) financial resources and its proxy (such as occupation, small families or having been to school); (3) a personal or familial history of cancer; (4) time availability (extensive family was a barrier for patient interval and having occupation for diagnosis and treatment intervals); (5) stage at diagnosis; (6) older age (as a facilitator until the diagnosis was made, than older age became a barrier to initiate treatment at the oncology centre); and (7) employee or private health insurance (with shorter patient and treatment intervals but longer diagnosis interval). Gender difference was observed only for the diagnosis interval, and the place of residence and place of stay during the ambulatory treatment did not have a clear impact on the intervals.

Findings from this study should be put within the context of Morocco. Morocco is a lower-middle-income country,[12] where poverty, illiteracy, poor health literacy, and poor cancer awareness are prevalent.[13] The word ‘cancer’ is still taboo.[14] As in many similar settings, the economic burden for cancer patients is immense, given the disproportions between treatment costs and household

Table 2
Determinants of diagnosis interval[a] (Casablanca centre data only).

Characteristics	Patients assessed (n = 215)	Crude relative risk (95% CI)		Adjusted relative risk (95% CI)	
Gender					
Men	59	1.00	(Reference)	1.00	(Reference)
Women	156	1.42	(1.02–1.88)	2.84	(1.65–4.25)
Age group (yrs)					
16–49	71	1.00	(Reference)	1.00	(Reference)
50–69	106	1.96	(1.42–2.60)	1.16	(0.66–1.79)
70+	35	1.36	(0.88–1.99)	0.53	(0.23–0.99)
Education					
No	134	1.00	(Reference)	1.00	(Reference)
Yes (primary, secondary, college)	81	0.43	(0.32–0.55)	0.48	(0.28–0.74)
Currently married					
Not	78	1.00	(Reference)	1.00	(Reference)
Yes	131	0.71	(0.53–0.92)	1.31	(0.71–2.09)
Total no. of children					
0–1	47	1.00	(Reference)	1.00	(Reference)
2–4	83	0.98	(0.64–1.36)	0.56	(0.25–1.05)
≥ 5	72	1.55	(1.04–2.19)	0.89	(0.32–1.85)
Currently employed					
No	184	1.00	(Reference)	1.00	(Reference)
Yes	30	1.53	(0.99–2.24)	1.63	(0.93–2.62)
Monthly household income (MAD)					
None	72	1.00	(Reference)	1.00	(Reference)
<2000	101	1.39	(1.01–1.86)	0.72	(0.43–1.11)
2000–4000	34	0.48	(0.31–0.71)	0.22	(0.10–0.40)
> 4000	6	0.32	(0.12–0.74)	0.29	(0.05–0.82)
Place of residence					
Urban	126	1.00	(Reference)	1.00	(Reference)
Suburban	41	0.74	(0.50–1.04)	0.82	(0.47–1.25)
Rural	47	1.11	(0.76–1.54)	0.76	(0.38–1.27)
Type of health insurance					
Basic health insurance (RAMED)	183	1.00	(Reference)	1.00	(Reference)
Civil servants and private insurance	21	1.40	(0.83–2.16)	2.21	(1.08–3.86)
None	8	0.89	(0.37–1.75)	2.52	(0.91–5.48)
Personal history of cancer					
No	199	1.00	(Reference)	1.00	(Reference)
Yes	13	0.10	(0.05–0.17)	0.06	(0.02–0.13)
Direct family history of cancer					
No	184	1.00	(Reference)	1.00	(Reference)
Yes	30	0.64	(0.43–0.93)	0.69	(0.40–1.04)
Healthcare navigator during the diagnosis interval					
No	96	1.00	(Reference)	1.00	(Reference)
Yes	119	0.96	(0.72–1.23)	0.93	(0.59–1.36)
Blocked to have doctor's appointment					
No	127	1.00	(Reference)	1.00	(Reference)
Yes	74	0.80	(0.59–1.04)	0.88	(0.48–1.41)
Blocked to have appointment for biopsy taking					
No	120	1.00	(Reference)	1.00	(Reference)
Yes	76	1.03	(0.75–1.37)	0.70	(0.36–1.14)
Blocked to have appointment for imaging					
No	122	1.00	(Reference)	1.00	(Reference)
Yes	50	2.01	(1.41–2.70)	2.25	(1.40–3.34)
High cost of histology exam, transport to medical visits, and treatment[b]	207	1.07	(1.01–1.14)	1.11	(0.95–1.26)
Appropriateness of doctors' attitude[b]	207	1.13	(1.06–1.19)	1.07	(0.97–1.17)
Belief that the disease can be cured by a healer or marabout[b]	207	1.28	(1.13–1.44)	1.43	(1.20–1.70)
Need additional support by selling property, borrowing and/or donations[b]	207	1.14	(1.08–1.22)	0.91	(0.82–1.01)
Anomaly or symptoms are minor, hence no need for medical consultation[b]	207	1.03	(1.01–1.06)	0.81	(0.73–0.90)

CI: confidence interval; MAD, Moroccan dirham.
[a] Diagnosis interval is defined as the time between the first consultation and diagnosis.
[b] Component scores created using principle component analysis with low scores indicating strongly agree and high scores strongly disagree.

incomes; households are often pushed into poverty due to cancer diagnosis and cancer treatment.[15] Patients must travel long distances to be diagnosed and to receive care, and transportation costs are often excessively expensive.[16,17] Another feature of Moroccan culture is its strong solidarity. It is mainly family-related, but help can come from the neighbourhood or even from private donors. The family management of healthcare is largely prevalent, reinforced by collective values that advocate family cohesion and solidarity.[18] Since the first National Cancer Control Plan in 2010, access to cancer care of the population has improved. Implementation of the Medical Assistance Plan (RAMED or medical assistance scheme for those with no/limited incomes) provided free healthcare in the public health sector for deprived and vulnerable populations, although out-of-pocket expenses remain high when diagnosis procedures or treatments are not available at the oncology centre. In 2019, 45% of the population lived without any health insurance, out-of-pocket expenditure for health represented 47%; only 19% of the total population was covered by RAMED.[19–21] In the present study, 81% of hospitalised patients were covered by RAMED, and 16% were covered by the employee or a private health insurance. This latter group represents wealthy and educated populations who promptly visit healthcare facilities following symptom

Table 3
Determinants of treatment interval[a] (Marrakech, Casablanca, Rabat, and Fez centres data).

