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A cohort study on adult hematological malignancies and brain tumors in relation to magnetic fields from indoor transformer stations

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ABSTRACT

Extremely low frequency (ELF) magnetic fields (MF) have been classified as possibly carcinogenic. This classification was mainly based on studies indicating increased risk of leukemia in children living near power lines. Increased risks of adult hematological malignancies and brain tumors have also been reported, but the results are mixed. We assessed incidence of adult hematological malignancies and brain tumors associated with residential MF exposure. All cohort members had lived in buildings with indoor transformer stations (TS). MF exposure was assessed based on apartment location. Out of the 256,372 individuals, 9,636 (165,000 person-years of follow-up) living in apartments next to TSs were considered as exposed. Associations between MF exposure and neoplasms were examined using Cox proportional hazard models. The hazard ratio (HR) for MF exposure $\geq$ 1 month was below one for most hematological neoplasms (HR for any hematological neoplasm: 0.75; 95% CI: 0.54–1.03), and decreased with increasing duration of exposure (HR for exposure $\geq$ 10 years: 0.47; 95% CI: 0.22–0.99). However, the HR for acute lymphocytic leukemia (ALL) was 2.86 (95% CI: 1.00–8.15), based on 4 exposed cases; the risk increased with duration of exposure (HR for exposure $\geq$3 years: 3.61; 95% CI: 1.05–12.4) and was particularly associated with childhood exposure (2 exposed cases, HR for exposure during the first two years of life: 11.5; 95% CI: 1.92–68.9). The HR for meningioma was 0.46 (95% CI: 0.19–1.11), with no evidence of exposure-response gradient with increasing duration of exposure. The HR for glioma was 1.47 (95% CI: 0.84–2.57). The hypothesis of a positive association between ELF MFs and adult hematological malignancies was supported only for ALL. The results suggested decreased rather than increased risk of most hematological neoplasms.

1. Introduction

Extremely low frequency (ELF) magnetic fields (MFs) occur wherever alternating current electric power is generated, transmitted, distributed or used. In 2002, the International Agency for Research on Cancer (IARC) classified ELF MFs as "possibly carcinogenic to humans", mainly based on epidemiological studies reporting an association between exposure to ELF MFs and childhood leukemia (IARC, 2002). Causality of this association is still unclear (Amoon et al., 2018; Juutilainen et al., 2018).

Epidemiological studies on ELF MFs and adult cancers have mainly focused on occupational exposure. Reviews and meta-analyses of these studies indicate that workplace MF exposure may be associated with small increases in risk estimates of leukemia and brain cancer (Huss et al., 2018; Kheifets et al., 2008a; 2008b; WHO, 2007). There is limited evidence that also lymphoma may be associated with occupational exposure to ELF MFs (Huss et al., 2018; Koeman et al., 2014). However, drawing conclusions from these studies is difficult for several reasons. Quality of exposure assessment is a major challenge in occupational MF epidemiology, and the risk estimates may have been affected by considerable misclassification of exposure. Furthermore, the results do not show clear evidence of an exposure-response relationship, cancer

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subtypes do not show a consistent pattern between studies, improved exposure assessment methods are not associated with increased risk estimates, and risk estimates in new meta-analyses tend to be lower than in previous ones (Kheifets et al., 2008b).

Relatively few studies have addressed adult cancers in relation to residential exposures to ELF MFs. In some of these studies, exposure was assessed using questionnaires or interviews to collect information regarding use of electrical appliances (Kleinerman et al., 2005; Mutnick and Muscat, 1997), which is prone to recall bias when conducted after disease occurrence. In many studies, exposure assessment was based on proximity to electrical installations, usually power lines (Baldi et al., 2011; Coleman et al., 1989; Lowenthal et al., 2007; McDowall, 1986). Distance alone is a poor proxy of MF exposure, involving substantial misclassification and complicating interpretation of the findings of studies that rely on distance alone (Maslanyj et al., 2009). Although some studies have reported increased risks for leukemia (or subtypes of leukemia) and brain cancer, the evidence is not consistent, even in studies with higher quality exposure assessment methods, such as residential MF measurements and calculation of residential MFs based on distance from power lines, current in the power lines and their structural characteristics (Elliot et al., 2013; Fazzo et al., 2009; Feychting et al., 1997; Klaeboe et al., 2005; Tynes and Haldorsen, 2003; Verkasalo et al., 1996). Low prevalence of high MF exposure and hence lack of precision is a general limitation of the studies that have investigated cancer risks near power lines – using a cutoff point higher than 0.2 μT has generally not been possible in adult cancer studies that have involved measured or calculated MFs. This is a serious limitation, given that childhood cancer seems to be associated with fields greater than 0.3 or 0.4 μT, with little or no evidence of increased risk below these levels (Ahlbom et al., 2000; Greenland et al., 2000). Moreover, like in childhood cancer studies (Ahlbom et al., 2000; Greenland et al., 2000), selection bias and confounding remain as potential explanation for the results of many adult leukemia and brain cancer studies. Overall, the conclusion by Ahlbom et al. (2000) concerning childhood cancer studies is also valid for studies on adult cancer: further studies will be helpful only if selection bias and confounding can be adequately addressed, and if exposure over 0.4 μT is sufficiently common.

In this paper, we report a cohort study on adult hematological malignancies and brain tumors among residents of buildings with indoor transformer stations. We have previously constructed a database of such buildings and their residents and it provides an opportunity to study possible health effects of ELF MFs using a high-quality study design that avoids the main limitations of previous studies (Khan et al., 2019). Previous validation studies have shown that the ELF MF exposure of the residents can be assessed with low exposure misclassification based solely on apartment location and field levels exceeding 0.4 μT are common in apartments directly above the transformers (Hareuveny et al., 2011; Huss et al., 2013; Ilonen et al., 2008; Röösli et al., 2011; Thuroczy et al., 2008). Exposed and referent individuals live in the same buildings, which minimizes variation in potential confounding factors such as socioeconomic status and other environmental exposures. Furthermore, selection bias can be avoided: all eligible subjects can be included without contacting the residents or obtaining access to the residences.

2. Methods

2.1. Study population and exposure assessment

The study cohort was identified using the Database of Finnish Buildings with Indoor Transformer Stations (DaFBITS). Details of the database, compiled by our research group, have been described elsewhere (Khan et al., 2019). Briefly, information of buildings with indoor transformer stations was obtained from electricity distribution companies and information of individuals who have lived in these buildings from the Population Information System, which is maintained by the Finnish Digital and Population Data Services Agency. The computer-based Population Information System started in 1971 and has extensive records of full residential history from 1983 to date. Information on earlier years is available for a limited number of individuals, and the follow-up started on the earliest available date for each individual. Personal identity codes can be used for record linkage to Cancer Registry only from January 1, 1967, so this was the earliest date for the start of follow-up. All individuals included in the study were aged 18 or above at the end of study (December 31, 2016) and had lived in the buildings included in DaFBITS. The Ethical Committee of the University of Eastern Finland reviewed and approved the study protocol in January 2017 (Statement 4/2017). As the study was conducted based on register data alone without any contact with the study subjects, no informed consents were required according to the Finnish regulations.

Exposure assessment was based on the information compiled for DaFBITS. All apartments of the buildings included in DaFBITS were classified into five ELF MF exposure categories (Khan et al., 2019, Fig. 1; Table S1) according to their location in relation to the transformer room, which is always located on the ground floor or basement. The transformers convert 10 kV or 20 kV to the supply voltage (230 V), and one transformer typically serves several buildings. The power generation frequency in Finland is 50 Hz. In the present study, a person was classified as “exposed”, if she/he had been living for at least one month in an apartment located directly above the transformer room (category 1 in DaFBITS) or in an apartment sharing a wall with the transformer room (category 2). These were all on ground or first floors. Person-years produced by individuals who had resided in apartments sharing only a corner with the transformer room (classified as an intermediate exposure category 3 in DaFBITS) were excluded, as this is a small group and measurements of exposure level are not available. Disease risk was estimated also for individuals who had lived for at least one month in apartments on the first or ground floor but not adjacent to the transformer room (category 4 in DaFBITS) to assess possible confounding associated with living on the first or ground floor. Hereafter, this group will be called “first or ground floor residents”. The reference group consisted of individuals who had resided for at least one month in apartments on any other floor than the first or ground floors of the building (category 5 in DaFBITS). Follow-up was started one month (in the main analysis) after an individual had moved into the apartment that defined her/his exposure, and continued until the end of the study (December 31, 2016), emigration from Finland, death or to the date of diagnosis of the outcomes studied (Table 1), whichever occurred first. Reference group members who later moved into an “exposed” or a first or ground floor apartment were followed as referents until the move and were changed to the relevant group after the move. If the transformer was installed in the building later than the start of residence, follow-up was started one month after the installation of transformer. For those individuals who were less than 18 years one month after the start of residence or the date of the installation of transformer, follow-up started from the 18th birthday.

A total of 203,663 individuals, of whom 97,410 (47.8%) were men and 106,253 (52.2%) women, were included in the main analyses (Table 2). The median age of the individuals at the start of the residence was 26.2 years, interquartile range (IQR) from 20.5 to 35.9. Altogether 9,636 individuals (4.7% of the cohort in main analysis) were included in the exposed group, while 194,027 individuals (95.3%) had been living in reference apartments. The total person-years of follow up were 165,240 for the exposed residents, 3,323,413 for the referents and 877,994 for the first or ground floor residents. In the main analysis, the median person-years of follow-up was 15.3 years (IQR from 7.0 to 25.5) for the cohort, 15.6 years (IQR from 7.3 to 25.6) for the exposed group, 15.2 years (IQR from 7.0 to 25.5) for the reference group and 14.9 years (IQR from 7.0 to 24.5) for the first or ground floor residents. Person-years were also calculated for different age intervals (Table S2). Median duration of residence varied from 2.4 to 3.0 years in the apartment categories included in the analyses (Table 2).

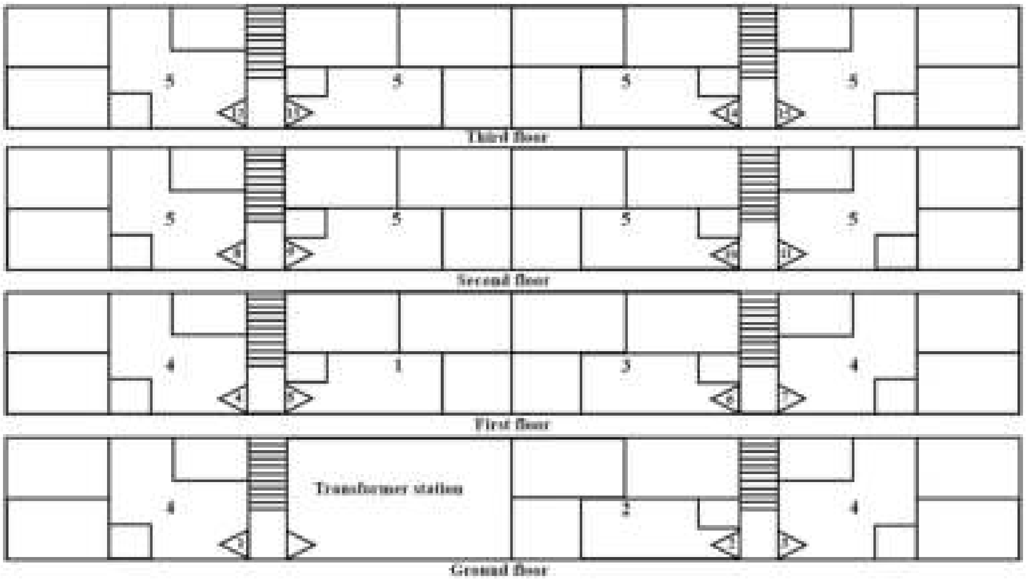

Fig. 1. Schematic representation of a building with an indoor transformer station showing the classification of apartments in relation to the transformer station. 1 = apartment located above the transformer station; 2 = apartment sharing a wall with the transformer station; 3 = apartment sharing a corner with the transformer station; 4 = apartment located on the same floor as apartment in category 1, 2 or 3; 5 = apartment located on any other floor of the building.

Table 1
Neoplasms included in the study and their codes according to the 10th revision of the International Classification of Diseases (ICD 10).

Neoplasm type	ICD 10 code	Total number of cases
Any hematological neoplasms	C81 – C96	1,102
All types of leukemia	C91 – C95	287
Lymphoid leukemia	C91	135
Acute lymphocytic leukemia	C91.0	32
Chronic lymphocytic leukemia	C91.1, 91.4	103
Myeloid leukemia	C92	134
Acute myeloid leukemia	C92.0, 92.3, 92.4, 92.5	88
Chronic myeloid leukemia	C92.1	37
Lymphoma	C81–C88	656
Hodgkin lymphoma	C81	97
Non-Hodgkin lymphoma	C82–C85, C88	559
Multiple myeloma	C90	157
Glioma[a]	C71.0 - C71.9	196
Meningioma[a]	C70.0, D32, D42.9	240

[a] International Classification of Diseases for Oncology (3rd edition) coding was used to classify the morphology of tumors.

2.2. Outcome information and data analysis

The cohort was linked to Finnish Cancer Registry. The unique personal identifiers assigned to each Finnish resident were used as the key in a deterministic linkage. Finnish Cancer Registry contains population-based data on cancer incidence starting from the year 1953 (Pukkala et al., 2018). Completeness of registration is high (about 99%) for all sites; registrations of non-solid tumors being less complete than that of solid tumors but still high (Pukkala et al., 2018). The outcomes considered were adult (diagnosis at age 18 or above) hematological malignancies and brain tumors. The complete list of neoplasm types included in the study is reported in Table 1. Information on possible dates of death or emigration from Finland was obtained from the Population Information System. The last day of follow-up was December 31, 2016.

The analyses were planned *a priori*. The only exception was a complementary visual analysis (see below). Cox proportional hazard models were used for estimating hazard ratios (HR) with 95% confidence intervals (95% CI) for the associations of residential ELF MF exposure with selected neoplasms. Time on study (in years) was used as the time scale in the analyses. Results were adjusted for gender and age at the start of residence. The Cox analyses were performed using IBM SPSS Statistics Version 25 (IBM Corp, Armonk NY, USA). If there were no exposed cases, the Cox model did not produce a useful upper limit for the 95% CI. In such cases, mid-P exact 95% CI for the conditional maximum likelihood estimate of rate ratio was calculated using Open Source Epidemiologic Statistics for Public Health version 3.01 (www.OpenEpi.com).

Our exposure classification does not produce estimates of exposure levels for each study subject in terms of magnetic flux density. Therefore, to assess existence of exposure-response relationship, we

Table 2
Characteristics of the study individuals according to extremely low frequency magnetic field exposure categories.

Apartment Category	1	2	3	4	5
Number of individuals	8,944	692	3,196	52,709	194,027
Gender			NI[a]		
Male	4,354	344		25,472	92,712
Female	4,590	348		27,237	101,315
Median age at the start of residence (years) (5th – 95th percentile)	25.7 (0.35–58.6)	25.9 (0.04–58.1)	NI[a]	26.2 (0.83–59.8)	26.3 (1.06–59.5)
Median duration of residence (years) (5th – 95th percentile)	2.7 (0.29–20.0)	3.0 (0.29–21.5)	NI[a]	2.4 (0.26–18.8)	2.5 (0.26–20.1)
First year in study: Median (5th – 95th percentile)	1995 (1974–2014)	1997 (1979–2013)	NI[a]	1997 (1974–2014)	1997 (1973–2014)

1 = apartment located above the transformer room; 2 = apartment sharing a wall with the transformer room; 3 = apartment sharing a corner with the transformer room, 4 = apartment located on the same floor as apartment in category 1, 2 or 3; 5 = apartment located on any other floor of the building.

[a] NI = not included in the present study.

investigated the relationship between duration of residence (as a proxy for duration of residential MF exposure) and risk of disease. Cox models were restricted to individuals who had resided in the buildings for <3 years, 3 to <10 years or ≥10 years. Follow-up in these analyses was started after the specified minimum duration of residence. If this was before the 18th birthday of the individual, follow-up was started from the 18th birthday. Linear regression weighted by sample size was used to examine trends over these exposure categories, with median duration of exposure as the exposure value in each category (Brownstein and Cai, 2019).

The findings of a study on adult lympho- and myeloproliferative diseases (Lowenthal et al., 2007), together with the studies reporting elevated risk of childhood leukemia, suggest that ELF MF exposure during the early years of life might be important also for induction of adult cancers. To study the impact of age at the start of exposure, Cox models were run for individuals who had resided in the buildings at different periods of life. The periods considered were first 2 years of life, ages from 2 to <15 years, and ages ≥15 years. After seeing the results of this analysis, we performed a complementary analysis to visualize the impact of age at the onset of exposure. The number of cases in the exposed and reference groups was calculated for each 5-year class of age at the start of residence in the buildings. The contribution of these cases to the observed final age-standardized incidence rates was examined by plotting the apparent incidence rate in each 5-year class (incidence rate that takes into account only persons with specified age at the start of residence) cumulatively as a function of age at the start of residence.

As a sensitivity analysis, we excluded person-years of category 2 apartments from the exposed group. No MF measurement data for this apartment category are available in Finland, but they were included in the main analysis based on studies in other countries (Huss et al., 2013; Röösli et al., 2011). The MF levels are likely to be lower in these apartments than in category 1 apartments, because category 2 apartments share only a wall with the transformer room. As the second sensitivity analysis, we included the first or ground floor residents in the reference group.

3. Results

3.1. Incidence rates

The truncated age-standardized incidence rate (cases per 100,000 person-years; follow-up started at 18 years) was in most cases lower in the exposed individuals than in the reference group (Table 3). Only the incidence rates of acute lymphocytic leukemia (ALL) and glioma were higher among the exposed individuals than among the referents.