Characteristics	Patients assessed (n = 761)	Crude relative risk (95% CI)		Adjusted relative risk (95% CI)	
Gender					
Men	260	1.00	(Reference)	1.00	(Reference)
Women	501	0.77	(0.66–0.89)	1.02	(0.84–1.21)
Age group (yrs)					
16–49	238	1.00	(Reference)	1.00	(Reference)
50–69	370	1.40	(1.16–1.62)	1.27	(1.06–1.52)
70+	151	2.13	(1.72–2.59)	1.98	(1.49–2.55)
Stage at diagnosis					
I-II	251	1.00	(Reference)	1.00	(Reference)
III-IV	381	0.88	(0.75–1.03)	0.81	(0.67–0.96)
Unknown	130	1.30	(1.04–1.62)	1.27	(0.98–1.61)
Personal history of cancer					
No	691	1.00	(Reference)	1.00	(Reference)
Yes	61	0.63	(0.46–0.83)	0.74	(0.53–0.99)
Education					
No	468	1.00	(Reference)	1.00	(Reference)
Yes (primary, secondary, college)	266	0.85	(0.72–0.99)	0.88	(0.72–1.04)
Marital Status					
Not currently married	219	1.00	(Reference)	1.00	(Reference)
Currently married	518	1.16	(0.98–1.36)	1.22	(0.98–1.47)
Total no. of children					
0–1	183	1.00	(Reference)	1.00	(Reference)
2–4	300	1.10	(0.90–1.30)	0.93	(0.74–1.14)
≥ 5	233	1.71	(1.40–2.06)	1.07	(0.81–1.36)
Currently employed					
Not	611	1.00	(Reference)	1.00	(Reference)
Yes	124	1.20	(0.97–1.46)	1.24	(1.10–1.39)
Personal history of cancer					
No	691	1.00	(Reference)	1.00	(Reference)
Yes	61	0.63	(0.47–0.83)	0.74	(0.54–1.00)
Direct family history of cancer					
No	660	1.00	(Reference)	1.00	(Reference)
Yes	88	1.10	(0.86–1.36)	1.04	(0.80–1.31)
Monthly household income (MAD)					
None	188	1.00	(Reference)	1.00	(Reference)
<2000	311	1.16	(0.92–1.43)	0.95	(0.74–1.20)
2000–4000	169	0.78	(0.61–0.98)	0.81	(0.62–1.05)
> 4000	72	0.66	(0.48–0.87)	0.55	(0.39–0.76)
Public transportation close to home					
No	252	1.00	(Reference)	1.00	(Reference)
Yes	499	1.09	(0.92–1.27)	0.81	(0.64–0.98)
Means to reach the oncology centre					
Public transportation	559	1.00	(Reference)	1.00	(Reference)
Own means (car/motorbike/bicycle)	130	0.63	(0.47–0.83)	0.74	(0.54–1.00)
Relative or friends' car	52	0.51	(0.37–0.67)	0.48	(0.35–0.65)
Place of residence					
Urban	437	1.00	(Reference)	1.00	(Reference)
Suburban	110	0.62	(0.49–0.76)	0.73	(0.56–0.92)
Rural	195	0.65	(0.54–0.77)	0.64	(0.49–0.82)
Place of stay during ambulatory treatment at the Cancer Centre					
Own home in the same city as the Cancer Centre	244	1.00	(Reference)	1.00	(Reference)
Other place in the city of the Cancer Centre	173	0.62	(0.51–0.75)	0.84	(0.63–1.06)
Outside the city of the Cancer Centre	341	0.88	(0.74–1.04)	1.08	(0.86–1.37)
Type of health insurance					
Basic health insurance (RAMED)	610	1.00	(Reference)	1.00	(Reference)
Civil servants and private insurance	114	0.95	(0.74–1.19)	0.78	(0.60–0.98)
None	27	1.41	(0.67–2.23)	0.84	(0.48–1.41)
Global cost of the disease (MAD)					
≤5000	268	1.00	(Reference)	1.00	(Reference)
>5000	410	1.46	(1.22–1.73)	1.00	(0.76–1.25)
High cost of histology exam, transport to medical visits, and treatment[b]	744	1.00	(0.96–1.04)	1.03	(0.99–1.08)
Appropriateness of doctors' attitude[b]	744	1.00	(0.96–1.03)	0.97	(0.93–1.01)
Belief that the disease can be cured by a healer or marabout[b]	744	1.00	(0.95–1.06)	1.03	(0.97–1.09)
Need additional support by selling property, borrowing and/or donations[b]	744	0.95	(0.92–0.99)	0.96	(0.92–1.01)
Enough health centres and accommodations in city of the oncology centre[b]	744	1.09	(1.05–1.12)	1.04	(0.99–1.10)
Anomaly or symptoms are minor, hence no need for medical consultation[b]	744	0.92	(0.89–0.96)	0.95	(0.91–1.00)

CI: confidence interval; MAD, Moroccan dirham.
[a] Treatment interval is defined as the time between diagnosis and treatment initiation.
[b] Component scores created using principle component analysis with low scores indicating strongly agree and high scores strongly disagree.

recognition and who are often diagnosed and treated within the private sector.[22] It should be noted that since the conduct of this study, Morocco has generalised the health insurance system (Assurance Maladie Obligatoire (AMO) or Compulsory Health Insurance). In July 2022, RAMED joined AMO. Morocco is making great efforts to implement Universal Health Coverage, with RAMED joining AMO being the first step.

Most of the population in Morocco use modern medicine and the proportion of individuals using traditional medicine is now low.[23] In the present study, 12% of patients declared having used traditional medicine before being admitted to the oncology centre. However, patients who disagreed with the statement that they "can be treated by marabout or traditional healers" were more likely to have a short diagnosis interval.

This study also found that having someone, very often a family member, to serve as a patient navigator to help coordinate and support the patient journey shortened (although not significantly) the diagnosis interval; this finding is consistent with previous studies.[24–26]

The current study reported a significantly shorter treatment initiation among those with advanced stage cancer than among patients with a localised cancer. This has been described as the 'sicker quicker' effect; doctors tend to speed up the process to manage the more severe patients as quickly as possible. However, these patients generally have poorer outcomes as they are more likely to be diagnosed at a later stage.[27]

Interestingly, the more patients disagreed with the statement that "the symptoms seem benign or not disturbing, there is no need to seek for a medical advice", the longer the intervals for diagnosis, treatment, and overall. This counter-intuitive finding can be explained by the fact that the questionnaire was administered after hospitalisation at a time when cancer diagnosis had already been received. The patients understood, retrospectively, that they should have considered the situation seriously as the symptoms would not clear naturally and that they should have consulted a healthcare provider much faster. In a systematic review, it was reported that the presentation for medical advice occurs only when symptoms become incapacitating or impact normal activities; existence of a symptom alone cannot explain the patient interval.[28]

Comparison of the treatment interval with international guidelines showed that Morocco was within the current Australian, Brazilian, Canadian, Colombian, UK, and US recommendations (≤28–31 days) but longer than the European Union recommendations (<15 working days [i.e., 21 days]). However, the primary care interval, the diagnosis interval, and the health service interval (sum of diagnosis and treatment intervals) were twice as long as the duration guidelines from Australia, the UK, and the World Health Organization (≤28–30 days) (Fig. 2).[29–38]

Delays in diagnosis and cancer treatment initiation are associated with a worse survival outcome and an increased mortality risk.[39–44] For instance, between 2004 and 2009 in the US, breast cancer treatment interval lengthened significantly and was associated with absolute increased risk of mortality ranging from 1.2% to 3.2% per week of delay.[41] In addition to improving survival and quality of life, shortening diagnosis and treatment intervals is a matter of equity in giving the opportunity to all patients to be managed in the same effective way. It is also a measure of the quality of health services.[45] Indeed, in the US, time to diagnosis and to treatment of breast cancer has become the subject of accreditation promoted by quality-control agencies.[46] And, in the UK, the data on Cancer Waiting Times system are used to monitor performance against operational standards for cancer waiting times and aid service improvement.[47] Having to wait for a cancer diagnosis confirmation or to start cancer treatment is a stressful and worrisome experience for the patient and the family. However, the majority of countries, including high income countries, do not yet have defined standards for diagnosis and treatment intervals. Moreover, these targets are mainly focused on the waiting times to start treatment once the cancer is histologically confirmed, not from when the person first sees the general practitioner who suspects a cancer. Establishing target times for urgent suspected cancer referral or after an abnormal screening test, such as mammography, is essential. For instance, England has implemented the 'Faster Diagnosis Standard' with a target of no more than 28 days to confirm or refute a cancer diagnosis.