3.2. Overall hazard ratios

The HRs for both all hematological neoplasms combined and all leukemias were below unity, indicating that the risk of these neoplasms was lower in the exposed than in the reference group (Table 4). The MF-related reduction in risk of total leukemia mainly reflected a very low risk estimate for myeloid leukemia. Among myeloid leukemias, the HRs of both acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) were low (only one AML case and no CML cases in the exposed group). With regard to lymphoid leukemia, the risk of ALL was elevated 2.86-fold among the MF-exposed individuals, while the HR for chronic lymphocytic leukemia (CLL) was reduced. The HR for all types of leukemia other than ALL was 0.43 (95% CI: 0.18–1.04). The HRs were below unity also for lymphomas. The HR for multiple myeloma was only slightly above 1.00. The HR for glioma was 1.47, while that for meningioma was 0.46-fold among the MF-exposed individuals.

The risk estimates were not materially affected by exclusion of the category 2 apartments from the “exposed” group (Table S3) or by inclusion of category 4 apartments into the reference group (Table S4). The HR for ALL increased in both sensitivity analyses, to 3.06 (95% CI: 1.07–8.73) in the first (Table S3) and to 3.52 (95% CI: 0.99–12.5) in the second (Table S4) sensitivity analysis. The HR for glioma, in contrast, decreased in both sensitivity analyses. The decreased HRs for lymphoma and meningioma were accentuated in the second sensitivity analysis. The HRs for individuals living in first or ground floor apartments (category 4) were all close to 1.00 (from 0.82 to 1.19), indicating that living on the lowest floors (where also all the “exposed” apartments are

Table 3
Truncated age-standardized incidence rates for hematological neoplasms and brain tumors by exposure to extremely low frequency magnetic fields from indoor transformer stations. The European Standard Population (Eurostat, 2012) was used for standardization. Only persons with age ≥18 years were followed up for neoplasm development. The total person-years were 165,240 for the exposed residents and 3,323,413 for the referents.

Neoplasm type	Age-standardized incidence rates (cases per 100,000 person-years)	
	Exposed	Reference
Any hematological neoplasms	26.4	43.1
All types of leukemia	4.69	11.6
Lymphoid leukemia	4.06	5.30
Acute lymphocytic leukemia	1.70	0.84
Chronic lymphocytic leukemia	2.36	4.46
Myeloid leukemia	0.32	5.42
Acute myeloid leukemia	0.32	3.40
Chronic myeloid leukemia	0.00	1.48
Lymphoma	16.1	24.8
Hodgkin lymphoma	0.46	2.74
Non-Hodgkin lymphoma	15.7	22.2
Multiple myeloma	6.38	6.75
Glioma	8.09	5.11
Meningioma	6.35	7.92

Table 4
Hazard ratios (HR) and 95% confidence intervals (95% CIs) for hematological neoplasms and brain tumors by exposure to extremely low frequency magnetic fields from indoor transformer stations. The total person-years were 165,240 for the exposed residents and 3,323,413 for the referents.

Neoplasm type	Exposed cases	Referent cases	HR[a] (95% CI)
Any hematological neoplasms	37	1,065	0.75 (0.54–1.03)
All types of leukemia	9	278	0.69 (0.36–1.35)
Lymphoid leukemia	7	128	1.17 (0.55–2.50)
Acute lymphocytic leukemia	4	28	2.86 (1.00–8.15)
Chronic lymphocytic leukemia	3	100	0.65 (0.21–2.05)
Myeloid leukemia	1	133	0.16 (0.02–1.15)
Acute myeloid leukemia	1	87	0.25 (0.03–1.77)
Chronic myeloid leukemia	0	37	0.00 (0.00–1.70)[b]
Lymphoma	20	636	0.67 (0.43–1.05)
Hodgkin lymphoma	1	96	0.20 (0.03–1.45)
Non-Hodgkin lymphoma	19	540	0.76 (0.48–1.20)
Multiple myeloma	9	148	1.33 (0.68–2.61)
Glioma	13	183	1.47 (0.84–2.57)
Meningioma	5	235	0.46 (0.19–1.11)

[a] Adjusted for age and gender.

[b] Conditional maximum likelihood estimate of rate ratio with mid-P exact confidence interval.

located) was not associated with unknown confounding factors (Table 5).

3.3. *Exposure gradient (duration of exposure)*

The analysis by duration of residence supported increased risk for ALL and glioma but decreased risk for most hematological neoplasms among individuals exposed to residential MFs (Fig. 2; see Table S5 for exact HRs and 95% CIs). The HR for ALL increased to 3.61 (95% CI: 1.05–12.4), when only residence times $\geq$ 3 years were considered, consistently with the expectation that longer duration of exposure is associated with increased effect size. The reduced risk of any hematological neoplasms was most pronounced for residence times $\geq$10 years (HR: 0.47; 95% CI: 0.22–0.99), while the HRs for residence times $<$ 3 years and 3 - $<$ 10 years were 0.79 (95% CI: 0.46–1.35) and 0.92 (95% CI: 0.56–1.52), respectively. Similarly, the risk of all leukemia types combined was low for long residence times, with a rate ratio of 0.0 (95% CI: 0–0.69) for residence time $\geq$ 10 years and HR of 0.85 (95% CI: 0.31–2.30) for residence time 3 - $<$ 10 years. The increasing trend for ALL and the decreasing trends for any hematological neoplasms and all leukemias were statistically significant. The HRs for CLL and lymphoma were also lowest for the longest durations of residence, but there was no statistically significant trend. This analysis was not meaningful for myeloid leukemia, because there was only one exposed case. Concerning brain tumors, the HR for glioma increased with increasing duration of residence. The trend was statistically significant although all 95% CIs included 1.0. In case of meningioma, the apparent effect size did not increase with exposure time: the risk reduction was largest among individuals who had resided in the buildings for $<$3 years and the HR exceeded 1.0 at the longest duration of residence.

Table 5
Hazard ratios (HR) and 95% confidence intervals (95% CIs) for hematological neoplasms and brain tumors among persons who have resided in first or ground floor (FGF) apartments. The total person-years were 877,994 for FGF residents and 3,323,413 for other floor residents.

Neoplasm type	Cases, FGF	Cases, other floors	HR[a] (95% CI)
Any hematological neoplasms	287	1,065	1.06 (0.93–1.21)
All types of leukemia	70	278	0.99 (0.76–1.29)
Lymphoid leukemia	28	128	0.87 (0.58–1.30)
Acute lymphocytic leukemia	6	28	0.82 (0.34–1.99)
Chronic lymphocytic leukemia	22	100	0.88 (0.55–1.40)
Myeloid leukemia	36	133	1.06 (0.73–1.53)
Acute myeloid leukemia	25	87	1.12 (0.72–1.75)
Chronic myeloid leukemia	9	37	0.95 (0.46–1.97)
Lymphoma	184	636	1.14 (0.96–1.34)
Hodgkin lymphoma	30	96	1.08 (0.71–1.64)
Non-Hodgkin lymphoma	154	540	1.13 (0.94–1.35)
Multiple myeloma	33	148	0.90 (0.62–1.31)
Glioma	52	183	1.10 (0.81–1.49)
Meningioma	71	235	1.19 (0.91–1.55)

[a] Adjusted for age and gender.

3.4. *Age at start of exposure*

Analysis of age at the start of exposure indicated that the risk of adult ALL may be particularly associated with childhood exposure, with HR (based on two cases) of 11.5 (95% CI: 1.92–68.9) for MF exposure during the first 2 years of life (Table 6). Early childhood exposure was associated with high HRs also for all lymphoid leukemia and all leukemia combined, but these were based on ALL alone. However, the increased adult ALL risk may not be totally dependent on childhood exposure, as a suggestive increase of HR (1.86; 95% CI: 0.44–7.89) was observed also for exposures starting at ages of 15 years and above. This type of analysis was not meaningful for myeloid leukemia, as there was only one exposed case. The suggestive MF-related reduction in lymphoma risk seemed to be associated only with exposure later in life ($\geq$15 years after birth), but it should be noted that the very low number of expected cases makes it difficult to observe any risk reduction associated with early exposure. The possible increase in glioma risk also seemed to be associated only with MF exposure at $\geq$ 15 years of age. However, it is hard to evaluate any differences by age at start of exposure, as the number of cases was very low (even in the reference group) among those who had resided in the study buildings in childhood. Meningioma occurred in the exposed group only among those who had moved into the buildings at the age of 15 years or higher, but the number of cases was low also among those referents who had resided in the study buildings in childhood.

The incidence rate in each group plotted cumulatively across age at the start of residence in the buildings (Fig. 3A) supports the relevance of childhood MF exposure in ALL but the data does not exclude the possibility that exposure at any age may increase the risk of ALL. As the risk of all other leukemias was tentatively decreased by MF exposure, the data of all leukemia but ALL were combined in this visualization. The resulting graph (Fig. 3B) suggests almost total depletion of new cases of most leukemia types (other than ALL) among those who have moved into the apartments next to transformer stations at the age of 30 or above. The graph for lymphoma (Fig. 3C) also suggests reduction in the proportion of cases among those who have moved into the "exposed apartments" at the age of 40 or above. The effect (if there is any) on glioma seems to be rather independent of age at the onset of exposure (Fig. 3D). The possible reduced risk of meningioma appears to be associated with MF exposure starting at any age (Fig. 3E).

4. Discussion

This study was designed to investigate possible increased risks of hematological malignancies and brain tumors in adults exposed to residential ELF MFs. The results of this study lend limited support to the hypothesis that ELF MFs affect the biology of hematological neoplasms. However, rather than a general increase in cancer risk, the data suggest differential effects depending on type of neoplasm: while an elevated HR was suggested for ALL (based on four exposed cases), the risk of most other hematological neoplasms seemed to be decreased by residential ELF MF exposure. The findings should be interpreted cautiously, as all 95% CIs of the HRs included 1.00 in the analysis that included all exposures $\geq$1 month. However, some effect directions observed in the main analysis were consistently supported by the results of the analysis evaluating exposure gradient (dependence of HR on duration of residence), suggesting enhancing effects on ALL and glioma and protective effects on overall hematological neoplasms, particularly leukemia.

The analysis focusing on age at start of exposure was based on very low numbers; the results are presented here only as hypothesis-generating findings that may be of interest for possible further studies. Also these results were consistent with differential effects on ALL and other hematological neoplasms: ALL appeared to be associated with childhood exposure to ELF MFs, while the incidence of other leukemia (and lymphoma to a lesser extent) showed an inverse association with exposure during adult life.

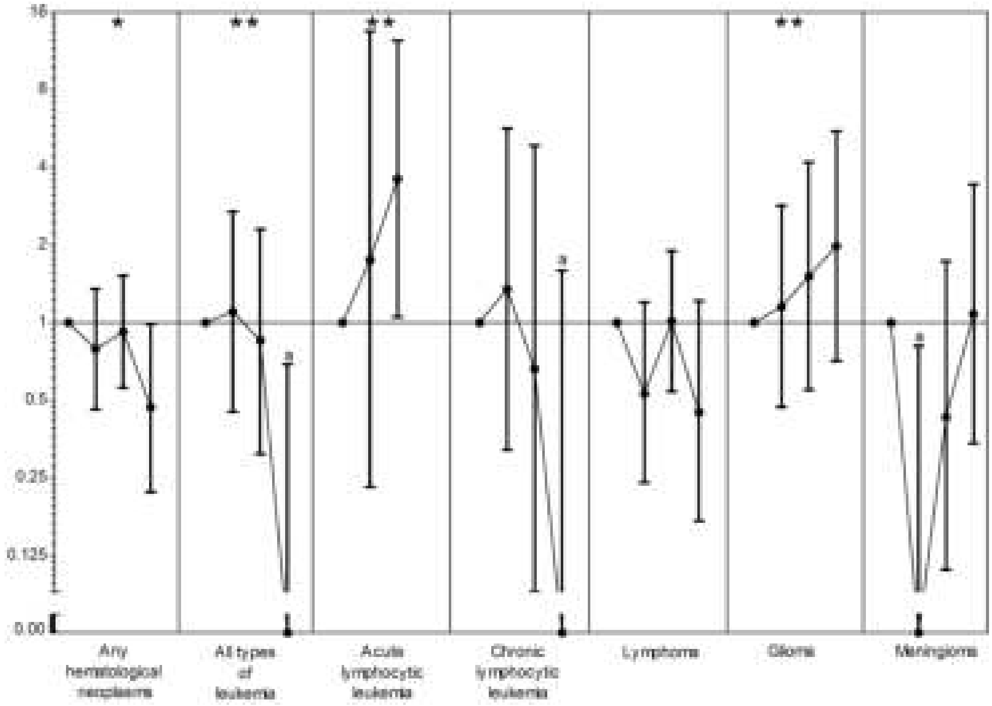

Fig. 2. Exposure gradient analysis: Adjusted hazard ratios (95% confidence intervals) for selected hematological neoplasms and brain tumors by duration of exposure to extremely low frequency magnetic fields from indoor transformer stations. For each type of neoplasm, the exposure durations from left to right are reference, < 3 years, 3 - <10 years and ≥10 years. The highest exposure category considered for acute lymphocytic leukemia was ≥3 years, because there were no cases exposed for ≥10 years and the number of expected cases was also very low (~0.3). [a] No observed case in the exposed group. Conditional maximum likelihood estimate of rate ratio with mid-P confidence interval is shown; **P for trend <0.01; *P for trend <0.05.

Table 6

Hazard ratios (HR) and 95% confidence intervals (95% CIs) for hematological neoplasms and brain tumors by age at start of exposure to extremely low frequency magnetic fields (referents: age at start of residence).

Age at start of exposure	Exposed cases	Referent cases	HR[a] (95% CI)
Any hematological neoplasm			
<2 years	2	17	1.86 (0.43–8.08)
2 - <15 years	2	39	0.74 (0.18–3.07)
≥15 years	33	1,009	0.71 (0.50–1.01)
All types of leukemia			
<2 years	2	4	8.70 (1.59–47.6)
2 - <15 years	0	7	0.00 (0.00–7.57)[b]
≥15 years	7	267	0.57 (0.27–1.21)
Lymphoid leukemia			
<2 years	2	3	11.5 (1.92–68.9)
2 - <15 years	0	3	0.00 (0.00–24.3)[b]
≥15 years	5	122	0.89 (0.36–2.17)
Acute lymphocytic leukemia			
<2 years	2	3	11.5 (1.92–68.9)
2 - <15 years	0	2	0.00 (0.00–49.2)[b]
≥15 years	2	23	1.86 (0.44–7.89)
Lymphoma			
<2 years	0	12	0.00 (0.00–4.48)[b]
2 - <15 years	2	31	0.94 (0.23–3.91)
≥15 years	18	593	0.66 (0.41–1.05)
Glioma			
<2 years	0	3	0.00 (0.00–27.1)[b]
2 - <15 years	1	13	1.08 (0.14–8.28)
≥15 years	12	167	1.53 (0.85–2.75)
Meningioma			
<2 years	0	3	0.00 (0.00–27.1)[b]
2 - <15 years	0	8	0.00 (0.00–6.44)[b]
≥15 years	5	224	0.49 (0.20–1.19)

[a] Adjusted for age and gender.

[b] Conditional maximum likelihood estimate of rate ratio with mid-P confidence interval is shown.

Suggestive effects on the risk of neoplasms were seen only in apartments classified in the high exposure category. In a sample of 30 residential buildings in three Finnish cities (Ilonen et al., 2008), exposure to fields above 0.4 μT was common in such residences (the whole-apartment 24-h average was ≥0.4 μT in 63% of apartments). No effects were found in other ground or first floor residences, in which the magnetic flux density is somewhat higher than in the reference apartments (see Table S1), but 0.4 μT is less common (24-h average ≥ 0.4 in 14% of residences) than in the high exposure category apartments. Assuming that this sample of 30 buildings is representative of Finnish buildings with indoor transformer stations, our results are consistent with the childhood leukemia studies suggesting increased risk when flux density is 0.4 μT or higher but showing little evidence of effects at lower flux densities (Ahlbom et al., 2000).

This study had several strengths. Assessing ELF MF exposure solely based on apartment location (without contacting the residents) enabled elimination of selection bias. This approach to exposure assessment has been validated in several studies. In the study by Ilonen et al. (2008), the specificity of exposure classification with the 0.4 μT cutoff point was 0.97. This was a limited sample of 30 buildings in three Finnish cities, but measurements performed in other countries (Hareuveny et al., 2011; Huss et al., 2013; Kandel et al., 2013; Röösli et al., 2011; Thuroczy et al., 2008; Yitzhak et al., 2012; Zaryabova et al., 2013) support the conclusion that residents of apartments above transformer stations are exposed to ELF MFs that are clearly higher than the average residential background level. A further advantage of the study was that outcome data was obtained from a reliable nationwide register with high completeness of registration. We were also able to follow the cohort members for long periods of time.

In comparison to studies based on residences near powerlines, the advantage of our approach is that exposure levels exceeding 0.4 or 0.2 μT are common in apartments next to transformer stations. Interestingly, a recent study on childhood leukemia in relation to distance from power lines and calculated MFs provided evidence that increased risk was associated with MFs ≥0.4 μT only very close to high voltage (>200 kV) power lines, not with similar field intensities produced solely by lower voltage lines (Crespi et al., 2019). This finding argues against MFs as the sole explanation for the increased risks observed close to power lines and suggests the involvement of other factors linked to power lines. Studies addressing high MF exposure from other sources, such as transformer stations, are therefore valuable for evaluating the possible causal role of ELF MFs.

A disadvantage resulting from our approach was that we had no

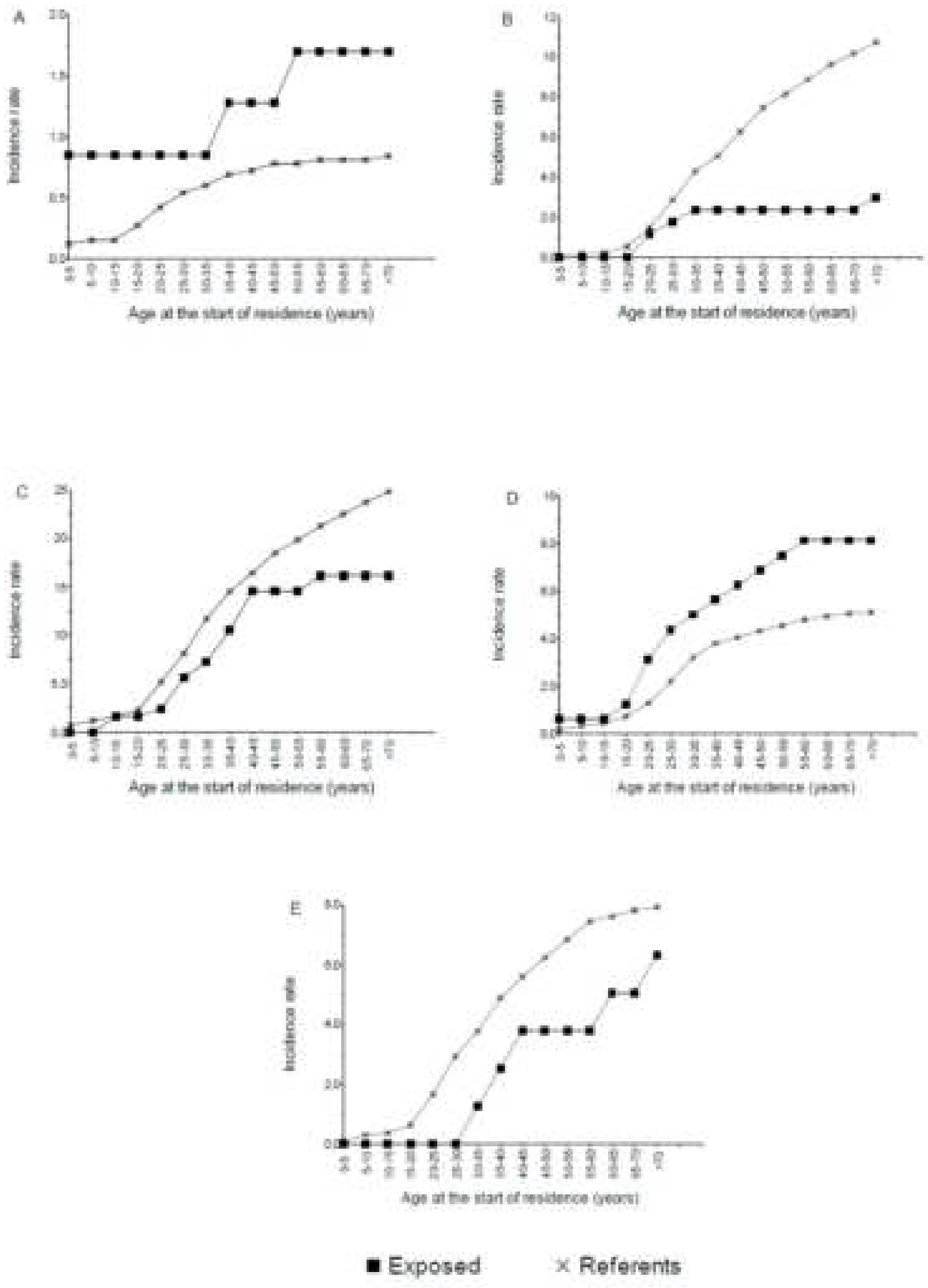

Fig. 3. Impact of age at start of exposure on the risk of neoplasms: contribution of the number of cases observed in each 5-year class to the final age-standardized incidence rate (per 100,000 person-years). Apparent incidence rate (taking into account only persons with the specified age at start of residence) is plotted cumulatively as a function of age at start of residence. The European Standard Population (Eurostat, 2012) was used for standardization. (A) acute lymphocytic leukemia; (B) all leukemia excluding acute lymphocytic leukemia; (C) lymphoma; (D) glioma; (E) meningioma.

information about exposure to ELF MFs sources other than transformer stations. Other residential sources are not likely to be important, as the transformer stations are dominating sources in the apartments that were classified as “exposed”, and clearly elevated levels are rare in other apartments of the buildings (Ilonen et al., 2008). Some members of the cohort may have experienced relatively high occupational exposures. However, there is no reason to assume that the distribution of occupations, and hence occupational ELF MF exposure, would differ between persons living next to a transformer stations and the rest of the cohort.

As the study subjects were not contacted, information about personal confounding factors such as smoking was not available. This limitation was at least partly overcome by the study design; selecting both exposed and referent individuals from the same buildings minimized differences in potential environmental confounders (e.g., air pollution), but it also favored similar distributions of all potential confounding factors including lifestyle-related factors, which are associated with socioeconomic status. Some remining confounding might be associated with living at the lowest floors of the buildings (where also all “exposed” apartments are), as apartment prices are slightly higher at higher floors (possibly causing differences in social status) and living near the ground level may affect the level of some environmental agents, such as radon (Valmari et al., 2012). The data allowed testing this possibility by assessing cancer risk among such first or ground floor residents who did not live next to a transformer station. This analysis did not provide any evidence of such confounding that would explain the suggested increased and decreased risks among the exposed residents. Another limitation of the study was low number of cases, which was evident especially when different cancer subtypes were studied individually or when analyzing the effect of age at the start of exposure. This led to broad confidence intervals in many analyses.

Estimation of MF exposure levels in apartment above transformer stations is possible, if information about structural characteristics of the transformers is available (Okokon et al., 2014). Unfortunately, it was not possible to get such data from the electricity distribution companies. As a result, we could not study dose response in relation to magnetic flux density. However, given the limited understanding of what comprises the MF “dose” (Auvinen et al., 2000; Eskelinen et al., 2003; Juutilainen et al., 1996), time-average magnetic flux density may not be the most pertinent exposure metric for predicting possible biological effects. In the present study, duration of residence in an “exposed” apartment (as a proxy for the duration of residential exposure to an elevated MF) was used in the exposure gradient analysis; duration of exposure may be the most relevant exposure metric, if the exposure-response relationship has a threshold and a plateau above the threshold (Eskelinen et al., 2002).

While many previous studies have investigated adult leukemia and brain tumors in relation to occupational ELF MF exposure (Huss et al., 2018; Kheifets et al., 2008b) only a few studies have addressed possible risks associated with residential exposure. Some past studies have reported increase or no risks associated with distance to power lines (Coleman et al., 1989; Baldi et al., 2011; Lowenthal et al., 2007; McDowall, 1986), but the most interesting ones are those that have assessed ELF MF exposure using more reliable methods such as MF measurements or model calculations to determine MFs caused by nearby power lines. Many of such studies on leukemia have reported either no risk increase (Verkasalo, 1996) or risk estimates above 1.0 but wide confidence intervals for MF exposures above cutoffs of 0.2 or 0.3 μT (Feychting et al., 1997; Li et al., 1997; Tynes and Haldorsen, 2003). As our study suggests differential effects on different types of leukemia, the results are not necessarily inconsistent with studies on overall leukemia suggesting no or weak effects. Unfortunately, only a few studies included separate analyses for different types of leukemia/hematological neoplasms. The study by Li et al. (1997) showed some consistency with our results. The risk of ALL was highest with an OR of 1.7 (95% CI: 1.0–3.1), while smaller risk estimates were reported for CLL (0.6; 95% CI: 0.1–2.6), AML (1.1; 95% CI: 0.7–1.7) and CML (1.5; 95% CI: 0.9–2.6). Verkasalo (1996) reported that the overall risk of leukemia associated with cumulative MF exposure $\geq$ 2 μT-years was below unity (SIR: 0.7; 95% CI: 0.19–1.81), while the risk estimate for CLL was 1.46 (95% CI: 0.30–4.26). The number of ALL and AML cases was low, and there were no cases exposed at $\geq$ 2 μT-years. The SIR for ALL in the 1.00–1.99 μT-year exposure category was 2.38 (95% CI: 0.06–13.3), based on one exposed case. The SIR for other leukemia associated with exposure $\geq$2 μT-years was 0.65 (95% CI: 0.02–3.59) (Verkasalo, 1996). Tynes and Haldorsen (2003) reported an OR of 1.5 (95% CI: 0.8–3.0) for all leukemia associated with exposure to MFs $\geq$0.2 μT. The risk estimate for CLL was highest with an OR of 2.8 (95% CI: 0.7–10.7), while the ORs for ALL and AML were 1.7 (95% CI: 0.2–13.3) and 1.6 (95% CI: 0.4–1.0), respectively. Feychting et al. (1997) reported a RR of 1.3 (95% CI: 0.8–2.2) for all leukemia associated with exposures $\geq$0.2 μT. The risk estimate for AML was the highest with a RR of 2.4 (95% CI: 0.9–5.7), while the RRs for CML and CLL were 2.1 (95% CI: 0.8–5.5) and 0.8 (95% CI: 0.3–1.8) respectively. Overall, other studies do not consistently support our findings suggesting increased risk of ALL but decreased risks of other leukemias. However, the highest exposure groups are small and the highest exposure levels low in all studies that have addressed leukemia and lymphoma subtypes in residences near power lines, and the confidence intervals are wide.

In the present study, the HR for glioma was above 1.00 and showed statistically significant increase with increasing exposure. However, the confidence intervals were wide. This result alone does not provide clear evidence for malignant brain tumor risk associated with ELF MF exposure, but it is not inconsistent with studies reporting increased risks associated with occupational exposure (Huss et al., 2018; Kheifets et al., 2008b). The below-unity HR for meningioma is in contrast with the studies reporting increased risks associated with occupational ELF MF exposure (Huss et al., 2018; Kheifets et al., 2008b). The results of previous studies on brain tumors in relation to residential exposure are inconsistent (Baldi et al., 2011; Elliot et al., 2013; Li et al., 1997), and some of them have not made a difference between glioma and other brain tumors (Elliot et al., 2013; Verkasalo et al., 1996). Interestingly, Li et al. (2003) reported that the average age at brain tumor diagnosis was higher among individuals whose estimated residential ELF MF exposure level was $\geq$0.2 μT than among those whose exposure was below this cutoff. This delay in diagnosis was observed only in “unclassified or other” brain tumors, not in glioma, consistent with inhibited development of meningioma.

There is no generally accepted biophysical mechanism that could explain carcinogenic effects of low-level ELF MFs (IARC, 2002; WHO, 2007). One of the most plausible mechanisms involves radical pairs as intermediates of chemical reactions. This radical pair mechanism (RPM) seems to be involved in the avian magnetic compass sense (Hore and Mouritsen, 2016), and it could therefore potentially explain also other effects of weak MFs. We have proposed a hypothesis for explaining how the primary biophysical interaction (i.e. RPM) could lead to cancer-relevant biological effects through dysregulation of the circadian system and DNA damage responses (Juutilainen et al., 2018). A related alternative hypothesis was proposed by Vanderstraeten et al. (2012). However, it remains a major challenge to explain how a 0.4 μT oscillating MF could induce carcinogenic effects in the presence of the much stronger (~50 μT) static MF of the earth (Hore , 2019; Juutilainen et al., 2018).

Apart from explaining increased risk of ALL, the putative mechanism would need to explain decreased risk of other hematological malignancies. Disruption of the circadian clock is believed to enhance the development of cancers, including leukemia and lymphoma (Rana et al., 2014; Yang et al., 2006; Zhu and Zheng, 2008). The hypothesized MF-induced disruption of the circadian clock would thus explain only increased risks. However, there is limited evidence from two studies that dysfunction of certain circadian genes might be associated with anti-leukemic effects in AML (Puram et al., 2016) and CLL but not ALL (Hanoun et al., 2012). These findings might be related to our observations suggesting inhibited development of AML and CML in adults who move into the apartments above transformer stations.

The results of previous studies on occupational MF exposure are consistent with a possible small increase in the risk of leukemia, the evidence being stronger for myeloid leukemia than for lymphoid leukemia (Huss et al., 2018; Kheifets et al., 2008b). If both the increased myeloid leukemia risk associated with occupational exposure and the reduced risk suggested by this study are assumed to be true effects, what could explain the opposite effects? The most obvious difference between occupational and residential MF exposure is the diurnal rhythm of exposure - residential exposure occurs at night, while (in most cases) occupational exposure occurs during the day. However, there is little evidence of different effects from daytime vs. nighttime exposure to MFs. A pooled analysis was carried out to evaluate the hypothesis that nighttime ELF MF exposure is more relevant to childhood leukemia than 24-h exposure (Schüz et al., 2007). No essential differences were seen between nighttime and 24-/48-h exposures, and the slope of the exposure-response trend was actually slightly steeper for 24-/48-h exposure than for nighttime exposure.

If the diurnal timing of MF exposure modifies biological responses, it is worth noting that the diurnal pattern of childhood exposure due to transformer stations differs from that of adults. Due to variation in power consumption (high during daytime) small children (those who do not go to school or kindergarten) experience higher exposure during day than at night, i.e., the diurnal variation in their exposure resembles that of occupationally exposed adults. Exposure from power lines follows a similar diurnal variation. It remains to be investigated whether the high day-time exposure plays any role in our observation that adult ALL risk may be associated particularly with childhood exposure, and in the previous findings showing a link between powerline MFs and childhood leukemia (which is mainly ALL).

The suggested inhibition of certain tumor types (particularly other leukemia than ALL) was an unexpected and unique finding. As discussed above, previous epidemiological studies provide little support for such anticarcinogenic effects, but their value as negative evidence is limited due to the lack of subjects exposed to MFs ≥0.4 μT. Although most animal experiments designed to test carcinogenic effects of ELF MFs have found no effects (Juutilainen et al., 2000), two studies reported slight (non-significant or marginally significant) reduction of radiation-induced lymphoma in mice exposed to MFs (Babbit et al., 2000; Heikkinen et al., 2001), while a third study with a different study design (small radiation dose, MF exposure started prenatally) reported increased incidence of lymphoma/leukemia (Soffritti et al., 2016).

5. Conclusions

The results lend limited support to the hypothesis that ELF MFs ≥0.4 μT influence the biology of hematopoietic and lymphoid tissue neoplasms. However, only the risk of ALL was increased among the cohort members exposed to MFs. This finding, suggesting an association between adult ALL and childhood MF exposure, was based on small number of exposed ALL cases. The risk of most other hematological malignancies was decreased, in contrast to many previous epidemiological studies. The slightly increased HR for glioma does not alone provide clear evidence for malignant brain tumor risk associated with ELF MF exposure, but it is not inconsistent with increased risks reported in previous studies. There was weak evidence that the risk of meningioma might be reduced rather than increased by MF exposure. The suggested differential effects on different types of neoplasms call for additional studies that could shed light on the mechanisms and overall public health impact of ELF MF exposure.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2021.113712.

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Review

Extreme weather events in europe and their health consequences – A systematic review

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ABSTRACT

Background: Due to climate change, the frequency, intensity and severity of extreme weather events, such as heat waves, cold waves, storms, heavy precipitation causing wildfires, floods, and droughts are increasing, which could adversely affect human health. The purpose of this systematic review is therefore to assess the current literature about the association between these extreme weather events and their impact on the health of the European population.

Methods: Observational studies published from January 1, 2007 to May 17, 2020 on health effects of extreme weather events in Europe were searched systematically in Medline, Embase and Cochrane Central Register of Controlled Trials. The exposures of interest included extreme temperature, heat waves, cold waves, droughts, floods, storms and wildfires. The health impacts included total mortality, cardiovascular mortality and morbidity, respiratory mortality and morbidity, and mental health. We conducted the systematic review following PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis). The quality of the included studies was assessed using the NICE quality appraisal checklist (National Institute for Health and Care Excellence).

Results: The search yielded 1472 articles, of which 35 met the inclusion criteria and were included in our review. Studies regarding five extreme weather events (extreme heat events, extreme cold events, wildfires, floods, droughts) were found. A positive association between extreme heat/cold events and overall, cardiovascular and respiratory mortality was reported from most studies. Wildfires are likely to increase the overall and cardiovascular mortality. Floods might be associated with the deterioration of mental health instead of mortality. Depending on their length, droughts could have an influence on both respiratory and cardiovascular mortality. Contradictory evidence was found in heat-associated morbidity and wildfire-associated respiratory mortality. The associations are inconclusive due to the heterogeneous study designs, study quality, exposure and outcome assessment.

Conclusions: Evidence from most of the included studies showed that extreme heat and cold events, droughts, wildfires and floods in Europe have negative impacts on human health including mental health, although some of the associations are not conclusive. Additional high-quality studies are needed to confirm our results and further studies regarding the effects of other extreme weather events in Europe are to be expected.

1. Introduction

Climate change is a great challenge for global health (Patz et al., 2014). The average global temperature has been rising rapidly since the 1970s, at a rate of about 0.2 °C per decade, leading to multiple impacts on human health, mostly adverse (Hansen et al., 2006; McMichael et al., 2006). As a result of the rise in temperature and a decrease in summer precipitation, the frequency, severity and intensity of extreme weather events like as heat waves, droughts and wildfires, will increase, whereas cold spells are projected to increase. Other extreme weather events like

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inland and coastal floods are also likely to increase in the regions of Europe due to extreme precipitation events, reduced snow and sea level rise (Seneviratne et al., 2012; McMichael and Lindgren, 2011; Franchini and Mannucci, 2015; Wolf et al., 2015; Füssel et al., 2017; Ponjoan et al., 2017).

Seneviratne et al., (2012) expressed a low general confidence in projections of change in storms due to a small number of studies and insufficiencies in the simulations of these incidents. However, in the North Atlantic and northern, northwestern and central Europe the risk for severe winter and autumn storms might increase (Seneviratne et al., 2012; Füssel et al., 2017).