Indeed, while many countries present poor referral systems and inadequate patient-navigation systems, standard protocols for referrals should be developed between the primary care level and

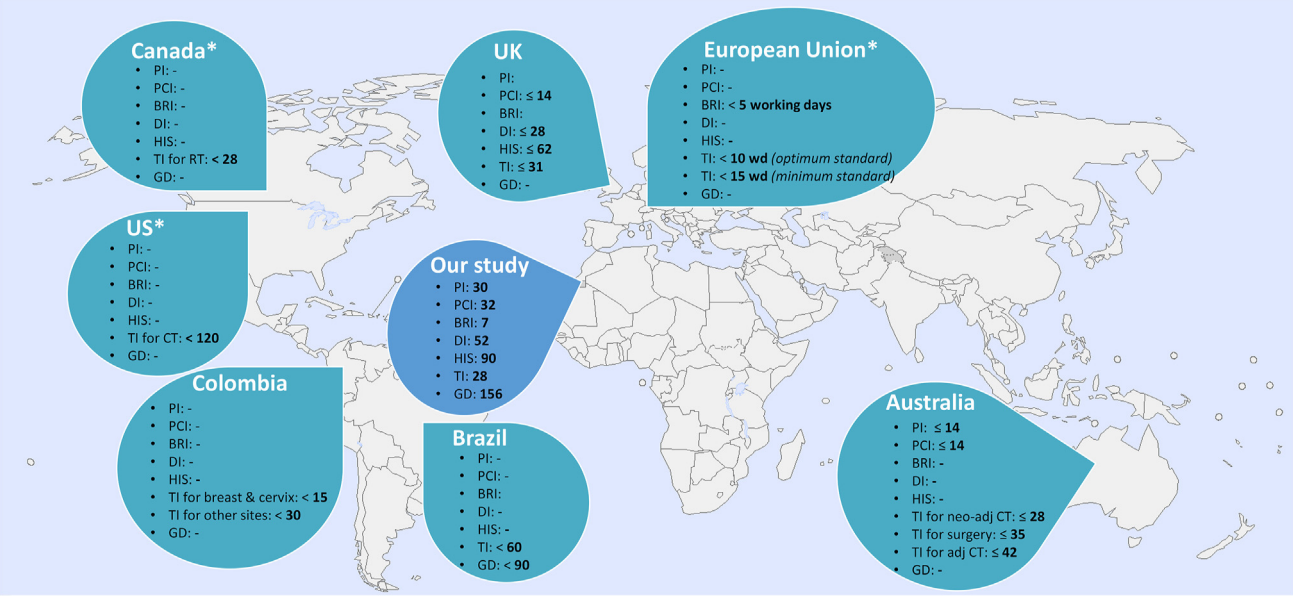

Fig. 2. Comparison of intervals with international standards or timeframes (in days).

diagnosis and treatment facilities. Building local capacity and strengthening the referral system will help ensure timely and appropriate access to both local and tertiary care. Furthermore, patient navigation allows patients and carers to access available health services and reduce the number of health encounters and unnecessary steps. Navigators, such as community workers and health professionals, should be trained to assist patients in helping with appointment scheduling and coordination of care.[48] A prompt referral could be realised by scheduling rapid appointments for imaging, biopsy, endoscopy, colposcopy, biological exams, etc., grouped in one health facility and during a single visit but also by speeding up the waiting time for delivery of test results. Additionally, a multidisciplinary team approach (e.g., surgeons, medical oncologists, radiologists, nurses) should be in place to improve treatment plans and reduce duplication of care.[48]

This study presents several limitations. The main limitation is the reliability of the date of symptom recognition from which several intervals were estimated. Best estimates for this date were made according to major personal or national events and in using information, if any, from the referral letter. Also, patients were interviewed just after the treatment initiation, minimising a potential recall bias. A second limitation is that some intervals were only based on data from patients in Casablanca, thus raising the question on the representativeness of the findings. Indeed, patients in Casablanca mainly came from the region and the southern part of Morocco. Finally, the study participants were mainly covered by the RAMED health insurance. Those covered by employee or private insurance were more likely to be treated in the private sector, where referral, biopsy, and treatment intervals are usually shorter.[15] Therefore, the present study population is not representative of the Moroccan population in general but representative of the RAMED population who are treated in the public sector.

In conclusion, this study showed that in Morocco, the biopsy report interval and the treatment interval are within international standards; however, the diagnosis interval and the health services interval need to be improved. Current evidence suggests that interventions should firstly increase affordable and quality healthcare access and secondly, enhance cancer awareness within the population and the healthcare providers to productively speed up the referral once cancer is suspected; for instance, through implementation of Universal Health Coverage with a protection against catastrophic health expenditures.[21,49] It is recommended that health systems should define and regularly monitor interval targets through quantitative data in order to be more equitable, more effective, and ensure that cancer patients are treated within a defined timeframe.

Author Statements

Acknowledgements

The Authors are grateful to the patients and families who agreed to participate in the study. We are also grateful to the nurses and doctors who administered the questionnaire.

Ethics Approval

This study was approved by the IARC Ethics Committee and the Ethics Committee for Biomedical Research, Medical and Pharmacy School, Mohammed V – Souissi University, Rabat, Morocco.

Funding

Funding was received from the Lalla Salma Foundation, Morocco.

Competing Interests

The authors declare no competing interests.

Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.07.015.

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Public Health 223 (2023) 193–201

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Unmasking the COVID-19 pandemic prevention gains: excess mortality reversal in 2022

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ARTICLE INFO

Article history:
Received 11 March 2023
Received in revised form
11 July 2023
Accepted 2 August 2023
Available online 5 September 2023

Keywords:
Mortality displacement
Harvesting effect
COVID-19
Health policy
Control measures
Post-pandemic transition period
Public health interventions
Non-pharmaceutical interventions

ABSTRACT

Objectives: The purpose of this study was to assess the long-term effectiveness of COVID-19 pandemic prevention measures in saving lives after European governments began to lift restrictions.
Study design: Excess mortality interrupted time series.
Methods: Country-level weekly data on deaths were fitted to the Poisson mixed linear model to estimate excess deaths. Based on this estimate, the percentage of excess deaths above the baseline during the pandemic (week 11 in 2020 to week 15 in 2022) (when public health interventions were in place) and during the post-pandemic period (week 16 in 2022 to week 52 in 2022) were calculated. These results were fitted to the linear regression model to determine any potential relationship between mortality during these two periods.
Results: The model used in this study had high predictive value (adjusted $R^2 = 59.4\%$). Mortality during the endemic (post-pandemic) period alone increased by 7.2% (95% confidence interval [CI]: 5.7, 8.6) above baseline, while each percentage increase in mortality during the pandemic corresponded to a 0.357% reduction (95% CI: 0.243, 0.471) in mortality during the post-pandemic period.
Conclusions: The most successful countries in terms of protective measures also experienced the highest mortality rates after restrictions were lifted. The model used in this study clearly shows a measure of bidirectional mortality displacement that is sufficiently clear to mask any impact of long COVID on overall mortality. Results from this study also seriously impact previous cost-benefit analyses of pandemic prevention measures, since, according to the current model, 12.2% (95% CI: 8.3, 16.1) of the gains achieved in pandemic containment were lost after restrictions were lifted.