The effect of heat on human health will become more severe, especially in large cities or urban heat islands and will also be pronounced in areas where extreme temperatures were not experienced as frequently in the past (Basu and Samet, 2002; Basu, 2009; Paz et al., 2016). Although winters will be warmer than usual and the frequency of cold events are likely to decrease, the effects of low temperature on human health might become an issue in warmer areas (Basu and Samet, 2002; McMichael et al., 2008; Wolf et al., 2015; Ponjoan et al., 2017). Southern and south-eastern Europe are the most affected areas by extreme weather events in Europe, with heat waves being the deadliest and floods as the most frequent extreme weather events (Giorgi and Lionello, 2008; Fernandez et al., 2015; Forzieri et al., 2017; Füssel et al., 2017).

Extreme weather events influence human health in two ways. They could directly cause injuries or deaths, or indirectly lead to physical illnesses, mental health disorders, damages to properties and infrastructures, water contaminations, as well as resurgence and redistribution of infectious diseases (Forzieri et al., 2017; Füssel et al., 2017). As the number of extreme weather events will increase in the future, the number of people suffering from cardiovascular diseases, respiratory diseases and mental health disorders could also rise accordingly (Friel et al., 2011). Impacts of climate change are ubiquitous. They will be even more pronounced among vulnerable populations, in particular the elderly people over 65 years of age, children and infants, people with pre-existing or chronic illnesses and socially isolated individuals (Basu, 2009; Franchini and Mannucci, 2015; Wolf et al., 2015).

The scientific community’s awareness on climate change and health has been growing significantly. From 2007 to 2016, the number of annually published articles on this topic had increased threefold (Watts et al., 2018a,b). However, no synthesis of the literatures has yet been conducted to investigate the health impacts of various extreme weather events in Europe. Therefore, the purpose of this systematic review is to evaluate the available evidence on the associations between extreme weather events in Europe and their impact on health.

2. Methods

The systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Hutton et al., 2015). This review was registered in PROSPERO (International Prospective Register of Systematic Reviews) with ID CRD42018114451.

2.1. Search strategy

The systematic literature search was carried out for studies published from January 1, 2007 to May 17, 2020 in three electronic databases: Medline (PubMed), Embase (Ovid) and Cochrane Central Register of Controlled Trials (Wiley Online Library). The following U.S. National Library of Medicine’s Medical Subject headings (MeSH) and their adaptations for corresponding databases and keywords were used in literature search:

(“Climate change” OR “Global warming” OR “Extreme heat” OR “Hot spells“ OR “Extreme cold” OR “Cold spells“ OR “Heat waves“ OR “Wildfires“ OR “Forest Fires” OR “Floods” OR “Droughts“ OR “Windstorms“ OR “Heavy rain” OR “Heavy precipitation”) AND (“Mortality” OR “Morbidity”) AND (“Cardiovascular diseases“ OR “Respiratory tract diseases“ OR “Mental health“).

Studies conducted out of Europe as well as studies regarding certain infectious diseases, allergies, skin diseases and viral diseases were excluded using NOT operators. Endnote X8 software (Clarivate, Philadelphia, United States) was used to store and manage the bibliographic references.

2.2. Selection of studies

Two authors of the present study carried out the study selection procedure independently of each other. Uncertainties were discussed after each step among all authors until a solution could be found. Studies had to meet the following inclusion criteria:

Types of studies: Observational studies written in English or German.

Types of participants: European population.

Types of exposures: Studies on the health effects of extreme weather events, such as extreme temperature, heat waves, cold waves, droughts, floods, storms and wildfires were included.

Types of outcomes: Health outcomes including total mortality, cardiovascular mortality and morbidity, respiratory mortality and morbidity, and mental health were considered. Food- and water-borne infectious diseases were also included as they might be highly relevant to direct post-flood mortality and morbidities (Alderman et al., 2012).

Studies, which met the following criteria, were excluded:

Types of studies: Reviews, reports, letters to the editor and prognostic studies.

Types of participants: Non-European population.

Types of exposures: air pollutions, seasonal effects on human health (e.g. comparison of the differences between winter- and summer-related mortality or morbidity).

Types of outcomes: Vector-borne infectious diseases, tick-borne infectious diseases, allergies, skin diseases, viral diseases.

The reasoning for the selection of extreme whether events and health outcomes listed above is provided in the discussion section.

2.3. Data extraction and synthesis

For each included study, the basic information (authors and publication time), study location, study design, participants, exposure, exposure assessment, outcome, outcome assessment, covariates and main results were extracted. A narrative synthesis of the findings from the included studies was then performed, structured around types of exposures and health outcomes. The effect estimates from each study were extracted and reported. On this basis, conclusive or inconclusive associations between extreme weather events and health outcomes were revealed.

2.4. Quality appraisal of studies

The quality of the individual studies was appraised using NICE quality appraisal checklist (National institute for health and care excellence (NICE) 2012). This tool appraises the internal and external validity of a study based on some key features of study design: characteristics of study population, definitions of independent variables, outcomes assessed and methods of analyses. The checklist contains five sections rated with five responses: ++, +, -, NR (not reported) and NA (not applicable). Section one evaluates the external validity of a study, and section two to five determines the internal validity. In conclusion, the overall quality of a study respecting its internal and external validity is awarded with three grades: ++ (high), + (medium) and – (low).

3. Results

3.1. Search results

The literature search yielded 1263 articles after the removal of duplicates; 1194 of the articles were then excluded after title and abstract screening. The remaining 69 studies underwent a full-text evaluation. As a result, 35 articles met the inclusion criteria for a qualitative data synthesis in our study. The selection process and reasons for exclusion are illustrated in a flowchart (Fig. 1).

Characteristics of the 35 included studies are summarized in Table 1, ordered by types of exposures and years of publication. Most studies (n = 26) examined the health impacts of extreme temperatures, among them 15 focused on extreme heat events only, two dealt with the effects of droughts, five looked into extreme cold events only and four studied the effects of both extreme heat and cold events. Three studies investigated wildfires and the other six researched floods. All of the 35 studies are retrospective observational studies. To be specific, the study designs included time-series study (n = 19), case-crossover study (n = 4), ecological study (n = 6), cross-sectional study (n = 3), case-control study (n = 1), and cohort study (n = 2). Participants of the included studies covered populations in 14 European countries (Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Portugal, Russia, Spain, Sweden, UK). No studies regarding windstorms, heavy precipitation or water- and food-borne infectious diseases were included.

3.2. Quality appraisal

The results of the quality appraisal for individual studies can be found in Table 1. Among the 35 studies assessed, the internal validity of 14 studies were ranked with the highest grade (++), the other 21 studies were graded with medium internal validity (+). 19 and 16 studies were estimated to have high (++) and medium (+) external validity, respectively. No studies were found to have low quality (-). Therefore, the overall quality of the included studies with regard to internal and external validity is on a medium-to-high level.

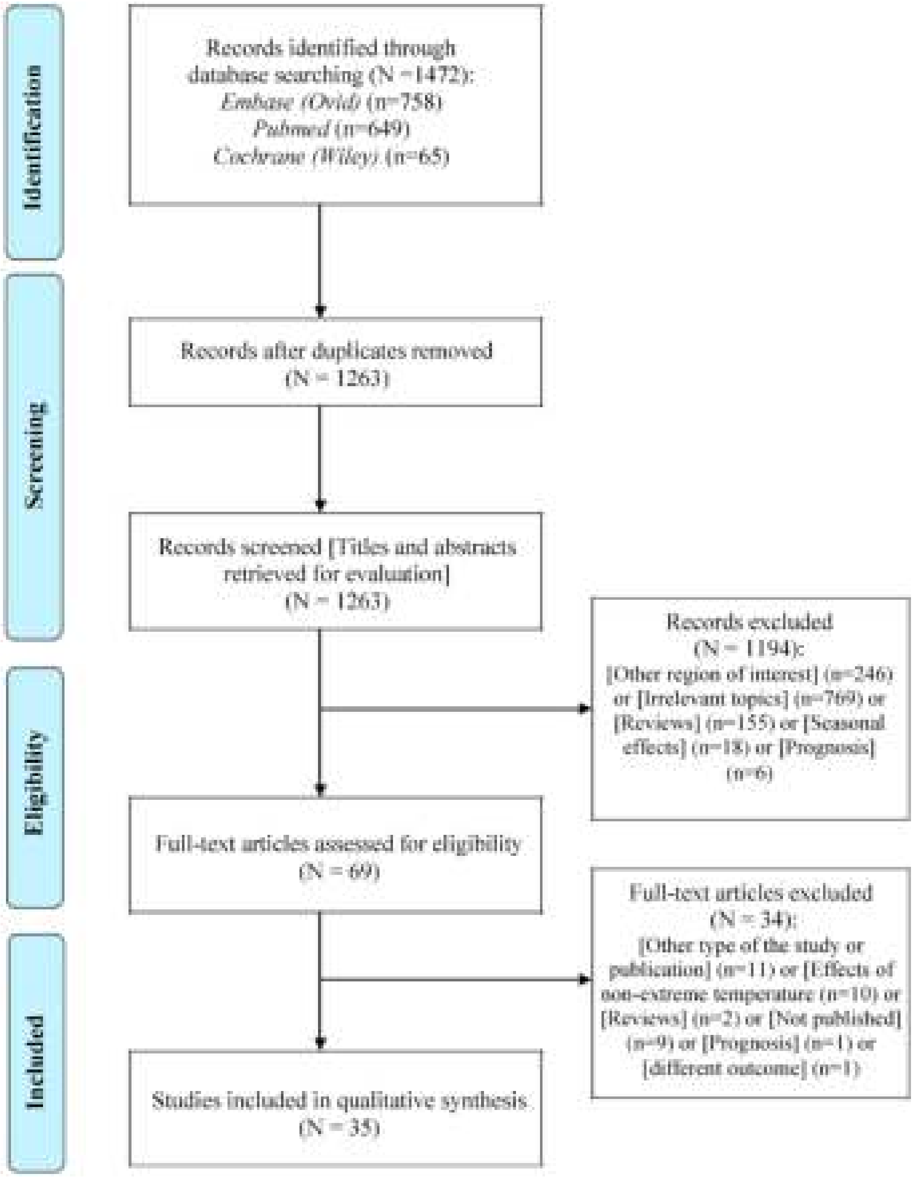

Fig. 1. Study flow diagram.

Table 1
Study characteristics.

Reference	Study location	Study design	Study population	Co-variables	NICE
Extreme Heat Events Only					
Royé et al. (2020)	Barcelona, Bilbao, Madrid, Sevilla	Time-series study	All deaths (1990–2014)	Age, gender, population, season, urban heat island	(+/+)
Kouis et al. (2019)	Thessaloniki	Time-series analysis	Deaths (circulatory, respiratory) in all public hospitals of Thessaloniki (1999–2012): N = 28.927	Air pollution, economic crisis, relative humidity, seasonality, sex, SES, trends	(++/++)
Lopez-Bueno et al. (2019)	Madrid	Ecological, retrospective study	Deaths in five areas of the Madrid region (2000–2009)	Age, air pollution, atmospheric pressure, energy, green areas, heat islands, income level, old housing, poverty, relative humidity, trends, seasonality	(+/++)
Analitis et al. (2018)	Athens, Barcelona, Budapest, Helsinki, London, Paris, Rome, Stockholm, Valencia	Time-series Study	Deaths from official registries of each city (2004–2010)	Age, barometric pressure, calendar month, day of the week, holiday, lags, NO_2, O_3, PM_{10}, wind speed, time trend	(++/++)
Green et al. (2016)	England	Case-crossover Study	Deaths from June–September 2013	Age, region	(+/++)
Smith et al. (2016)	England	Time-series Study	Morbidity data from a suite of national surveillance systems: June–September 2012–2014	Age, influenza vaccination, seasonality, trends	(+/++)
Urban et al. (2016)	Czech Republic	Time-series Study	Deaths from cardiovascular diseases in 76 districts (1994–2009)	population density, SES, altitude, impervious surface (in %), summer temp, lags	(+/++)
Oudin Astrom, Schifano et al. (2015)	Rome, Stockholm	Cohort Study	N = 1,106,511 (Rome), N = 512,964 (Stockholm), aged 50+, general or low-risk population (2000–2008)	Age, gender, lags, susceptible groups	(+/+)
Analitis et al. (2014)	Athens, Barcelona, Budapest, London, Milan, Munich, Paris, Rome, Valencia	Time-series Study	Deaths in EuroHEAT database from 9 countries (1990–2004)	SO_2, PM_{10}, NO_2, O_3, CO, wind speed, age	(++/++)
Shaposhnikov et al. (2014)	Moscow	Time-series Study	Deaths in the city of Moscow (2006–2010)	time trend, seasonal, age, periodicity, day of week, relative humidity, PM_{10}, O_3,	(++/+)
Hertel et al. (2009)	Essen	Time-series Study	Death of residents of Essen at the time of death (2000–2006)	PM_{10}, O_3, humidity, influenza, long-term & seasonal trends, days of week, bank holidays	(++/++)
Linares and Diaz (2008)	Madrid	Time-series Study	49,572 hospital admissions (May–September, 1995–2000)	PM_{10}, NO_x, O_3, lags, seasonality, over dispersion, trend, weekdays, age	(++/++)
Conti et al. (2007)	Genoa	Case-crossover Study	Death (July–August 2003): N = 962	Age, lag-time	(+/+)
Mastrangelo et al. (2007)	Veneto Region	Ecological Study	People aged ≥75, admitted to hospital (June–August 2002–03)	Day of week	(+/++)
Rey et al. (2007)	France	Time-series Study	Deaths during major heat waves (1971–2003)	Age, gender	(+/+)
Droughts					
Salvador et al. (2020)	Spain	Retrospective-ecological study	Deaths: capital city, towns >10,000 people, (2000–09)	Heatwaves, atmospheric, pollution, seasonality, trends	(++/++)
Salvador et al. (2019)	Galicia	Retrospective-ecological study	Deaths in the capital & towns >10,000 people (1983–2013)	Trend, seasonality, air pollution, heatwaves, SES	(++/+)
Extreme Heat and Cold Events					
Martinez-Solanas and Basagana (2019)	Spain	Time-series study	Hospital admissions (1997–2013) N = 10,550,849	Age, fuel poverty, heat-health prevention plan	(+/++)
Rodrigues et al. (2019)	Lisbon	Time-series study	Deaths from cerebrovascular diseases	Season, age, gender, chronic diseases, SES, region	(++/+)
Rocklov, Ebi et al. (2011)	Stockholm County	Time-series Study	Deaths in Stockholm county (1990–2002)	Age, flu, calendar time, trends, lags, NO_x, O_3	(+/+)
Rocklov and Forsberg (2008)	Stockholm	Time-series Study	Deaths in Greater Stockholm (1998–2003)	Influenza, season, time trends, week day, holidays, lags, age	(+/++)
Extreme Cold Events					
Hanefeld et al. (2019)	Bochum	Time-series study	Emergency calls (2014, 2015), N = 16,767	Day of the week, holidays, year	(+/++)
Antunes et al. (2017)	Lisbon Oporto	Time-series Study	Deaths (1992–2012)	influenza activity, population size, day of the week, age	(+/++)
Carmona et al. (2016)	Spain	Ecological Study	Deaths in provincial capitals & in towns >10,000 people (2000–2009)	weekly influenza incidence rate, seasonality, trend, lags	(+/++)
Sartini et al. (2016)	The UK, Republic of Ireland, the Netherlands	Case-crossover Study	Participants: of the British Regional Heart Study (BRHS) & PROSPER	Long-term changes in environmental exposures, day of the week, stable participant characteristics (e.g. smoking)	(++/++)
Monteiro et al. (2013)	Porto	Time-series Study	COPD-patients of 4 main public hospitals (2000–2007)	Lags	(+/+)
Wildfires					
Faustini et al. (2015)	10 southern European cities in Spain, France, Italy, Greece	Case-crossover Study	Deaths in each city, for a variable period of 3–8 years, 2001–2010	Time trends, seasonality, year, month, day of the week, influenza epidemics	(++/++)
Analitis et al. (2012)	Athens	Time-series Study	78,568 deaths on days with & without forest fires, 1998–2004		(++/+)

(*continued on next page*)

Table 1 (*continued*)

Reference	Study location	Study design	Study population	Co-variables	NICE
				Temp, heat wave days, relative humidity, wind speed, wind direction, day of the week, holidays, black smoke, age	
Caamano-Isorna et al. (2011)	Galicia	Ecological Study	2,036,722 residents during the 12 months pre- & post-August 2006	Gender, pension status	(+/+)
Floods					
Mulchandani et al. (2020)	England	Cohort study	819 Participants at year 3 of follow-up as part of the English National study of flooding & health	Age, sex, ethnic group, pre-existing illness, deprivation score, marital status, education, employment	(++/+)
French et al. (2019)	Cumbria	Cross-sectional study	All adults in postcode areas known to have been affected by the 2015/16 floods	Age, sex, local authority, ethnicity, marital status, educational, employment, deprivation score, pre-existing illness	(+/++)
Graham et al. (2019)	England	Cross-sectional study	7525 members of the Adult Psychiatric Morbidity Survey (APMS) 2014/15	Sex, age, ethnicity, education, employment status, financial strain area deprivation, household level, region	(++/+)
Lamond et al. (2015)	England	Cross-sectional Study	A sample of 280 owner occupied households that had experienced flooding of their homes during the 2007 floods in England.	Age, household income, occupation of the main income earner, number of people the household	(+/+)
Obrova et al. (2014)	Czech Republic	Case-control study	Deaths from May to August, 1994–1997, N = 985	Gender	(+/+)
Milojevic et al. (2011)	England, Wales	Time-series Study	1464 deaths in the year before & after flooding, 1994–2005	Age, gender, cause & place of death, urban rural status, Index of Multiple Deprivation score	(+/+)

3.3. *Extreme heat events*

Twenty-one articles studied the health effects of extreme heat events (extreme hot temperatures, heat waves, hot days, hot spells, droughts) according to various definitions of exposure.