Introduction

COVID-19, caused by a new severe acute respiratory syndrome (SARS-CoV-2), originated in Wuhan, Hubei Province, China, in December 2019.[1] The virus spread rapidly around the world and, within a matter of months, had been recorded in every country.[2] COVID-19 quickly became a global health crisis, creating unprecedented challenges for healthcare systems. The first cases of COVID-19 in Europe were detected and reported in France on 24 January 2020.[3] The scale of the crisis grew during the spring of 2020 and, on 11 March 2020, the World Health Organisation (WHO) declared COVID-19 to be a pandemic.[4]

From the very beginning of the pandemic, it was argued that, in order to stem the rapid spread of the new virus, early control measures were required. Although the use of face masks, sanitisers and social distancing were widely recognised as important means to limit the spread of infection, they were sometimes considered as half-measures that would be ineffective in meeting public health targets. Especially since some countries (e.g. Singapore, South Korea, Taiwan, China, Australia) showed the effectiveness of the 'hit early, hit fast, hit hard!' paradigm, including the widespread use of personal protective equipment (PPE) and social distancing, coupled with extensive testing, isolation, quarantine and lockdown.[5–7] It was consequently argued that the absence of fast, strong and comprehensive public health interventions and non-pharm-

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https://doi.org/10.1016/j.puhe.2023.08.004

aceutical interventions (NPIs) would result in high morbidity and mortality.[2,8,9]

Since the initial reports of COVID-19 infections in Europe, the priority was to protect public health and the well-being of citizens. National governments implemented a range of public health interventions and control measures to curb the transmission of the virus. While the European Union (EU) aimed to unify and coordinate its strategy, the response to the outbreak varied significantly across countries.[10] While Eastern European countries demonstrated early success in their response during the first COVID-19 wave, they later experienced a significant increase in infections and deaths during the second wave, while Western European countries responded more effectively.[11,12] Some countries focused on testing strategies, including rapid antigen tests, while others launched mass-vaccination campaigns and implemented vaccination certificates. Additionally, many countries closed borders, imposed travel restrictions, quarantined travellers from affected regions, restricted mass gatherings, closed public places, including hospitals and long-term care facilities to external visitors, and implemented social distancing measures, hand hygiene practices, and mandatory isolation for COVID-19-positive individuals and quarantines for close contacts.[13] Despite these efforts, by the end of 2022, over 163,000 Europeans had lost their lives according to official records,[14] although this number should be seen as a conservative estimate. Excess mortality studies indicate significantly higher figures.[12,15,16] The significant death toll, along with the extensive social and economic ramifications resulting from the preventive measures, sparked a heated debate about their efficacy.[11,17]

COVID-19 still circulates and causes serious ill health, so it may seem somewhat premature to declare that the pandemic is over, especially so soon after the initial Omicron wave. However, if such a standard was applied, then it could be said that the Spanish Flu pandemic persists. While Spanish Flu is no longer as acute as it was between 1918 and 1920, its related strains remain not only in circulation but are also the dominant strains during the annual flu seasons.[18] Modern flu strains are also not terribly distant, as in 2009, the H1N1 flu vaccines were shown to provide mice with some cross-immunity against Spanish Flu.[19] A similar pattern emerged with COVID-19. On 27 April 2022, the European Centre for Disease Prevention and Control declared that most EU countries were 'transitioning beyond the acute phase of the pandemic and towards a more sustainable and integrated approach' and that such a shift has been ongoing from since 2022.[20] In both cases, after 2 years of the pandemic, the acute impact of the infection diminished and restrictions were de-escalated. It had been tentatively suggested by scholars, as early as 2022, that the virus may be transitioning to an endemic state.[21] With the benefit of hindsight, it can now be confirmed that the virus has indeed become endemic. However, it is important to note that endemicity does not imply harmlessness, as demonstrated by the influenza virus, which caused deadly local epidemics in the 1920s[18] and significant pandemics in 1957 and 1968.[22]

While the COVID-19 pandemic was ongoing, initial predictions were made to anticipate its ultimate impact on mortality. Three mechanisms were predominantly examined. The first mechanism involved a rebound in infections and mortality due to the relaxation of NPIs before achieving sufficient vaccination coverage, aiming for virus eradication or high protection among high-risk groups.[23–27] The second mechanism led to a lasting increase in mortality following the pandemic, associated with long-term health complications caused by the virus,[28,29] disruptions in healthcare services, including missed oncological screenings and delayed surgeries,[30–32] and the emerging mental health challenges stemming from social isolation measures.[33] The third mechanism involved the expected harvesting effect, whereby the virus was hypothesised to primarily impact the most vulnerable individuals, potentially resulting in a decrease in mortality in subsequent periods; however, initial studies suggested a relatively weak impact of this mechanism.[34] Some studies revealed a contrasting pattern, indicating a higher vulnerability to COVID-19 fatalities in individuals with chronic obstructive pulmonary disease (COPD) and chronic cardiovascular disease, while observing a comparatively lower risk of death in those with cancer. This observation, along with concerns about delayed cancer diagnoses during the pandemic, suggested a potential harvesting effect in relation to some pre-existing conditions, concurring with a possible increase in cancer-related mortality.[35]

While most studies have focussed on the short-term effects of COVID-19 restrictions on saving lives, the purpose of this study was to assess their long-term consequences after the pandemic prevention measures had been lifted. Previous research primarily focused on assessing the effectiveness of these measures using short-term data. However, the current study aimed to address key unanswered questions: What is the impact on mortality when pandemic restrictions are eventually lifted? Will subsequent mortality be primarily influenced by an increase in COVID-19–related deaths, particularly in societies with low vaccination rates among vulnerable populations? Alternatively, will it exhibit a pattern resembling a harvesting effect, similar to that observed in the aftermath of influenza pandemics?

Methods

Study design

While some studies examining the impact of the pandemic focussed on the confirmed deaths from COVID-19, this study considered excess mortality to be a more comprehensive measure because COVID-19 fatality was likely to be under- or over-estimated. Indeed, while some European countries only reported COVID-19 deaths confirmed by tests, others included only deaths that occurred in hospitals, while others also included cases that, while patients tested positive for COVID-19, their deaths resulted from other causes.[36–41] Excess mortality also captures not only the confirmed and reported COVID-19 deaths but also measures all deaths that resulted from other causes attributable to the overall crisis conditions. Excess mortality therefore captures the total impact of the pandemic on mortality.[15,16,42,43]

The WHO declared the COVID-19 pandemic on 11 March 2020, so that week (week 11 in 2020 [2020-W11]) was considered to be the first week of the pandemic. The precise timing of the shift from pandemic to endemic was more blurred, as there were significant differences in the timing of this wave and the timing of the lifting of restrictions. Additionally, the less deadly but highly infectious Omicron variant often rendered more restrictive policies untenable during the peak of its wave, even when measures were fully removed afterwards. Somewhat arbitrarily, therefore, 2022-W15 was selected to mark the end of the acute pandemic and the end of restrictions. The COVID-19 pandemic was consequently considered the period between 2020-W11 and 2022-W15 (2020-03-09 to 2022-04-17). The post-pandemic transition period (endemicity) was defined as the period 2022-W16 to 2022-W52 (2022-04-18 to 2023-01-01). This included a part of the year beyond the usual influenza season, thus any significant increased mortality could not be attributed to the usual, annual influenza pattern alone.