14 studies dealt with the health effects in the Mediterranean area. According to one study in France, all of the major heat waves between 1975 and 2003 were associated with a significant excess in mortality, with the mortality ratios ranging from 1.17 (1983) to 1.78 (2003) (Rey et al., 2007). Conti et al. (2007) discovered that the peak value of the maximum temperature was correlated with the peak value of mortality ($\rho = 0.430$, $p < 0.01$) with the greatest correlation between the number of observed deaths and the maximum temperature values for the three preceding days ($\rho = 0.568$, $p < 0.01$). For the age-specific effects, Oudin Åström et al. (2015) reported an increase of 22% (95% CI, 18%–26%) in mortality during heat waves (2 or more days >95th percentile of T_{max}) compared to non-heat (<95th percentile of T_{max}) wave days during the summer months May to September between 2000 and 2008 in Rome among the population aged 50+.

In terms of cardiovascular mortality during heatwaves, one study conducted in France reported relative risks (RRs) from 0.91 to 1.05 for six major heatwaves compared to the expected deaths (Rey et al., 2007). Lopez-Bueno et al. (2019) reported a RR for cardiovascular mortality of 1.10 (95% CI, 1.04–1.17) for days above the determined threshold temperature in various study locations in Spain during summer between 2000 and 2009. The RR for respiratory mortality during heat waves in the two studies were 1.03–1.34 (Rey et al., 2007) and 1.07 (95% CI, 0.99–1.16) to 1.12 (95% CI, 1.03–1.21). (Lopez-Bueno et al., 2019). Royé et al. (2020) examined the effects of heat wave intensity on mortality in Spain and observed increased RRs of 1.35 (95% CI, 1.26–1.45), 1.64 (95% CI, 1.28–2.09) and 1.51 (95%CI, 1.36–1.67) for natural-, respiratory- and cardiovascular mortality for the heat wave with the highest intensity compared to the heatwave with the lowest intensity between 1990 and 2014. Similarly, in Thessaloniki, cardiovascular and respiratory mortality risk rose per degree Celsius increase in temperature above 33 °C by 4.4% (95%CI, 2.7%–6.1%), 5.9% (95%CI, 1.8%–10.3%) respectively (Kouis et al., 2019). Rodrigues et al. (2019) studied the effects of heat wave duration with an increased risk of mortality for a 30-day cumulative exposure to heat, compared to a one-day exposure with a RR of 1.65 (95% CI, 1.37–1.98).

For the influence of extreme heat on morbidity and hospital admissions, one high quality study reported an increment of 17.9% (95% CI, 9.5%–26.0%) and 27.5% (95% CI, 13.3%–41.4%) in emergency hospital admissions from organic and respiratory causes in 75+ year olds for each degree of maximum daily temperature surpass 36 °C in Madrid (Linares and Diaz, 2008). A study in Italy found that the excess risk of hospital admissions rose by 16% ($p < 0.0001$) for heat related diseases and 5% ($p < 0.0001$) for respiratory diseases with each additional day of heatwave duration (Mastrangelo et al., 2007). In Spain, hospital admissions for respiratory causes increased by 14% (95%CI, 9%–19%) during a heat wave between 2000 and 2013 (Martinez-Solanas and Basagana 2019).

Six included studies investigated the effects of heat in temperate climate areas. A high-quality study conducted in Germany showed a significant maximum daily RR of 1.28 (95% CI, 1.06–1.53) for mortality during the heat wave in 2003 (Hertel et al., 2009). Green et al. (2016) found, that during the 2013 heatwave in the UK, the daily number of deaths in 65+ years old was consecutively above the modelled baseline, despite that cumulative significant excess was only seen in 0–44 years old. Hertel et al. (2009) reported a RR of 1.25 (95%CI, 0.95–1.65) for cardiovascular mortality during heatwaves. Respiratory mortality was found to be especially affected by periods with sustained heat in one study (RR: 1.66, 95% CI: 1.19–2.23), with a delayed effect after 6 days post-heatwave (Hertel et al., 2009). Regarding the impact on morbidity and hospital admissions, a study on the 2013 heatwave in England identified no evidence of increased morbidity of cerebrovascular accident, myocardial infarction or myocardial ischaemia during the heatwave (Smith et al., 2016).

Four studies examined the impacts of heat events in the subpolar area. Concerning the mortality during heat waves, a RR of 1.024 (95% CI, 1.010–1.038) was detected in Stockholm (Rocklöv et al., 2011), while a study in Moscow reported a higher RR of 1.90 (95% CI, 1.84–1.97) (Shaposhnikov et al., 2014). For each degree increase during summer, an increase of 1.4% (95% CI, 0.8–2.0) in RR for mortality was observed (Rocklöv and Forsberg, 2008). Within the population aged 50+, Oudin Åström et al. (2015) reported an increase of 8% (95% CI, 3%–12%) in mortality in Stockholm during a heat event. A RR of 1.020 (95% CI, 1.000–1.041) was reported for cardiovascular mortality also in Stockholm during heatwaves (Rocklöv et al., 2011). Shaposhnikov et al. (2014) found an increased risk of 2.29 (95% CI, 2.18–2.40) for ischemic heart diseases mortality in Moscow. The RRs for respiratory mortality during heat waves in Moscow and Stockholm were 2.05 (95% CI, 1.80–2.39) (Shaposhnikov et al., 2014), respectively 1.039 (95% CI, 0.987–1.094) (Rocklöv et al., 2011). Rocklöv et al. (2008) also found a statistically significant increase in RR of 4.3% (95% CI, 2.2–6.5) for respiratory mortality for each °C increase during summer in Stockholm.

Health effects caused by droughts were investigated in two studies in Spain. Salvador et al. (2019) first examined the effects of droughts in Galicia. They discovered a greater influence from droughts on the mortality within the interior areas than at the coastal ones. Short-term drought conditions of one month had the greatest impact on respiratory mortality with RRs of 1.057 (95% CI, 1.020–1.095) and 1.046 (95% CI, 1.007–1.087) in the two interior areas. Similarly, Salvador et al. (2020) found the same correlation when they extended the study to all of Spain. No correlations between respiratory mortality and droughts were observed in the coastal regions of Galicia (Salvador et al., 2019). In terms of cardiovascular mortality, the highest impact occurred after three months of drought conditions in the interior areas of Galicia with a RR of 1.049 (95% CI, 1.027–1.071) respectively 9 months at the coastal areas with a RR of 1.017 (95% CI, 1.004–1.030) (Salvador et al., 2019). In contrast, no link between cardiovascular mortality and droughts was found when the whole of Spain was investigated (Salvador et al., 2020).

Interactions between heat waves and air pollutions were treated in three studies. A study conducted in nine cities among all climate zones in Europe showed that the effect of heat waves on mortality was significantly larger on days with high ozone (14.6%) or high PM_{10} (13.1%) (Analitis et al., 2014). One study found that air pollution and temperature-air pollution interaction shared 9% and 20% of the mortality during heat waves in Moscow, respectively (Shaposhnikov et al., 2014). Nevertheless, Analitis et al. (2018) found different results, where no synergistic effects or consistent evidence for interactions between heat wave days and ozone, PM_{10}, and NO_2 was observed.

To summarize, a statistically significant excess of deaths in extreme heat events was reported from most studies, despite the variations in study locations, study designs, qualities and definition of exposure. Increased risks of cardiovascular and respiratory mortality were also found to be associated with heat waves, but the associations from many studies were not statistically significant. Contradictive results existed in heat-associated morbidities and heat-air pollution interactions. Only two studies have addressed the effects of droughts with partially consistent results.

3.4. *Extreme cold events*

The health effects of extreme cold events, namely extreme cold temperatures, cold waves and cold spells, the definition of which varies among studies, were mentioned in nine included studies.

Five studies examined the impact of extreme cold events in the Mediterranean area. The relative risks for mortality associated with extreme cold were 1.66 (95% CI, 1.57–1.76) in Lisbon, 1.57 (95% CI, 1.48–1.67) in Porto (Antunes et al., 2017) and 1.13 (95% CI, 1.11–1.16) in Spain (Carmona et al., 2016). Antunes et al. (2017) discovered that the effect of cold temperatures in mortality presented a 1–2-day delay, reaching the maximum after 6–7 days and lasting up to 20–28 days. The relative risks for cardiovascular mortality and respiratory mortality in Spain during extreme cold events were 1.18 (95% CI: 1.15–1.22) and 1.24 (95% CI: 1.20–1.29) (Carmona et al., 2016). For combined mortality from cardiovascular and respiratory causes, the relative risk was 1.96 (95% CI, 1.81–2.13) in Lisbon and 1.76 (95% CI, 1.61–1.93) in Porto (Antunes et al., 2017). Rodrigues et al. (2019) investigated the impact of cold spell durations in Lisbon with an increased RR of 2.09 (95% CI 1.74–2.51) for a 30-day-cumulative exposure to cold temperatures compared to a one-day exposure. Another study investigated morbidity due to extreme cold events. Monteiro et al. (2013) observed a 59% excess of chronic obstructive pulmonary disease (COPD) admissions during winter in Porto, with the effect of cold spells on the aggravation of COPD occurring with a lag of at least two weeks. In regards to hospital admissions in Spain, extreme cold was associated with a 34% (95% CI, 29%–38%) increase in hospitalization for cardiovascular diseases and 38% (95% CI, 31%-45) for respiratory diseases (Martinez-Solanas and Basagana, 2019).

Two studies investigated the effects of extreme cold events in temperate climate areas. One study conducted on participants from two cohorts found a statistically significant association between cold spells and cardiovascular disease events in one cohort, consisting of British men between 60 and 79 years (Risk ratio 1.86, 95% CI: 1.30–2.65, $p < 0.001$). In the other cohort, consisting of 70 to 82-year-old men and women from the United Kingdom, Ireland and the Netherlands, no association was found. (Sartini et al., 2016). A further study examined emergency calls in Bochum (Germany) during and after a cold spell with an increase for calls due to pulmonary cases up to three days after the cold spell (RR = 1.17; p = 0.021). Calls based on cardiovascular cases increased on the same day (RR = 1.14; p = 0.033) and up to three days after the cold spell (RR = 1.12; p = 0.049) (Hanefeld et al., 2019).

Two further studies dealt with the effects of cold events in the subpolar area. The relative risk for mortality associated with extreme cold in Stockholm were 1.007 (95% CI, 0.990–1.025) (Rocklöv et al., 2011). The relative risks for cardiovascular mortality and respiratory mortality in Stockholm during extreme cold events were 0.994 (95% CI, 0.970–1.019) and 1.022 (95% CI, 0.970–1.077) (Rocklöv et al., 2011). Rocklöv et al. (2008) also reported in another study that for each °C increase during winter in Stockholm, the mortality decreases by 0.7% (95% CI, 0.5%–0.9%).

Increased risk of all-cause mortality, cardiovascular mortality and respiratory mortality in extreme cold events were shown in most studies, suggesting possible positive associations between periods with extreme cold and those outcomes. The effect of cold spells on cardiovascular and COPD morbidity is also not conclusive due to the limited number of studies.

3.5. *Wildfires*

All three studies were carried out in Mediterranean areas. Two of the three studies on the health effects of wildfires specifically focused on forest fires (Analitis et al., 2012; Faustini et al., 2015). Consistent results were shown in both studies regarding deaths from all natural causes and cardiovascular causes. Faustini et al. (2015) reported an increase of 1.78% (95% CI 0.91%–4.53%) in overall mortality and of 6.29% (95% CI 1.00%–11.85%) in cardiovascular mortality on smoky days in ten southern European cities. Analitis et al. (2012) found that medium-sized forest fires increased the overall and cardiovascular mortality by 4.9% (95% CI 0.3%–9.6%) and 6.0% (95% CI 0.3%–12.6%) in Athens, respectively. However, with regard to respiratory mortality, Analitis et al. (2012) reported that medium-sized fires are associated with an increase of 16.2% (95% CI 1.3%–33.4%) in the number of respiratory deaths, while the other study found no association (Faustini et al., 2015).

A drug utilization research was conducted to study the respiratory and mental health effects associated with wildfires (Caamano-Isorna et al., 2011). The result showed that the consumption of drugs for obstructive airway diseases increased by 10.29% and 12.09% among male and female pensioners, respectively, during the months following the wildfires ($p < 0.05$). In addition, a statistically significant increase in the consumption of anxiolytics-hypnotics was observed in male pensioners (15.88%) and non-pensioners (12.2%) (Caamano-Isorna et al., 2011).

Although two studies of relatively high quality reported similar results in the association between the increased total and cardiovascular mortality and forest fires, the different measures of exposure classification add to their uncertainty. Studies produced inconsistent results regarding respiratory mortality. Based on the results from one single study, wildfires are likely to increase respiratory morbidities among pensioners and mental health morbidities among men, which remain to be further confirmed due to its medium quality of study and limitations in the study population.

3.6. Floods

Six studies reported the impacts of floods with respect to different health outcomes in temperate climate areas. Two of them failed to find any statistical significant positive associations between floods and mortalities. One study on the long-term effects of floods in England and Wales during 1994–2005 found a relative deficit of deaths in flooded areas in the post-flood year compared to adjacent areas, with a relative mortality-change ratio of 0.90 (95% CI 0.82, 1.00) (Milojevic et al., 2011). The other study conducted in the Czech Republic showed a noticeable increase of cardiac mortality during the Great Flood of 1997 compared with the same months in previous years ($p = 0.088$) (Obrova et al., 2014).

In a study from England, which compared flood victims with non-affected persons, it was shown that there are, after adjusting for socio-demographic factors, elevated odds for depression (aOR: 7.77, 95% CI: 1.51–40.13), anxiety (aOR: 4.16, 95% CI: 1.18–14.70) and PTSD (aOR: 14.41, 95% CI: 3.91–53.13) (French et al., 2019) among the flood exposed group. Similarly, Mulchandani et al. (2020) reported elevated odds for depression (aOR: 8.48, 95% CI: 1.04–68.97) and PTSD (aOR: 7.74, 95% CI: 2.24–26.79) but no significant increase for anxiety in the flooded group. Graham et al. (2019) found an increased odds for common mental disorders for flood exposure, OR = 1.5 (95% CI, 1.08–2.07) but no significant associations between flood exposure and PTSD. Participants who were disrupted by flooding had increased odds of PTSD with an aOR = 4.33 (95% CI, 1.26–14.92) compared to the unaffected group (Mulchandani et al., 2020).

One cross-sectional study explored the long-term mental health impact of the 2007 flood event across England on a household level (Lamond et al., 2015). The authors found that 6 years after the flood, respondents reported experiencing anxiety (>60%), increased stress level (<40%), frequent flashbacks (23%), sleeplessness (18%), depression (18%) and nightmares (<10%) always or very often, with the psychological symptoms all correlated with one another ($p < 0.01$) (Lamond et al., 2015). Another study showed a decrease in mental illness in the years after the flood for depression (year one = 20.8%; year three = 7.8%), anxiety (year one = 27.6%; year three = 11.8%) and PTSD (year one = 33.2%; year three = 17.1%), but compared to the prevalence before the flood, mental illness was still higher (Mulchandani et al., 2020).

These six studies suggest that floods might not be directly associated with overall or cardiac mortalities but could possibly lead to the deterioration of mental health.

4. Discussion

The present systematic review is to our knowledge one of the first attempts conducted on the associations between multiple extreme weather events (extreme temperatures, wildfires, floods, droughts) and multiple health consequences (overall mortality, cardiovascular mortality and morbidity, respiratory mortality and morbidity, mental health effects) in the European region. After a systematic literature search in three databases, we included 35 eligible studies with a variety of study designs, study populations, exposure & outcome assessments and qualities into this review.

The effects of extreme heat events were evaluated by the largest number of studies, most of them reported adverse impacts on the overall, cardiovascular and respiratory mortality, regardless of the climatic region. In most studies, the greatest effect on mortality was reported immediately in the first three days after the heat wave began. Although the magnitude of the effect estimates remains unclear, this result is supported by a few similar studies conducted outside of Europe (Ghumman and Horney, 2016; Lee et al., 2016; Ragettli et al., 2017). Several included studies in the Mediterranean region reported more respiratory hospital admissions during heat waves. For the other regions, there were either no studies or no findings. According to a meta-analysis on 64 studies, the pooled risk of cardiovascular hospitalization slightly increased by 2.2% (RR = 1.022, 95% CI: 1.006–1.039) for heatwave exposures (Phung et al., 2016). Results of a further meta-analysis suggested a RR of 1.003 (95% CI, 1.001–1.005) for myocardial infarction admissions associated with heat exposures with a 1 °C increase (Sun et al., 2018). The duration and intensity of a heat wave seems to play an important role in both mortality and morbidity, regardless of the climatic region. A multi-country study showed that although heat waves of all definitions correlated with mortality, stronger associations were found when higher temperature thresholds (Guo et al., 2017) defined heat waves. Similar effects were detected in a meta-analysis, where the increase of heat-related mortality risks reached up to 16% under the definition of mean temperatures ≥97th percentile for ≥5 days (Xu et al., 2016). The studies on the effects of droughts in the Mediterranean area showed significant links between drought and mortality with strong regional differences. However, the problem is that droughts are not uniformly defined (Salvador et al., 2020) and, due to their simultaneous occurrence with heat waves, air pollution or forest fires, could only reflect the effects of these phenomena (Salvador et al., 2020). A major concern in drawing conclusions from the selected studies, however, is the heterogeneous definitions of exposures among studies. Since there is no universally consistent definition of extreme heat available yet, the exposures were termed as heat waves, hot spells, hot days or extreme heat temperatures, with variations in temperature metrics, thresholds (intensity), and durations.