Data sources

The number of weekly deaths for European countries were obtained from Eurostat as of 10 February 2023. Data sets from 2015-

W01 to 2022-W52 were used, while countries were excluded if either more than five observations were missing or if for any week the number of deaths was below 100.

The vaccination rate as of mid-2022 (Week 26) was obtained from the European Centre for Disease Prevention and Control. As the effectiveness of the primary vaccination course was gradually diminishing and regional variations in vaccination rates were exacerbating over time,[44] the rate of first booster doses within the population aged ≥60 years was used as a proxy for vaccination rate. This population group was selected as they represented highly vulnerable individuals who were potentially at a higher risk of death than younger individuals.

Data analyses

To calculate the number of excess deaths in both pandemic and post-pandemic periods, a suitable model had to be selected. As some countries were relatively small, it was necessary to use the Poisson model. A high level of excess mortality during the COVID-19 waves required a mixed linear regression, where excess observations were to be filtered out from any fitting. The Poisson mixed linear regression was thus used.

Based on prior research,[41] the following formula was used to calculate excess deaths:

$$ln(Y_i) = a + b\left(T + \frac{t}{52.25}\right) + csin\left(\frac{2\pi t}{52.25}\right) + dcos\left(\frac{2\pi t}{52.25}\right) + \varepsilon$$

where, Y_i – the predicted number of weekly deaths, a – base number of weekly deaths, b – annual change in the number of weekly deaths, T – year, t – ISO week of the year, c, d – season-dependent component of weekly deaths, created by superimposed sine and cosine function, ε – error of prediction.

The model was set up as follows. First, the model was fitted to an unweighted linear model. Subsequent observations that diverged upwards by more than 1.5 standard deviation were excluded from further fittings, and the model was fitted to the remaining data. Ultimately, in order to achieve greater precision, the process was iterated one more time, but this time excluding observations that deviated from a prior weighted model.

To compare countries of different population sizes and compositions, deaths were converted to the average percentage of excess deaths above the base level for available weeks of analysed periods. As a base level was used, the value was fitted by the model after removing seasonal factors, which was necessary to account for seasonal variations in deaths (otherwise the same number of excess deaths in summer would be counted as a higher relative increase than in winter).

Subsequently, the study aimed to determine the factors explaining the excess mortality that followed. Assuming that the main mechanism was COVID-19 rebounding after the lifting of restrictions, the determining factor should be the vaccination rate among the most vulnerable individuals. While the relationship may be a bit skewed by the observed high level of natural immunity in countries with less effective restrictions, the continuation of vaccination efforts should produce tangible results. Alternatively, if this less virulent variant simply becomes one of many viruses causing upper respiratory infections, the focus shifts to assessing how many vulnerable individuals survived the pandemic rather than the vaccination rate alone. In such a scenario, mortality displacement would become the predominant mechanism. These hypotheses were tested using linear regression models, with a statistical significance threshold set at $P < 0.01$.

A deeper insight into observed mortality patterns is afforded by a more thorough comparison of selected countries with different pandemic responses. Neighbouring countries were selected in order to rule out geographical differences in the spread of viruses or weather events. Sweden, which was distinguished by its relatively mild pandemic response, was compared with neighbouring Finland and Norway. As there were clear differences in outcomes between EU core and former Eastern Bloc countries, this also warranted a deeper analysis. To detect overall trends less affected by random fluctuation, larger countries were more suitable for analysis; thus, Germany and Poland were selected.

Excess deaths were calculated using Python script (libraries: pandas 1.4.3, numpy 1.23.2 and statsmodel 0.13.2), regression was calculated using Gretl 2022a and maps were generated using GeoDa 1.20.0.20. Confidence intervals of 95% were used.

Ethics

Because the analysed reports used in this study are publicly available, no ethical approval was required.

Results

Excess deaths as a percentage over baseline are presented for both the pandemic (2020-W11 to 2022-W15) and the post-pandemic transition period (2022-W16 to 2022-W52) in Fig. 1. During the pandemic, there was both a visible, modest North-South divide and a strong East-West divide along the former Iron Curtain. The countries most affected were former Eastern Bloc countries, especially the Balkans, while the pandemic's impact on excess mortality in Norway and Finland was minimal. When restrictions began to be lifted, the mortality remained overall somewhat elevated, but the highest mortality was observed in the countries initially most successful in their responses to the pandemic, while some, such as Romania and Bulgaria, had mortality rates even slightly lower than their baseline.

Fig. 2 presents the relationships between excess deaths during the post-pandemic transition period of 2022 and the booster rate among the elderly population (aged ≥60 years). The relationship was statistically significant, with a *P*-value <0.001, and the adjusted R-squared explains 55.6% of the variability. Strikingly, the relationship was positive, indicating that a higher vaccination rate was, paradoxically, associated with a higher mortality rebound after the lifting of restrictions.

When incorporating both vaccination rate and pandemic excess mortality as explanatory variables, the vaccination rate proved to be non-predictive. As shown in Fig. 3, post-pandemic mortality can be better explained by pandemic mortality alone (adjusted R-squared = 59.3%). The findings revealed a noticeable linear relationship, indicating that each percentage point increase in mortality during the pandemic corresponds to a 0.357% reduction (95% CI: 0.243, 0.471) in mortality during the post-pandemic period. Furthermore, the model suggested an elevated mortality of 7.2% (95% CI: 5.7, 8.6) above the baseline, which was comparable to the flu seasons observed between 2015 and 2019.

In early 2020, both Poland and Germany were doing well in terms of their mitigation measures to control the spread of COVID-19. Lockdowns in Poland even resulted in mortality slightly below the baseline during the first half of the year (Fig. 4, left panels). Divergence between Poland and Germany in terms of mortality started in the autumn of 2020, and, from that moment onward, Germany fared much better than Poland, as peaks in excess mortality in Germany were much smaller and slightly delayed, which is consistent with effective measures to slow down the spread of the virus. After the peak of the Omicron wave in early 2022, both countries remained at the same level, even though Poland was quicker to lift the restrictions. A modest convergence began in the