An excess of total mortality, cause-specific mortality and morbidity was reported from most studies related to extreme cold events in the Mediterranean area. The effects on mortality were highest after six days and present up to 30 days after the cold event. In contrast to the observations during heat waves, there was an increase in both respiratory and cardiovascular hospital admissions during cold events. Intensity and duration also seem to play an important role in the effects of cold waves. A systematic review and meta-analysis confirmed our results by estimating that cold spells were positively associated with mortality from all causes (RR = 1.10, 95% CI: 1.04–1.17), cardiovascular diseases (RR = 1.11, 95% CI: 1.03–1.19), and respiratory diseases (RR = 1.21, 95% CI: 0.97–1.51) (Ryti et al., 2016). Studies of the other regions showed, also due to the small number of studies, either no significant correlation or unclear results. A possible explanation could be the better adaptation of the population in the central and northern regions to extreme cold (Daanen and Van Marken Lichtenbelt, 2016). Similar to the cases of studies on extreme heat events, ambiguities among terms and definitions of cold waves, cold spells and extreme cold temperatures exist, adding to the difficulties in making the findings conclusive. Therefore, adopting a universal definition of extreme heat or cold events is highly recommended for future studies, which would not only produce comparable results across studies, but also help to prevent heat- or cold-related adverse health impacts through region-specific early warning systems based on the study results (Xu et al., 2016).

For included studies on extreme temperatures, possible confounders such as humidity, wind speed, day of the week, time trend, influenza etc. were generally well controlled. However, controversies were introduced by air pollution in that it is unclear whether the air pollution as a whole or specific pollutants (ozone, PM_{10}, $PM_{2,5}$ SO_2, NO_2, etc.) are acting as confounders and/or effect modifiers or neither (Basu, 2009; Analitis et al., 2014). When predicting changes in the concentration of air pollutants due to high temperatures, a distinction must be made between the effects of short-term extreme events and long-term changes. While models for predicting long-term changes are contradictory and uncertain (Ebi and McGregor, 2008; Doherty et al., 2017), short-term extreme events such as heat waves can increase the concentration of air pollutants, which can have negative effects on chronic respiratory diseases (Solberg et al., 2008; Francis et al., 2011). We found contradictive evidences from the studies included as well. It should also be noted that there was a lack of adjustment for air pollution factors in all the studies on extreme cold events, which might lead to certain bias. Thus, further studies focusing on identifying the role of air pollution under extreme temperatures are needed.

Effects of increased all-cause mortality, cardiovascular mortality and consumption of drugs for obstructive airway diseases were found in studies regarding wildfires, but contradictive evidences existed for respiratory mortality. The results are inconclusive due to insufficient number of studies included. From other review studies, wildfire smoke is associated with 1.2–10 times higher level of PM_{10}, with most consistent results indicating a correlation with the risk of respiratory morbidity, specifically exacerbations of asthma and chronic obstructive pulmonary disease (Liu et al., 2015; Reid et al., 2016). As with the confounding issue mentioned above, identifying air pollutants specifically caused by wildfires is also a key challenge in exposure assessment for studies on wildfires and health consequences, which requires the development of new methods to separate wildfire air pollution from that of ambient sources (Liu et al., 2015).

No statistically significant associations between floods and mortality were shown. Rather, it can be concluded that floods could have an influence on various mental diseases. Especially in the long term, it became apparent that floods could still have effects on mental health years later. This result was supported by a cross-sectional study on long-term psychological outcomes of flood survivors, where the prevalence of post-traumatic stress disorder (PTSD) and anxiety was 9.5% and 9.2%, respectively, after 17 years post-flood (Dai et al., 2017). Increased risks of PTSD, anxiety, depression and psychological distress among people from the flood-affected areas were also proven by a systematic mapping review (Fernandez et al., 2015).

An increased risk of disease outbreaks after floods related to food and water, such as gastrointestinal diseases, hepatitis E, and leptospirosis, was found in another systematic review, where the mortality rates in the first year post-flood was reported to be raised by up to 50% (Alderman et al., 2012). Precipitation frequency and intensity as well as air and water temperature may also influence the occurrence of waterborne (O’Dwyer et al., 2016) and foodborne diseases (Lake and Barker, 2018). Floods and increased water flows could lead to contamination of drinking water supplies and recreational and irrigation water (Semenza, 2020). Heavy precipitation or prolonged rainfall may increase the runoff from agriculture land and transporting microbiologically rich medium into rivers, coastal waters, groundwater storages or directly into local waterways (O’Dwyer et al., 2016). Flooding can create vast areas of standing water and with it new areas for potential pathogen exposures (O’Dwyer et al., 2016) which may contaminate cropland of e.g. raw food (Lake and Barker, 2018). However, none of our reviewed studies took water contamination or food safety issues caused by floods into consideration, and none of them focused on food- or water-borne diseases as health outcomes, which might have potentially underestimated the impact of floods.

In our search, we excluded studies on the effects of climate change and extreme weather events on infectious diseases. It should be noted that climate is only one of several factors that influence the distribution of infectious and vector-borne diseases (Vonesch et al., 2016). The introduction of exotic diseases and disease vectors in Europe is primarily facilitated by air travel and globalization (Semenza and Suk, 2017). In contrast, climate change has the greatest impact on seasonal expansions and contractions of vector-borne diseases in Europe (Semenza and Suk, 2017). Although cases of tropical diseases like dengue fever, chikungunya or West Nile virus have been repeatedly reported in Europe in recent years (Semenza and Suk, 2017), the spread and susceptibility of mosquito-borne infectious diseases within a population also depends on various other risk factors (Vonesch et al., 2016).

The pattern of extreme weather events in climate change varies regionally in the world. Only studies from Europe were included in the search strategy. One of the reasons for this is the influence of climate change on all included extreme weather events in Europe (Anders et al., 2014). Southern Europe is expected to experience heat waves and droughts in summer, while in the north, predicted average temperatures rise sharply in the winter due to the absence of the albedo effect of snowmelt (Anders et al., 2014). Influence on the hydrological cycle may change precipitation conditions with increased precipitation, especially in winter, in northern Europe and decreased precipitation, especially in summer, in southern Europe (Stagl et al., 2014). In addition, Europe is a multitude of industry nations where the data availability investigating the impact of climate change on health is more abundant compared to less developed regions around the globe. Most of the reviewed studies investigated the impact of extreme weather events on mortality or morbidity. Several factors such as the health care system or the populations’ state of health determine mortality and morbidity in a society (Gaber and Wildner, 2011).

Apart from meteorological impacts, future studies should also consider social and political aspects. More reviews on region-specific health effects of extreme weather events are expected to be conducted to make results comparable globally.

One of the strengths of the present systematic review, is the comprehensive way that we looked into the associations between extreme weather events and their health consequences in Europe, providing insights on the variety and severity of the impacts of climatic problems at a regional level. The systematic approach and three databases used to identify relevant studies increased the sensitivity of literature search and reduced the risk of missing relevant articles. The medium-to-high quality of the included studies suggested that the studies were carefully conducted with possible confounders identified and controlled and that the results are generalizable in different settings. Furthermore, the missing topics and research gaps found among the included studies should be able to guide future researches to be conducted in Europe.

Additionally, there are several limitations in our study that should be considered. Firstly, the included studies were found to have heterogeneous study designs, study populations, methods and quality, making it impossible to conduct a meta-analysis or to draw definitive conclusions. Secondly, this review was not able to cover all aspects of health consequences of all types of extreme weather events in Europe because studies on some topics were not found. More climate-sensitive health indicators, such as direct injuries, accidents, nutritional status, food security, and other non-communicable diseases might also be interesting to take into consideration (Watts et al., 2018a,b). There were possible chances where some relevant studies were neglected accidentally, even though we attempted to include all the eligible studies. Uncertainties were discussed among the authors until a solution was found. However, it seems that our search strategy could not find all studies matching our objectives. Nevertheless, the present systematic review provides a valuable overview of climate-change-related health effects in Europe. Furthermore, the literature search in our study was restricted to publications in English and German only, inevitable publication bias or selective reporting might exist. Nevertheless, to our knowledge this is the first approach to conduct a systematic overview about climate change related extreme weather events and their effect on human health in Europe.

5. Conclusions

The present systematic review adds to the growing body of evidence that some extreme weather events affect human health adversely. Most studies suggested that extreme heat or cold events lead to increased overall and cause-specific mortality. The effects of droughts are not clear due to its simultaneous occurrence with heat waves, wildfires or air pollution. Wildfires raise overall mortality and cardiovascular mortality within the European population. Floods might not be associated with mortality, but with the deterioration of mental health. Based on these findings and future prognosis of extreme weather events in Europe, an adaptation is needed to deal with these events. With regard to extreme temperatures and wildfires, early warning systems should be set up in particular, as well as preparedness and prevention in vulnerable population groups. The aim should be to create a climate-resilient health system. In order to prevent flood-induced damage to health, flood victims should be supported, for example through appropriate insurance policies in endangered areas. With regard to changes in precipitation, floods and droughts, the focus must be specifically on the adaptation of the agriculture to prevent food insecurity and malnutrition. To date, the evidence from observational studies published is often inconclusive. Besides high-quality studies with standardized exposure assessment, systematic reviews focusing on a single extreme weather event would account for the continually growing body of publications in the field of climate change and health.

Declaration of competing interest

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Review

Health, work performance, and risk of infection in office-like environments: The role of indoor temperature, air humidity, and ventilation

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ABSTRACT

Epidemiological and experimental studies have revealed the effects of the room temperature, indoor air humidity, and ventilation on human health, work and cognitive performance, and risk of infection. In this overview, we integrate the influence of these important microclimatic parameters and assess their influence in offices based on literature searches.

The dose-effect curves of the temperature describe a concave shape. Low temperature increases the risk of cardiovascular and respiratory diseases and elevated temperature increases the risk of acute non-specific symptoms, e.g., dry eyes, and respiratory symptoms. Cognitive and work performance is optimal between 22 °C and 24 °C for regions with temperate or cold climate, but both higher and lower temperatures may deteriorate the performances and learning efficiency. Low temperature may favor virus viability, however, depending on the status of the physiological tissue in the airways.

Low indoor air humidity causes vulnerable eyes and airways from desiccation and less efficient mucociliary clearance. This causes elevation of the most common mucous membrane-related symptoms, like dry and tired eyes, which deteriorates the work performance. Epidemiological, experimental, and clinical studies support that intervention of dry indoor air conditions by humidification alleviates symptoms of dry eyes and airways, fatigue symptoms, less complaints about perceived dry air, and less compromised work performance. Intervention of dry air conditions by elevation of the indoor air humidity may be a non-pharmaceutical treatment of the risk of infection by reduced viability and transport of influenza virus. Relative humidity between 40 and 60% appears optimal for health, work performance, and lower risk of infection.

Ventilation can reduce both acute and chronic health outcomes and improve work performance, because the exposure is reduced by the dilution of the indoor air pollutants (including pathogens, e.g., as virus droplets), and in addition to general emission source control strategies. Personal control of ventilation appears an important factor that influences the satisfaction of the thermal comfort due to its physical and positive psychological impact. However, natural ventilation or mechanical ventilation can become sources of air pollutants, allergens, and pathogens of outdoor or indoor origin and cause an increase in exposure. The "health-based ventilation rate" in a building should meet WHO's air quality guidelines and dilute human bio-effluent emissions to reach an acceptable perceived indoor air quality. Ventilation is a modifying factor that should be integrated with both the indoor air humidity and the room temperature in a strategic joint control to satisfy the perceived indoor air quality, health, working performance, and minimize the risk of infection.

1. Introduction

Indoor air quality (IAQ) reflected in perceived comfort and reported health (i.e., signs and symptoms) have been the issue in indoor (non-industrial) environments since the World Health Organization (WHO) declaration of the "Sick-Building-Syndrome", more than three decades ago (WHO, 1986). Large national and international epidemiological questionnaire studies have been carried out showing high prevalence (20–40%) of reported acute mucous membrane (e.g., dry eyes and dry nose) related symptoms, central nervous system related symptoms (e.g.,

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headache and fatigue), and usually simultaneously with complaints of poor IAQ (e.g., dry or stuffy air). The syndrome is to-day considered obsolete (Carrer and Wolkoff, 2018), rather, the focus is on the specific symptom or cluster of symptoms and identification of associated causalities. Most recently, also infectivity of virus in indoor environments has been in focus (Chen et al., 2009; Chen and Liao, 2010; Rosa et al., 2013).

Since the WHO declaration, an increasing effort has focused on testing and assessing the chemical emission from construction and consumer products, thus leading to various kinds of emission test programs and labeling schemes, ultimately resulting in labeled low-emitting construction products with anticipated low risk of health problems in public and residential buildings; generally applied as so-called "source control" of indoor volatile organic compounds (VOCs) (Brown et al., 2013; Wolkoff and Nielsen, 1996). Parallel with chemical, physical, and biological testing of construction products, new ventilation methodology has been developed, researched, and implemented in the modern office. Further, the role of psychological and psychosocial factors in the office environment have been explored (Azuma et al., 2015; Marmot et al., 2006). Two important and crucial events have occurred within the last two and half decades; these are the introduction of open-space offices and an ever-increasing elderly office working force.

From a qualitative perspective, the prevalence of reported poor IAQ and symptoms has not really declined over the last three decades, rather, it appears to remain without a clear reduction (Bluyssen et al., 1996, 2016). This is surprising in view of the increased focus during the last decades on source control, i.e., the introduction of low emitting construction materials and products and simultaneously the use of modern ventilation methodology. For some countries, the use of certified and emission labeled construction products is compulsory and for some countries labeling schemes are voluntary. Furthermore, the WHO (2010) and some countries have developed national IAQ guidelines for specific indoor air pollutants (Azuma et al., 2020a; Fromme et al., 2019).

Major national and international questionnaire studies in offices during the last two decades have reported complaints about perceived IAQ and symptoms or signs in eyes and upper and lower airways (i.e., effects on mucous membranes, usually mediated through Trigeminus nerve) and symptoms associated with the central nervous system, see (Nielsen and Wolkoff, 2017; Wolkoff, 2013). Complaints are repeatedly, since the first studies, the perception of dry, still or stuffy air and/or poor IAQ, e.g. (Bluyssen et al., 2016; Wolkoff, 2018b), apart from noise and inadequate self-control of the microclimate (Sakellaris et al., 2019). "Dry or burning eyes" and unusual fatigue are often among top-two reported symptoms jointly with runny or blocked nose (Bluyssen et al., 2016; Wolkoff, 2013). While the prevalence of dry eye-like symptoms remains largely unaltered (Filon et al., 2019), "unusual fatigue" might have decreased comparing the outcome of the EU AUDIT and OFFICAIR studies, respectively (Bluyssen et al., 1996, 2016).

Inadequate IAQ not only influences perceived IAQ, comfort, and health, but also indirectly impacts office work performance (Wyon, 2004). Thus, high indoor room temperature (IRT), low indoor air humidity (IAH), and various kinds of inadequate ventilation (proxy for temperature, IAH, and indoor air pollution) have all been associated with deteriorated work performance and/or decision-making. Furthermore, the COVID-19 epidemic has addressed how temperature, IAH, and ventilation influences the risk of infection (Azuma et al., 2020b). Thus, the aim of this study is to assess how the indoor thermo-microclimatic parameters in modern office environments as IRT, IAH, and ventilation influence perceived IAQ, health, work performance, and infectivity of virus, mainly with focus on temperate and continental cold climate regions.

2. Method

In general, literature from the last decade has been compiled from own collections, reviews, and by online literature database searches across major electronic databases, including PubMed and Google Scholar, and J-Dream III, in the last five years by use of dedicated keywords for the search. PubMed was primarily used to identify potential literature that qualified the search criteria, and others were used as complementary databases. Additional literature for temperature, humidity, and ventilation was identified by manual screening of the bibliographies of the retrieved literature.

The following key words were used as search criteria for temperature: "temperature OR cold OR heat" AND "eye OR airway"; indoor AND "temperature OR cold OR heat" AND "comfort OR performance OR productivity". The literature was selected from two stages: screening of titles and abstracts and followed by full-text review. Exclusion were no measurement in temperature, instantaneous change in temperature with heat shock, learning performance in children, thermal comfort not directly associated with health. The literature for humidity was mainly derived from previous key reviews (Arundel et al., 1986; Derby et al., 2016; Wolkoff, 2018a, 2018b, 2020a) and further supplied with dedicated literature searches from 2017 to 2020. Furthermore, issues of high/low temperature and humidity in housing is dealt with by (WHO, 2018). The literature for ventilation was mainly derived from previous key reviews (Carrer et al., 2015, 2018) and further supplied with literature searches from 2017 to 2020.

2.1. Definitions

In this article, temperature represents indoor air room temperature in office environment. Absolute humidity (AH) represents the water vapor content in grams per kg of air (g/kg) at a defined pressure, thus independent of temperature. Relative humidity (RH) is % water vapor content in the room air relative to the total amount of vapor in the same room air may contain at a given temperature. Low IAH levels are tentatively between 0 and 30% RH and high IAH is considered >60–80% RH; these limits are to be considered fluent depending on the specific case and climate region. Ventilation is the process of exchanging indoor air with preferably clean outdoor air to ensure healthy and comfortable indoor spaces, i.e., dilution of the (polluted) indoor air. Ventilation is in some cases also used to control the indoor thermal environment (temperature and air humidity) by providing heating or cooling, and by adjusting the humidity (by adding or removing moisture). The ventilation air supply rate (VR) is currently expressed in air changes per hour or as liters per second per person (L/s per person), which accounts for the occupancy density of the building/room. The most frequent method used for measuring ventilation involves the use of tracer gases (Persily, 2016). Often carbon dioxide (CO_2) is measured and considered as an indicator of the efficiency of ventilation to dilute and remove pollutants (Persily, 2017).

3. Results

3.1. Temperature

3.1.1. General comments

High and low IRTs are common risk factor for human health. The WHO provided evidence-based recommendations for high and low IRTs for housing in 2018 (WHO, 2018), see Table 1a for additional information. WHO recommended 18 °C as a safe and well-balanced IRT to prevent cardiovascular and respiratory morbidity and mortality during cold seasons for regions with temperate or cold climate. However, as there are few studies of the direct effect of high IRT on human health, the evidence was assessed as low to exceptionally low about reduced morbidity and mortality by lowering high IRT. Thus, WHO was unable to identify a threshold for high IRT. While the physiological responses to environmental heat or cold have been well-understood about comfort (ANSI/ASHRAE, 2017; Goromosov and WHO, 1968), their impact on cognitive or work performance has been a focus of interest among

Table 1a
Summary of key reviews about the impact of indoor temperature on performance and health effects.