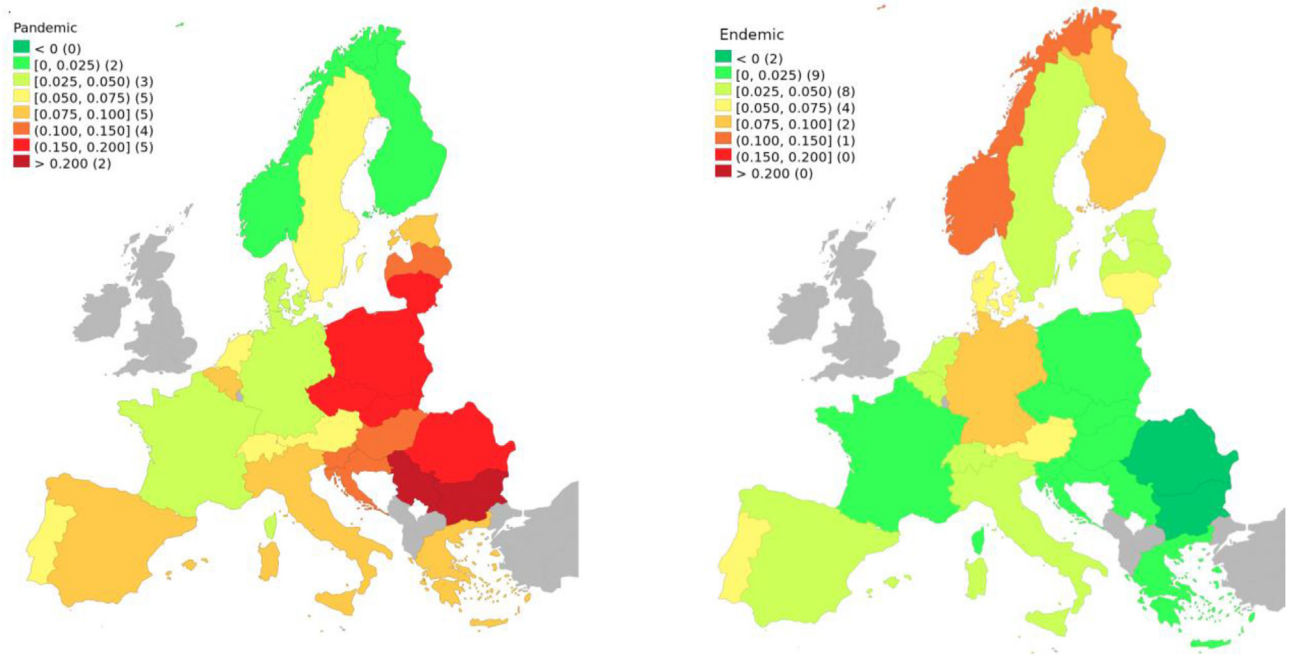

Fig. 1. Percentage of excess deaths above the baseline during the pandemic (2020-W11 to 2022-W15) and in the post-pandemic (endemic) transition period (2022-W16 to 2022-W52).

summer of 2022, when Germany began to experience elevated mortality, and by the end of 2022, the gap narrowed by 20.7% compared to the peak in 2022-W08.

In Scandinavia, the pandemic developed in a different direction (Fig. 4, right panels). Notably, overall excess mortality was much lower. Even Sweden fared only slightly worse than Germany. Fig. 4 shows that Sweden stood out among Scandinavian countries not only because it initially experienced elevated mortality but also because its neighbours maintained negative excess mortality, although this reversed in mid-summer 2021. From that point on,

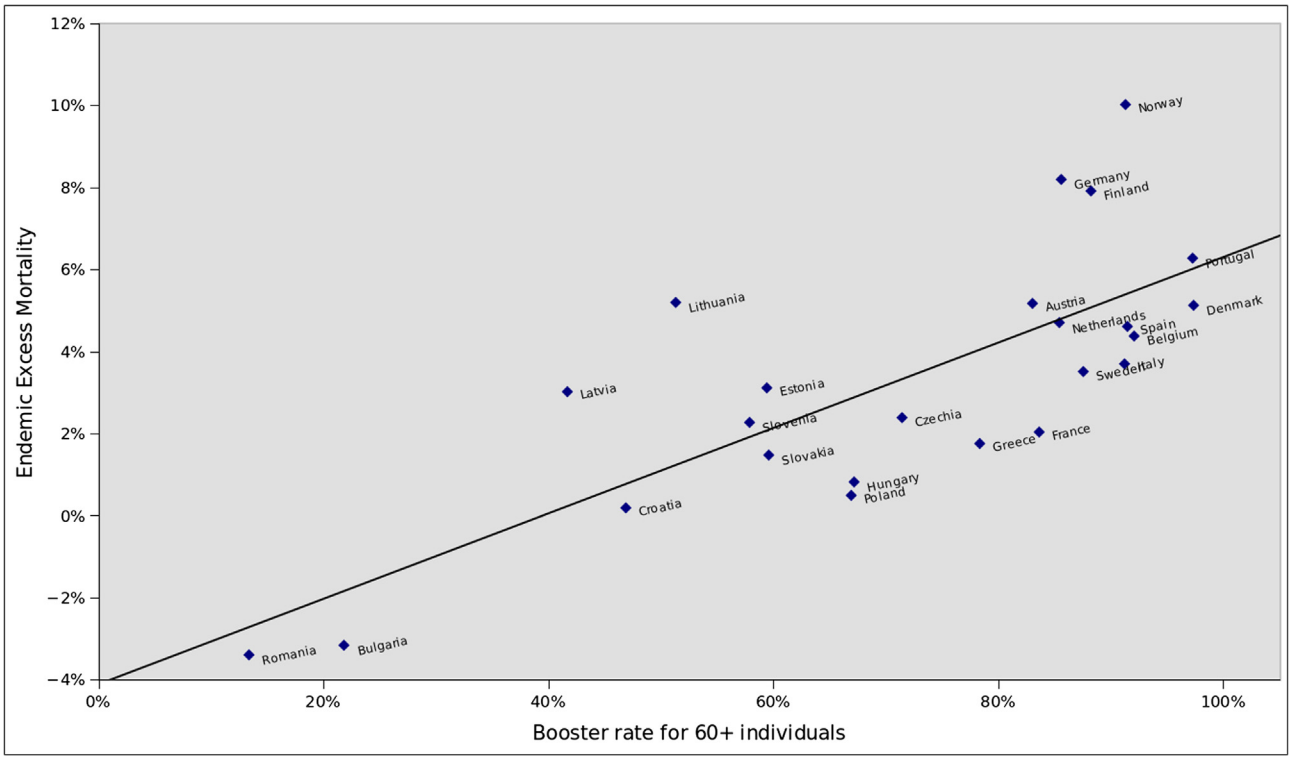

Fig. 2. Relationship between percentages of excess deaths above the baseline post-pandemic (endemic) transition period (2022-W16 to 2022-W52) and percentage of people aged 60+ years who had received their first booster by 2022-W26.