Study	Research focus	Main conclusions
WHO (2018)	Adverse health effects	*Respiratory morbidity and mortality*: Three eligible studies on people with chronic obstructive pulmonary disease and asthma showed that colder IRTs increased respiratory morbidity, suggesting warming a cold house (perhaps to a minimum IRT of 18 °C) would reduce the risk of respiratory mortality and morbidity. *Cardiovascular morbidity and mortality*: Six eligible human epidemiological studies conducted in Japan, Scotland, and the United Kingdom showed that lower temperatures were associated with higher blood pressure, suggesting warming a cold house (to a minimum IRT of 18 °C) would reduce the risk of cardiovascular mortality and morbidity. *High indoor temperature and morbidity*: Eight eligible studies on the effect of indoor heat on health outcomes, including sleep disorders, general health, blood pressure, respiratory and cardiovascular disease, body temperature, mental health, and pregnancy outcomes were assessed. However, the mixed findings and the relatively small amount of evidence showed that the certainty of the direct evidence that reducing high IRTs would reduce morbidity or mortality was assessed as low.
Cheung et al. (2016)	Work performance	This review illustrates the major occupational impact of exposure to extreme thermal environments and existing employment standards. This review indicated that there are rarely any standards regarding enforced heat or cold safety for workers in most occupations, although there is a large body of knowledge concerning the physiological effects of thermal stress.
Zhang et al. (2019)	Cognitive performance	This review compares two dominant conceptual models linking thermal stress to cognitive performance; (1) the inverted-U model specified a single optimum temperature at which performance is maximized and (2) the extended-U model posited a broad central plateau across, which there is no discernible thermal effect on cognitive performance. This review suggested that the extended-U model fits the relationship between moderate thermal environments and cognitive performance.

IRT= Indoor room temperature.

indoor environmental researchers (Cheung et al., 2016; Zhang et al., 2019). However, an extremely narrow optimum range of IRT in the performance may require high energy consumption in the buildings. A view of a cost-benefit balance is also required (Wargocki and Wyon, 2017). The optimal IRT range depends on the specific region, because people are acclimatized to different temperatures in different climate regions. Recently, evidence has been identified about the optimal range for regions with temperate or cold climate based on the effects on human health and performance. This section summarizes recent evidence on the effect of the thermal environment on health effects and performance, see Table 1b for additional information.

3.1.2. *Health effects*

3.1.2.1. Ocular effects. A human exposure study indicated that the ocular surface was directly affected by the air temperature. Tear evaporation rate, non-invasive tear breakup time, and lipid layer thickness of the precorneal tear film increased with elevated temperature (5 °C–25 °C). This may cause symptoms of dry eye and ocular surface disorders (Abusharna et al., 2016). For instance, epidemiological studies suggested that an increase of temperature was associated with dry eye diseases (Zhong et al., 2018) and exacerbation of allergic conjunctivitis (Hong et al., 2016). Higher traction retinal detachment was significantly associated with increase of the outdoor temperature (15 °C–25 °C) (Auger et al., 2017).

3.1.2.2. Respiratory effects. Controlled animal studies have indicated that airway inflammation was directly affected by exposure to variation of the air temperature in 26 °C/10 °C cycle (Du et al., 2020) and decrease of temperature (30 °C–20 °C) (Liao et al., 2017), which may exacerbate asthma, see Table 1b. Human studies have suggested that high IRT was associated with acute upper respiratory symptoms (Azuma et al., 2018a; Maula et al., 2016). Respiratory diseases, asthma, and chronic airway obstruction were associated with longer-term exposure to lower average temperature. On the other hand, respiratory diseases and chronic airway obstruction in elderly people were associated with longer-term exposure to higher average IRT. The diseases increased at 18 °C and 30 °C compared to the centered temperature with the lowest prevalence (Wang and Lin, 2015). Patients with chronic obstructive pulmonary disease and asthma showed that colder IRTs increased respiratory problems and impacted the lung function, respectively, suggesting minimum IRT of 18 °C (WHO, 2018).

3.1.2.3. Cardiovascular effects. Several epidemiological studies conducted in the regions with temperate climates during the cold season showed that lower IRT was associated with higher blood pressure, suggesting a minimum IRT of 18 °C (WHO, 2018). Significant and independent association between lower IRT ($\leq$14.35 °C) compared to higher IRT ($>$17.92 °C) and higher platelet count, which may be a potential cause of cardiovascular disease mortality, was observed among elderly people during the cold season (Saeki et al., 2017). Although a few epidemiological studies reported the associations of high IRT with blood pressure and cardiovascular disease, the mixed findings and the risk of bias indicated low certainty of a direct causality (WHO, 2018).

3.1.2.4. Other effects. A human exposure study indicated that acute symptoms, which include thinking difficulty, poor concentration, fatigue, and depression, increased above 26 °C (30 °C, 33 °C, and 37 °C) at a RH of 70% (Fan et al., 2019).

3.1.3. *Work and cognitive performance*

When the weather is hot, it is hard to concentrate. In general, the rise in IRT and the decline in work performance is linear. At $\geq$25 °C, mental alertness declines, and at $\geq$30 °C, the ability to concentrate is gone (Wei, 2020). As shown in Table 1b, many recent studies have suggested that high and low IRTs in comparison to the temperature with the highest performance affected the brain response, cognitive and work performances, productivity, and learning efficiency. Highest performance was obtained in the accuracy of brain executive functions at 22 °C compared to 18 °C, 26 °C, and 30 °C (Abbasi et al., 2019). Significant decrease in cognitive test performance was observed at 26.2 °C compared to 22.4 °C (Barbic et al., 2019), at 27 °C compared to 23 °C (Lan et al., 2020), and at 26.3 °C compared to 21.4 °C (Laurent et al., 2018). Highest cognitive test performance was observed at approximately 25 °C compared to 18.7 °C and 28.8 °C (Hong et al., 2018) and 22–23 °C (Yeganeh et al., 2018). One study suggested that cognitive test performance was not significantly affected between 22 °C and 25 °C (Zhang et al., 2017a). Cognitive performance was relatively stable or even slightly promoted at 22 °C compared to 24 °C (Zhang and de Dear, 2017). Optimal productivity was observed from 20 °C to 26 °C, especially 22 °C–24 °C (Geng et al., 2017). Work performance significantly negatively affected at 29 °C compared to 23 °C (Maula et al., 2016) and 17 °C and 28 °C compared to 21 °C (Vimalanathan and Babu, 2014). One study suggested that slightly warm (28.6 °C) environment resulted in a relatively higher mental workload compared to 21.7 °C and 25.2 °C (Wang et al., 2019). The highest learning efficiency was observed at 22 °C compared

Table 1b

Selected papers about the impact of temperature on various health effects, physiological responses, and cognitive performance.

Type of study	Subjects	Exposure	Effects and measurements	Main findings
Animal exposure studies:				
Du et al. (2020)	Ovalbumin induced asthma model BALB/c mice	Steady 26 °C, 26 °C/18 °C cycle, and 26 °C/10 °C cycle	*Respiratory effects*: Transient receptor potential A1 (TRPA1) channel blocker, lung function, bronchoalveolar lavage fluid (BALF), and pulmonary inflammation.	26 °C/10 °C cycle exacerbated airway inflammation, increasing total-IgE and IgG1 serum levels, inflammatory cells, and cytokines in BALF. Repeated exposure to very cold and changed temperatures aggravated airway hyper-responsiveness. Significant upregulation of TRPA1 expression was revealed at 26 °C/10 °C cycle.
Liao et al. (2017)	Ovalbumin induced asthma model BALB/c mice	Standard temperature (ST, 20 °C) and thermo-neutral temperature (TT, 30 °C) for mice	*Respiratory effects*: Airway inflammatory in bronchoalveolar lavage fluid (BALF), airway hyper-responsiveness (AHR), and T-regulatory cell function.	Airway inflammatory cell counts in BALF and AHR were significantly reduced at 30 °C compared with 20 °C. Imbalance of Th1/Th2 response in the lung was improved at 30 °C. Pulmonary Treg cells were increased after 30 °C treatment.
Controlled chamber studies:				
Abbasi et al. (2019)	35 male students	18 °C, 22 °C, 26 °C and 30 °C in 4 separate sessions with 50%RH and 0.15 m/s air flow	*Physiological responses and cognitive performances*: Electrocardiogram (ECG) signals, respiration rate, and working memory.	Compared to 22 °C, 30 °C and 18 °C had profound effect on changes in heartbeat rate, the accuracy of brain executive functions and the response time to stimuli. There were statistically significant differences in the accuracy by different workload levels and various air temperature conditions.
Abusharna et al. (2016)	12 healthy subjects	5 °C, 10 °C, 15 °C, 20 °C, and 25 °C with 40% RH for 10 min	*Ocular effects*: Tear film parameters including tear evaporation rate, non-invasive tear breakup time (NITBUT), lipid layer thickness (LLT), and ocular surface temperature (OST).	Evaporation rate and NITBUT significantly linearly increased from 5 °C to 25 °C. LLT median ranged between 20 and 40 nm at 5 and 10 °C and significantly increased to 40 and 90 nm at 15, 20, and 25 °C. Reduction of 4 °C OST was significantly linearly observed from 25 to 5 °C.
Barbic et al. (2019)	12 university students	22.4 °C (Day 1) and 26.2 °C (Day 2) during 2 h in classroom	*Physiological responses and cognitive performances*: Electrocardiogram (ECG) signals including heart rate variability (HRV) and cognitive performance.	During 26.2 °C, a shift of the cardiac autonomic control towards a sympathetic predominance was observed compared to 22.4 °C. Short-term memory, verbal ability and the overall cognitive C-score scores were lower during 26.2 °C compared to 22.4 °C.
Fan et al. (2019)	32 sub-tropically acclimatized subjects	26 °C, 30 °C, 33 °C, and 37 °C at 70% RH for 175 min	*Physiological responses and cognitive performances*: Self-reported acute health symptoms (S-AHSs), heart rate (HR), weight loss, and heart inter-beat interval (IBI).	Thinking difficulty, poor concentration, fatigue, and depression increased with increasing temperature, but it was no more than moderate at the highest temperature; dryness of skin and eye were alleviated. The eardrum temperature, skin temperature and moisture, HR, end-tidal CO_2, and weight loss increased significantly with increasing temperature, whereas the percentage of adjacent IBI significantly decreased.
Geng et al. (2017)	21 subjects	16 °C–28 °C with a step of 2 °C for 2 h	*Productivity work performance*: Productivity test (Icon matching, number summing, and text memory and typing).	Optimal productivity was range from 20 °C to 26 °C, especially 22 °C–24 °C in almost accordance with optimal thermal satisfaction.
Hong et al. (2018)	22 building occupants	Change of the operative temperature (OT) from 18.7 to 25 °C (Test 1) and from 28.8 to 25.3 °C (Test 2) during 8-hour work period	*Cognitive performances*: Cognitive tasks of visual reaction time (VRT), subitizing, stroop test, backward corsi block tapping (BCBT), N-back, and typing.	In Test 1, accuracy of VRT and subitizing significantly increased and reaction time of BCBT significantly decreased, which mean their performances improved. In Test 2, accuracy of VRT increased significantly.
Lan et al. (2020)	12 subjects	23 °C and 27 °C with a step of 2 °C for 225 min	*Cognitive performances*: Cognitive tasks of text typing and addition, neurobehavioral tests of mental reorientation, grammatical reasoning, digit span memory, number calculation, and stroop, mental load by the NASA TLX, and Tsai-Partington test.	Significant decrease in task performance was observed at 27 °C for Tsai-Partington, typing, and stroop. An increase of mental load at 27 °C was also reported.
Maula et al. (2016)	33 university students	23 °C and 29 °C for 3.5 h	*Physical symptoms and cognitive performances*: Cognitive tasks of typing, star counting, vigilance, operation span, N-back, and long-term memory. Symptoms of difficulties in concentration, headache, and mucous symptoms.	N-back working memory tasks significantly negatively affected at 29 °C compared to 23 °C, caused at 29 °C. Throat symptoms increased over time at 29 °C, but no temporal change was seen at 23 °C.
Richardson et al. (2018)	25 female office workers	Control of 20.0 °C and warm condition of 25.8 °C for 7 h	*Caloric intake and work performance*: Food intake and self-reported productivity.	Caloric intake significantly decreased in warm condition. More productive than usual in warm condition compared to control.

(*continued on next page*)

Table 1b (*continued*)

Type of study	Subjects	Exposure	Effects and measurements	Main findings
Vimalanathan and Babu (2014)	10 male university students	17 °C, 21 °C, and 28 °C for 40 min	*Productivity work performance*: Neurobehavioral test (letter search, direction, object overlapping, memory span, picture detection, figure-digit, logical sequences, comprehensive reading, numerical addition, logical conclusion, picture match, and reasoning).	Optimum level of IRT for work performance was at 21 °C.
Wang et al. (2019)	15 university students	Slightly cool (21.7 °C), neutral (25.2 °C), and slightly warm (28.6 °C) with 23% RH for 2 h.	*Productivity work performances in office room*: Mental workload using electroencephalography (EEG) signals.	Slightly warm (28.6 °C) environment resulted in a relatively higher mental workload than the other two environments to achieve the same performance.
Xiong et al. (2018)	10 university students	17.3 °C, 22.2 °C, and 27.1 °C for 65 min	*Learning performance in classroom*: Learning efficiency of accuracy rate, reaction time, and performance indicator.	The highest learning efficiency came at 22 °C with thermos-neutral and learning efficiency peaked to maxima at 22 °C with thermo-neutral.
Xiong et al. (2019)	16 elderly subjects	21 °C, 25 °C, 28 °C, and 31 °C for 1 h	*Physiological responses*: Electrocardiogram (ECG) signals including heart rate variability (HRV).	The lowest HRV was at 25 °C.
Zhang et al. (2017a)	26 office workers	Typical (22 °C) and higher (25 °C)	*Physiological responses and cognitive performances*: Electroencephalogram (EEG), heart rate (HR), and cognitive performances.	Cognitive performance tests, EEG, and HR were not significantly affected by difference of temperature.
Zhang and de Dear (2017)	56 university students	22 °C and 24 °C	*Cognitive performances*: Cognitive performances including memory, concentration, reasoning, and planning.	Cognitive performance was relatively stable or even slightly promoted at 22 °C. Reasoning and planning performance observed a trend of decline at 24 °C. Simpler cognitive tasks are less susceptible to temperature effects than more complex tasks.
Case EPI studies:				
Case-crossover study Auger et al. (2017)	14,302 individuals with inpatient procedures for retinal detachment	Outdoor summer temperature in the preceding week between 2006 and 2013 in Canada	*Ocular effects*: Subtypes of retinal detachment (traction, serous, rhegmatogenous, and breaks).	Relative to 15 °C, weekly temperature of 25 °C was significantly associated with a higher likelihood of traction retinal detachment at < 75 years.
Cross-sectional study Azuma et al. (2018a)	107 workers in 11 offices during winter and 207 workers in 13 offices during summer	IRT in air-conditioned office buildings in Japan	*Respiratory effects*: Building-related symptoms including eye irritation, general, upper respiratory, and skin symptoms.	Upper respiratory symptoms showed a significant correlation with increased IRT from 21.9 to 27.0 °C during winter.
Case-control study Laurent et al. (2018)	44 university students	Non-air conditioning (AC) with 26.3 °C and AC with 21.4 °C for 12 days during heat waves	*Cognitive performances*: Cognitive speed and working memory (reaction time and 2-digit visual addition/subtraction test [ADD]).	Students living in non-AC spaces experienced significant decrements on cognitive test performance: an increase in reaction time and ADD, and reduction in throughput of reaction time among non-AC compared to AC.
Cohort study Hong et al. (2016)	31,2012 outpatients with allergic conjunctivitis	Ambient temperature in the past 1 week between 2008 and 2012 in China	*Allergic conjunctivitis*: Number of outpatient visits for allergic conjunctivitis.	The outpatient visits for allergic conjunctivitis was significantly increased with increased temperature.
Cross-sectional study Saeki et al. (2017)	1,095 elderly	Indoor temperature during cold seasons (October to April) from 2010 to 2014 in Japan	*Cardiovascular effects*: Platelet count.	A 1 °C lower daytime IRT was associated with a significant increase in platelet count. Compared with the warmest group (>17.92 °C), the coldest group (≤14.35 °C) showed a 5.2% higher platelet count.
Retrospective study Walkden et al. (2018)	4229 corneal scrapes from patients with microbial keratitis	Ambient temperature (1.2 °C–20.8 °C) between 2004 and 2016 in the UK	*Ocular effects by microbial keratitis*: Organisms of microbial keratitis.	Gram-positive bacteria and Pseudomonas sp. significantly grew with increasing temperature. Fungi and Moraxella sp. significantly grew with decreasing temperature.
	1,040,898 outpatients with respiratory diseases		*Respiratory effects*: Outpatient visits for respiratory diseases, asthma, and chronic airway	Respiratory diseases, asthma, and CAO for <65 years significantly increased at 18 °C compared to the centered temperature with the

(*continued on next page*)

Table 1b (*continued*)

Type of study	Subjects	Exposure	Effects and measurements	Main findings
Cohort study Wang and Lin (2015)		Ambient temperature (10 °C–30 °C) in the last 8 days between 2000 and 2008 in Taiwan	obstruction not elsewhere classified (CAO) associated with 18 °C and 30 °C.	lowest visits. Respiratory diseases and CAO for 65+ years significantly increased at 30 °C compared to the centered temperature with the lowest visits.
Case-crossover study Zhong et al. (2018)	25,818 subjects with dry eye diseases (DED)	Ambient temperature in monitoring station adjacent to subjects' locations of clinics between 2004 and 2013 in Taiwan	*Ocular effects:* Same subjects experiencing exposures on DED diagnosis days as cases and those on other days as controls.	Temperature was positively associated with DED.
Review-Meta-analysis:				
Yeganeh et al. (2018)	28 reports between 1980 and 2018	Air temperature in controlled laboratory experiments	*Cognitive performances:*	Studies with the weighted mean of 4.34 °C, 10.04 °C, and 26.68 °C increase from reference temperature of 22–23 °C show about 0.40%, 5.37%, and 7.97% reductions in cognitive performance. Heat stress causes the most significant decline in the most attention-demanding tasks.