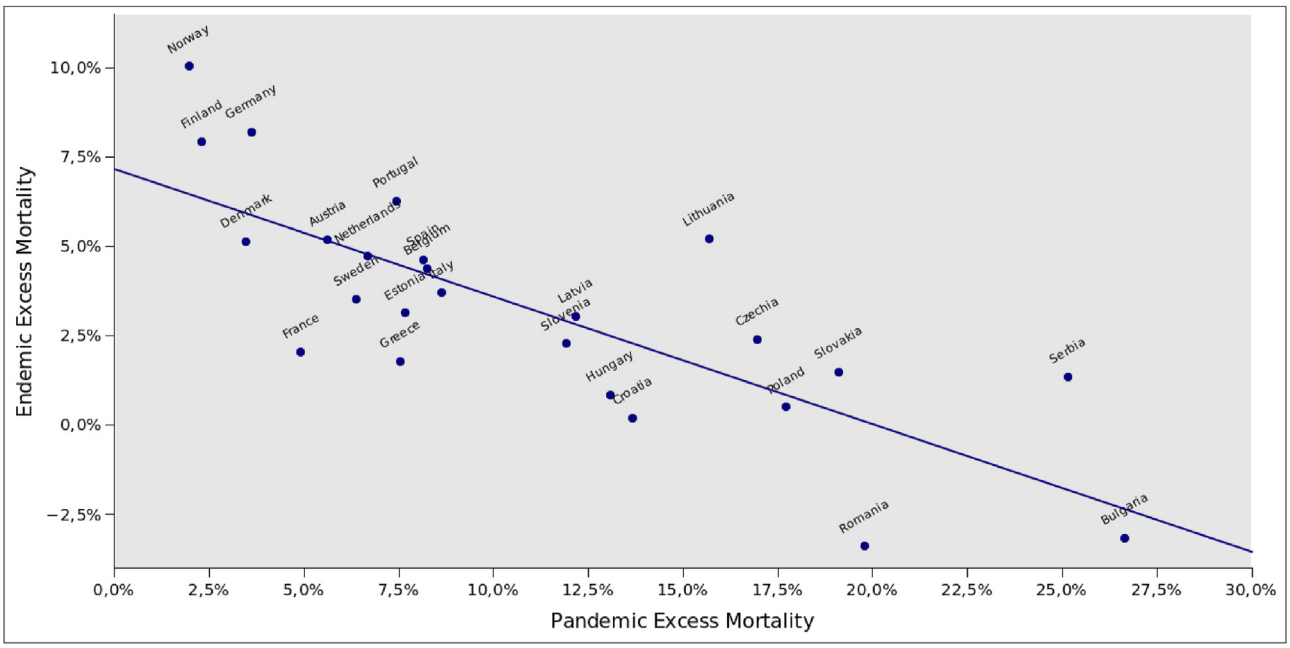

Fig. 3. Relationship between percentages of excess deaths above the baseline during the pandemic (2020-W11 to 2022-W15) and during the post-pandemic (endemic) transition period (2022-W16 to 2022-W52).

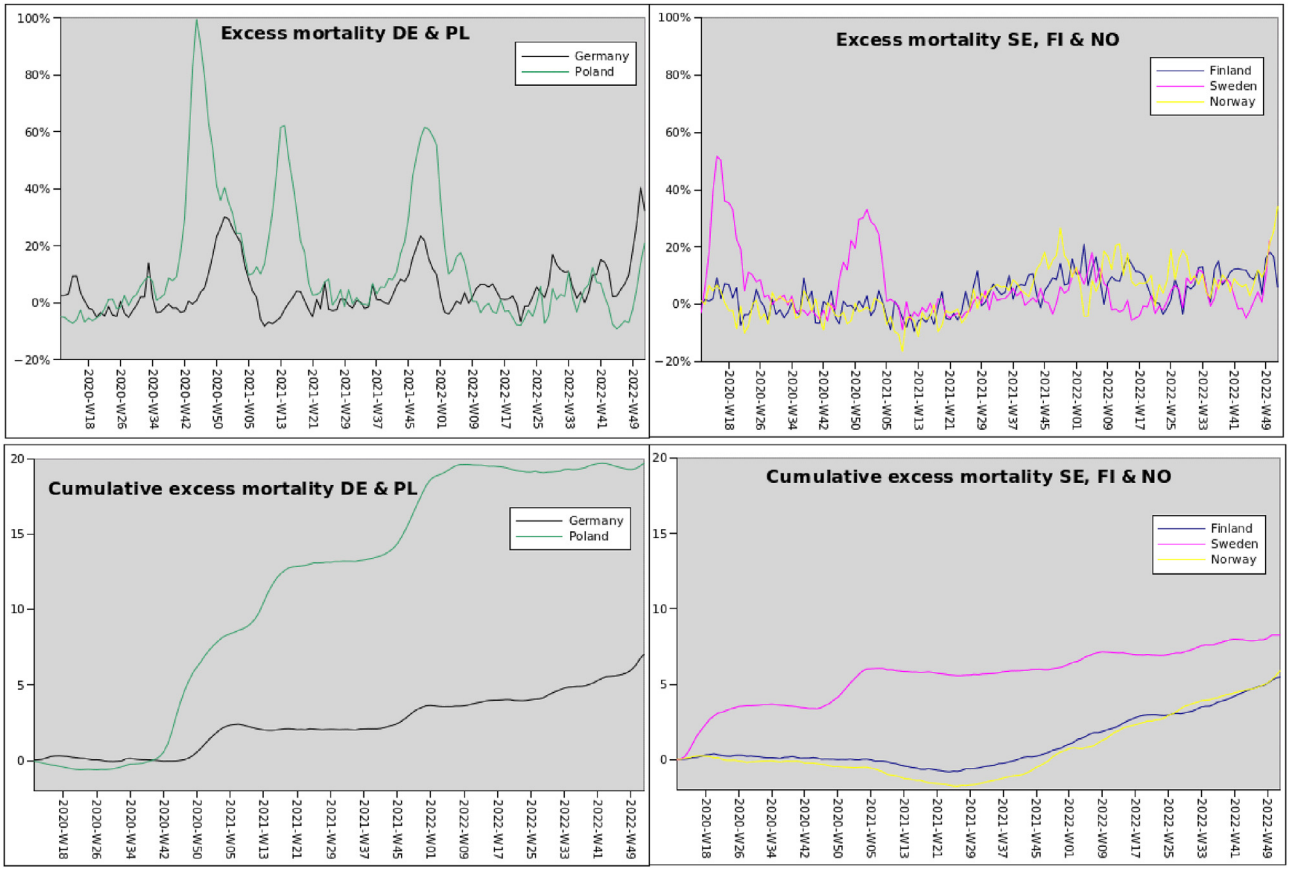

Fig. 4. Weekly and cumulative excess deaths during the period 2020-W10 to 2022-W52 in selected European countries. DE, Germany; PL, Poland; SE, Sweden; FI, Finland; NO, Norway.

there was a strong convergence, and by the end of 2022, the excess mortality gap in Sweden narrowed by 56.9% compared to Finland and by 67.7% in relation to Norway.

Discussion

The results from this study may initially appear paradoxical, but when considering the broader context, they start to align logically. The implementation of social distancing measures and other broad restrictions had a significant impact on the circulation of viruses in general, including not only a marked reduction in influenza transmission,[45] but even the B/Yamagata lineage extinction.[46] The reduced number of infections resulted in periods of decreased mortality below baseline. Furthermore, countries like Finland or Norway reported some COVID-19 deaths, although they did not experience noticeable excess mortality, suggesting that although net mortality remained within the natural range, different groups of people were actually affected. The subsequent events involving other viruses are well-documented, revealing a notable surge in infections, particularly in children who had limited prior exposure.[47] Furthermore, epidemics of viruses such as respiratory syncytial virus (RSV) were reported in Italy[48] and Austria,[49] indicating an escalation beyond the usual trend or baseline. Similarly, an out-of-season wave of influenza was detected.[45,50]

The observation of periods during which winter mortality remained notably below average raises the question of what happened to those frail individuals who, under normal circumstances, would have been expected to succumb to infections. The pandemic restrictions could be seen as a blessing in disguise, protecting highly frail individuals from infection who would have otherwise died under normal conditions, but leaving them extremely vulnerable afterwards. With the exception of a single study where a related phenomenon was referred to as 'dry tinder',[51] there is currently no specific term in the literature to describe this mechanism. Therefore, we propose the term 'reverse harvesting effect'. This mechanism could have been further hastened by a surge of other infectious diseases, some of which were even observed outside of their usual peak season. The reverse correlation between COVID-19 vaccination and excess mortality after lifting restrictions can be attributed to the fact that, within the model, vaccination acts primarily as an indicator of a proficiently executed pandemic response. In essence, vaccination served as a central component of pandemic prevention measures, thus demonstrating a strong correlation with outcomes.

The estimates in the current study of excess mortality during the pandemic are highly consistent with findings from the WHO.[15] The strong relationship observed between mortality during the pandemic and during its aftermath suggests the presence of mortality displacement. However, in regions with less successful pandemic containment efforts, such as the Balkans, a typical harvesting effect was observed. Conversely, in more successful regions, exemplified by Scandinavia, a net reversed harvesting effect was observed. Extrapolating the results of the regression model, it was estimated that by the end of 2022, the convergence of excess deaths in the analysed countries reduced the gains achieved in pandemic containment by 12.2% (95% CI: 8.3, 16.1) compared to the period from 2020-W11 to 2022-W15. This should be considered a conservative estimate, as the actual comparison of neighbouring countries (Fig. 4) showed a much closer convergence in relation to the peak difference. Previous epidemiological studies have demonstrated a positive association between short-term exposure to sudden external events, such as heatwaves or influenza, initially leading to excess mortality followed by unusually low mortality.[52–57] It has also been suggested that in the short term, the pandemic was expected to lead to mortality displacement.[34,35,58] To the best of the authors' knowledge, the COVID-19 pandemic represents the first documented case in which significant bidirectional mortality displacement was observed.

The geographical distribution of excess deaths during the pandemic reveals a significant pattern, characterised by distinct East-West and North-South divides. However, the variations in policy choices within each region were minimally apparent. Sweden, with its relatively relaxed approach that did not include lockdowns and emphasised mask-wearing and COVID-19 passports primarily for mass events, demonstrated better long-term outcomes compared to Eastern European countries that implemented stricter measures. It is important to note that this pattern does not necessarily indicate the superiority or inferiority of specific policies, but rather emphasises the importance of the quality of institutional implementation. The behaviour of individuals in response to state policies also plays a role in mitigating the impact. When restrictions are perceived as excessively restrictive, people tend to be less cautious (known as risk compensation),[59] whereas in situations of perceived insufficiency, such as increasing infections, individuals tend to exhibit greater caution than what is mandated by regulations (known as voluntary behavioural change).[60]

Considering that some of the initial gains achieved in pandemic containment were already lost before the complete lifting of pandemic mitigation measures, it is crucial to approach the initially measured effectiveness of the pandemic response with caution. Nonetheless, the policy's ability to save lives and extend life expectancy by one or two years should still be regarded as a modest success. However, it is important to assess this success in relation to the societal costs incurred. The implementation of NPIs had significant repercussions on the healthcare system and the mental well-being of the population.[61]

During the early phase of the pandemic, lockdowns were widely implemented as a means of controlling the spread of infection. However, it became evident that lockdowns came with significant costs to society. Moreover, studies suggest that the effectiveness of lockdowns varied depending on the quality of local governance.[62] The impact of lockdowns extended beyond the reduction in viral spread, as evidenced by a 25% increase in the prevalence of anxiety and depression worldwide reported by the WHO.[54] In the UK, rates of anxiety and depression among the general population rose by 26.35% and 27.88%, respectively, compared to pre-pandemic levels.[63] Lockdown measures, along with social distancing and COVID-19 quarantine, have been associated with various negative consequences, including domestic conflicts, violence, financial crises and a deterioration of mental health. This has led to an increase in suicidal ideations, suicide attempts and suicide rates in many countries.[33,64–66] Furthermore, the closure of schools and universities disrupted education and contributed to mental health problems among students.[67–71]

Although the current analysis positions Norway as the most successful European country in terms of COVID-19 containment, it is important to acknowledge the findings of internal studies indicating a significant decline in the quality of life experienced by the Norwegian population.[72] The debate surrounding the appropriateness of lockdown policies[73] is further supported by the observations of Juul et al., who noted that while Sweden experienced an initial increase in mortality in early 2020, it was followed by a period of below-trend mortality, suggesting mortality replacement.[74] The current study adds to this discourse by revealing that by the end of 2022, approximately two-thirds of the initial gap between Sweden and its Scandinavian neighbours in terms of excess deaths had diminished.

Limitations

This study has several limitations that should be noted. The model operated under the implicit assumption that all mortality during the pandemic would have an equal impact afterwards, with any variations in vulnerability among the deceased balancing out due to the sample size. However, this assumption oversimplifies local demographic differences, variations in pandemic spread, and sub-national differences related to social exclusion. Moreover, the introduction of vaccinations and the consideration of nuanced differences in virality between pre-Omicron waves further complicate this assumption. Notably, the individuals who died despite being vaccinated were generally older and had a shorter life expectancy,[76] contributing to a more pronounced and visible harvesting effect.

In addition, the gradual and divergent process of overcoming vaccine hesitancy, intertwined with sociopolitical affiliations, social pressure and reactions to rising infection rates[77,78] oversimplified the actual level of protection. It did not fully consider factors such as waning protection, differences in vaccine efficacy[79] and the presence of natural or hybrid immunity.

The algorithm used assumed that baseline deaths exhibit a sinusoidal pattern, which is a commonly utilised approximation,[80] Although this methodology effectively detects abrupt increases in deaths, it may incorporate events that have a mild yet long-lasting impact into the baseline.

Conclusions

Theoretically, restrictions work, as previous literature has demonstrated. However, on a closer retrospective look at the European statistics, 3 years after the outbreak of the COVID-19 pandemic, it transpires that historical differences between countries are very important, while policy differences seem not to have mattered so much. When we consider the fact that people are sensitive in reaction to the changing epidemiological situation and adjust their behaviour accordingly, this is unsurprising.

This study enhances the current understanding by exploring the consequences of lifting restrictions, revealing that the subsequent increase in mortality is not influenced by variations in vaccination rates. While, based on theoretical considerations, it might be anticipated that lingering damage from prior infection or the impact of stringent pandemic prevention policies would have the greatest impact, the current model indicates that the predominant mechanism at play was the reverse harvesting effect. This effect suggests that pandemic prevention policies temporarily shielded the most vulnerable individuals from infections in general. The inevitable loss of the initial gains in pandemic prevention underscores the need to shift the recommended policy approach from a heavy-handed approach to one focused on harm reduction[75] in the context of future pandemics.

Author statements

Acknowledgements

We are indebted to Mr. Robert France for his assistance with the language editing of the manuscript.

Ethical approval

In accordance with Polish law and Good Clinical Practice on research involving human subjects this study did not require revision of an ethics committee.

Funding

This research received no funding.

Competing interests

The authors declare that they have no conflict of interest.

Author contributions

M.P.W. and D.W. participated in the original design of the study, and all authors contributed to the acquisition of data; M.P.W. performed the statistical analyses; and M.P.W. and J.D. wrote the original draft of the manuscript. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The data sets generated during the study are available from the corresponding author on reasonable request.

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