IRT= Indoor temperature.

to 17.3 °C and 27.1 °C (Xiong et al., 2018). This evidence suggested that the optimal range for the performance was overall 22 °C–24 °C, and the brain function is so sensitive to slight difference of the IRT. However, the underlying biological mechanism has not been explored, although the hypothesis on the role of transient receptor potential melastatin 8 (TRPM8) neuron has been suggested (Wei, 2020).

3.1.4. Infectious diseases

Infectious respiratory viruses such as influenza, rhinovirus, or coronaviruses can be transmitted via direct and indirect contact (via fomites), and through the air via respiratory droplets and/or droplets in enclosed environments (Memarzadeh, 2012; Nicas and Sun, 2006; Nicas and Jones, 2009; Tellier et al., 2019). The temperature is one of factors related to the virus transmission or virus viability in the environment. The range for the RH and the IRT reported in the previous studies vary and do not have scientifically determined demarcations (Hanley and Borup, 2010; Lowen et al., 2007; Memarzadeh, 2012). For example, temperature-dependent efficiency of influenza virus transmission among guinea pigs, as a function of the RH; see further discussion in section 3.2.5. At 20 °C, the relationship between transmission efficiency and RH is bimodal, while it is monotonic at 5 °C. No virus transmission among guinea pigs was observed at 30 °C (Lowen et al., 2007, 2008). Temperature can affect the state of viral proteins and the virus RNA or DNA. In general, virus viability decreases with increase of temperature. Maintenance of IRTs above 60 °C for more than 60 min will usually inactivate most viruses (Memarzadeh, 2012), including novel coronavirus SARS-CoV-2 (Chin et al., 2020). However, this can vary depending on the presence of physiological tissue (i.e., blood, feces, mucus, or saliva) included in the respiratory droplets and/or aerosols (Memarzadeh, 2012). SARS-CoV-2 stability was also enhanced when present with bovine serum albumin, which is commonly used to represent sources of protein found in human sputum (Pastorino et al., 2020).

3.1.5. Negative effects of room temperature

- Temperature–adverse effect curves have been described as U-, V-, or W-shaped. The optimal temperature range depends on the specific region, because people are acclimatized to different temperatures in different climate regions.
- Decreased temperature below 18 °C increases the risk of cardiovascular and respiratory morbidity and mortality during cold seasons for regions with temperate or cold climate.
- Elevated temperature above 26 °C increases the risk of acute symptoms including thinking difficulty, poor concentration, fatigue, and depression. The risk of respiratory symptoms increases above 30 °C.
- The optimal range for work and cognitive performance was 22 °C–24 °C for regions with temperate or cold climate.
- Low temperature increases virus viability; however, it varies depending on the presence of physiological tissue.

3.2. Humidity

3.2.1. General comments

Experimental, intervention, and clinical studies have demonstrated the beneficial effects by elevation of the IAH from dry conditions (Wolkoff, 2018b). Despite these positive effects, the IAH has been disregarded as an essential microclimatic parameter on equal terms as the temperature and ventilation in control of the IAQ, although the health risk of dry air conditions was discussed already back in 1937 by Yaglou (1937). Apart from previous technical problems of humidification, two important issues have hampered the appreciation of IAH as an important contributor of controlling the IAQ. First, the paradigm, that IAQ should be perceived as "dry and cool" in office environments, i.e., low RH and not too warm, was advocated, although it was derived from immediate short-term panel assessment of the perceived air quality from

Table 2a

Humidity: Summary of key reviews and selected field studies about the impact of indoor air humidity in offices on perceived indoor air quality, and ocular and respiratory health.

Type of study	Research focus	Main conclusions
Review:		
Baughman and Arens (1996)	High humidity and health effects	- Historical review with focus on health risks associated with high humidity by exposure to: Bacteria and virus, dust mites, fungi, formaldehyde, ozone, nitrogen, and sulfur dioxides. - Recommendations provided.
Alves et al. (2019)	Voice quality/performance	*Health*: "Laryngeal desiccation challenges by oral breathing led to surface dehydration, which had significant negative effects on several acoustic parameters such as, jitter, shimmer, noise-to-harmonics ratio, phonation threshold pressure, and perceived phonatory effort." Systemic hydration appears the most effective way to improve voice quality.
Derby et al. (2016)	Low humidity (≤40% RH)	*Indoor air quality*: - A minor effect. Ventilation is a confounding variable. - Variable influence on VOC emissions from materials and uneven influence on perceived air quality. *Health*: - Decrease of dust mites. - Generally, an increase of the viability of influenza virus; increase of eye symptoms and skin dryness. - Controlled exposure studies generally carried out with young subjects (i.e., difficult to anticipate effects in elderly persons).
Hurraβ et al. (2017)	Moisture damage/mold exposure	*Indoor air quality:* - Odor hedonics can influence perceived health and well-being and mood. - Odors may result in a cascade of secondary effects and be associated with airway symptoms (psychological effects). This depends on many personal factors, i.e., previous experience, familiarity, concerns, etc. - Annoyance reactions according to (Bullinger, 1989): Physiological, cognitive environmental process (concerns), and stress reactions. *Health*: - Sensory irritation: Evidence (no valid data) for an association with indoor mold exposure is considered limited. Risk of infection is considered low for healthy people. - Evidence for allergic bronchopulmonary aspergillosis and mycoses, allergic respiratory diseases, asthma, allergic rhinitis, alveolitis, respiratory tract infections. - Risk of sensitization is considered low; suggested to occur mostly in people with high risk for being sensitized by allergens by inhalation. - Susceptible people (risk groups) must be protected.
Marr et al. (2019)	Mechanistic view of influenza virus dynamics	*Risk of infection*: - The review illustrates the complexity of viability and transmission of influenza virus. Temperature and relative humidity appear better climatic parameters than absolute humidity, although they follow each other in the indoor regime. In summary, at lower relative humidity exhaled droplets stay suspended longer and likely to deposit in the lower airways due to smaller size than from their initial size after exhalation (e.g., cough) from evaporation to reach equilibrium. - The morphology and chemistry of the droplets are strongly affected by the evaporation, and this may influence the stability of the virus. In summary, the indoor humidity determines the extent of evaporation of an airborne droplet, which influences the chemical environment of the virus. - Substantial research is needed to fully understand the impact of the indoor humidity on the dynamic behavior of influenza virus and other virus and bacteria.
Wolkoff (2018a)	Integrating overview: IAQ and symptoms	*Indoor air quality*: - Perceived IAQ may be altered from low to normal IAH by change of VOC emissions from materials (VOC polarity dependent). The IAH may alter deposition and resuspension of respirable particles (e.g., dust pollen) and particles of microbiological origin (mold). This may impact the immediate perception of the IAQ at entrance to a building/room. - The resuspension of particles depends on several parameters, which *i.a.* include particle size and chemical/physical properties of the surface. - Dry air continues to be among top-two complaints about IAQ and the complaint rate appears to be more pronounced in open-space offices than in cellular offices. *Ocular effects*: - Ocular comfort is strongly affected by the IAH with increase of eye symptoms at dry air conditions. *Risk of infection*: - Many studies have shown alleviating effects of eye and airway symptoms by increase of the IAH from dry air conditions. - Studies show that survival and transmission of influenza virus are inversely associated with the IAH (rather than with RH). Still a strong need to understand the dynamics associated with the mechanistic picture of survival and transmission. The dynamics of bacteria (viability and transmission) appears more complex.

(*continued on next page*)

Table 2a (*continued*)

Type of study	Research focus	Main conclusions
Wolkoff (2018b), 2020a	Perceived "dry air" and association with dry eyes and airways	*Indoor air quality*: - "Dry and wet" indoor air is semantically misleading because we have no receptor for perceived humidity. - Reported "dry air" and "dry eyes" have multifactorial causalities from exposure to low IAH as a common denominator, and dry eye and nasal diseases, which are age and gender dependent. - Whether "stuffy air" correlates with "dry air" or it is an independent perception remains to be clarified. *Airway and ocular effects*: - Perceived dry air may have different causalities other than low IAH, like immanent nasal diseases, e.g., rhinitis. - Many epidemiological studies have demonstrated the beneficial effect on symptom reporting by elevated IAH from low humidity conditions, especially dry eye symptoms and dry air symptoms. - Exposure to low IAH conditions aggravates the stability of the precorneal tear film (in eyes) and subsequently initiates a cascade of reactions due to hyperosmolarity in the tear film that leads to increase of symptom reporting. - Exposure to low IAH also results in desiccation of the nasal cavity, which becomes vulnerable to indoor air pollutants by lowering the mucociliary clearance rate, which is strongly age dependent (i.e., elderly are more vulnerable than young subjects). - Further, an aggravated precorneal tear film, e.g., induced by dry air conditions, becomes vulnerable to indoor air pollutants as combustion particles (e.g., from traffic) and aggressive chemicals like ozone. - Overall, incomplete humidification of the eyes and mucous membranes in the airways appears enough to cause dry air and dry eyes. - Perceived dryness in the eyes may be confused with reporting of irritated eyes induced by sensory irritation or mimic the proto-state of sensory irritation as a cooling sensation or due to the odor perception.
Field study in offices:		
Azuma et al. (2017)		*Ocular and general symptoms*: - Strong association between low IAH and dry eye symptoms. -Indoor air humidity was an important risk factor for general symptoms in summertime.
Lukcso et al. (2016)		*Eye and airway effects*: - A negative correlation was found between lower respiratory symptoms and maximum and minimum values of relative humidity in one study area. Thus, suggesting that dry air conditions may exacerbate lower and upper respiratory symptoms. - Data suggest that low IAH (dry eyes) may interact with glare to cause additional ocular discomfort.
Razjouyan et al. (2020)		*Stress*: - Heart rate variability (longer-term circulation differences and circadian rhythm) was measured in office workers (n = 134) over three consecutive days. The office workers that were exposed to relative humidity between 30 and 60% were more likely to experience 25% less stress than those exposed in much of their time to drier conditions. - The finding is important, because the elevated stress might be initiated by reactions from desiccation of the ocular surface and mucous membranes in the airways.

emissions of various building materials, which were exposed to different combinations of humidity and temperature (Fanger, 2000). Second, the lack of distinction between potential adverse health risks from moisture-damaged construction products versus the IAH (Borchers et al., 2017) as in office-like environments. One third reason is the misinterpretation of the study by Andersen et al. (1974), who concluded "subjects' assessment of humidity is unreliable"; furthermore, the mucociliary clearance rate was found independent of the IAH among young (smoking) subjects, which contradicts other studies, as discussed in Wolkoff (2018b). The IAH influences not only the perceived IAQ, but also health, work performance, and infectivity of virus, as presented below. For supporting information, see Tables 2a and 2b.

3.2.2. *Perceived indoor air quality*

Humans is a hygroreceptor–lacking species but perceives, in part, humidity by thermo-mechanosensory pathways, e.g., on the skin (Filingeri, 2015), and indirectly by the perceived IAQ as a pseudo-proxy for the air humidity (dryness vs wetness). Thus, an increase of the IAH from low (≤30% RH) to 40–60% RH may alter the perceived IAQ (i.e., odor profile) by an altered VOC emission from material surfaces (building materials, furniture, etc); this, to some extent depends on the polarity of the single VOC and their sorption properties on the material surface, cf. Wolkoff (2018b). This may alter the perceived IAQ, i.e., the odor hedonics may change; usually, in an unpredictable manner, sometimes resulting in odor annoyance. Odor annoyance may result in secondary psychological reactions, sometimes depending on personal traits, e.g., affectivity, concerns, experience, familiarity, cf. Dalton and Jaén (2010).

The IAH also influences the physical/chemical properties of particles and the dynamics of their deposition and resuspension to surfaces and from floor surfaces by people walking (Mølhave et al., 2000; Qian et al., 2014). Many parameters influence such as particle size distribution, surface chemistry (e.g., polarity), and the physical/chemical properties of the material surface. The deposition and resuspension of particles that occur from surfaces may influence the perceived IAQ and furthermore their potential health effect in the eyes and airways. The resuspension of particles depends on the ground floor material and the particles sizes. For instance, the resuspension is lower from certain hard surfaces (e.g., hardwood and vinyl flooring) at high RH for fine particles sizes (0–5 μm); however, no or minor effects is seen for textile carpets (Qian et al., 2014; Tian et al., 2014; Zheng et al., 2019). Further, ultrasonic humidification has been shown to substantially reduce the particle concentration (20–1000 nm) (Feng et al., 2018; Kim et al., 2020). Further details to be found in Wolkoff (2018b).

Floors are reservoirs of human-associated bacteria and virus in deposited debris and droplets, thus, resuspended floor dust particles from human activity may be an important contributor of exposure to bioaerosols, cf. Hospodsky et al. (2012). This, of course, also includes resuspended microbiological contaminants from moisture infested surfaces. Studies indicate that the re-emission of bioaerosols from infested surfaces are higher at low RH than at high RH (Madsen, 2012; Frankel and Madsen, 2014). For virus viability on surfaces, see 3.2.5.

The concentration of indoor particles, that includes microbiological species like virus (and fomites), may differ by altered deposition and resuspension to and from floor surfaces, which partially depends on the chemical and physical properties of the particles and the surfaces, cf. Wolkoff (2018a). However, detailed knowledge about the IAH dependence on the deposition and resuspension from surfaces, e.g., from walking activities is complex. Particles may also be carriers of influenza

Table 2b

Humidity: Summary of experimental studies about the impact of indoor air humidity on work performance in offices.

Literature	Work performance Conditions	Number of subjects Exposure duration, min	Main conclusions
Benton et al. (2016)	30 °C, 43–62% RH	101 undergraduates 240	Body mass loss (0.72%) of water showed memory loss. Thirst reduced memory and drinking water improved memory and cognitive attention.
Fang et al. (2004)	20 °C/40% RH, 23 °C/50% RH, 26 °C/60% RH 10 l/s per person 3.5 l/s per person	30 young females 480	Neither temperature nor relative humidity showed significant effects on the performance in form of text typing, proofreading, addition, and creative thinking. Eye irritation symptoms were unaffected. Fatigue and headache increased at 26 °C/60% RH. Some precaution of interpretation due to random significance.
Shan et al. (2016)	RH from 58% to 74%	39 healthy university students 120 per session, morning, noon, afternoon	The exposure to different types of ventilation and draft in a tutorial rooms with controlled temperature and RH. Elevation of RH from 58% to 74% resulted in significantly fewer dry eye symptoms. The air velocity was considerably higher at the high RH condition; thus, the finding should be considered cautiously. Lowering carbon dioxide and increase of RH improved short-term work performance presumably by reduction of dry eye symptoms.
Tsutsumi et al. (2007)	1: 70% RH/30 °C 2: 30, 40, and 50% RH at 25 °C	12 adults 1: 15 2: 180	- Perceived pleasantness going to lower humidity (more comfortable due to evaporation). - Perceived more tiredness at 70% RH. - No difference in subjectively reported performance at 30–50% RH.
Wyon et al. (2006)	22 °C 5, 15, 25, 35% RH	30 students (17 females) Two sessions of 150 divided by break of 15	A few percent reduced visual data acquisition for certain office tasks was observed and concurrent with higher blink frequency at 5% RH in comparison to 35% RH. Slight elevated eye symptoms at 5% RH.

virus and should be considered an additional risk of virus exposure, see 3.2.5.

3.2.3. *Acute health effects*

3.2.3.1. Ocular effects. The ocular health depends strongly on the IAH and with elevated prevalence of dry eye symptoms at low IAH conditions (Wolkoff, 2018a,b, 2020a). Experimental exposure of subjects to dry IAH conditions demonstrates that the precorneal tear film deteriorates, mimicking dry eye diseases, by desiccation of the ocular surface; this is further confirmed in animal studies (Wolkoff, 2018a, 2020a). Furthermore, a destabilized (desiccated) precorneal tear film, e.g., from prolonged low IAH exposure, is more vulnerable to external stimuli by pollutants, like ozone, nitrogen dioxide (combustion proxy), and various combustion-related particles (traffic, wildfires). Vice versa, a deteriorated precorneal tear film by pollutants or occupational conditions is more vulnerable to low IAH conditions, thus exacerbating the development of dry eye symptoms. For instance, extended visual display unit work and other visual cognitive demanding work, and without appropriate breaks including microbreaks, increases the instability and vulnerability of the precorneal tear film, see (Wolkoff, 2020a).

3.2.3.2. Airway effects. Intervention studies have shown that elevation of IAH from dry air conditions relieves acute airway symptoms, as reviewed in Wolkoff (2018b). Extended dry air exposure also desiccates the airways and consequently increases the host vulnerability; for instance, the mucociliary clearance rate in the upper airways is markedly reduced and thus its defense mechanism by inactivation of the mucous layer (Moriyama et al., 2020; Wolkoff, 2018b), as demonstrated in the elegant mice study by Kudo et al. (2019). Thus, low IAH increases the vulnerability of the nasal cavity and to some extent the pulmonary region, especially among elderly people. This may further enhance the deposit of combustion particles, e.g., from traffic, ozone, and bioaerosols (e.g., pathogens) on the airways.

Aqueous loss in the respiratory epithelium is important by the continuous need for evaporation from its surface (i.e., desiccation). Increased airflow (ventilation) in the nose causes more aqueous loss and a greater hyperosmolaric surface, which may move more distal. This stimulates the release of inflammatory mediators from epithelial cells, which possibly may lead to nasal congestion, e.g., by swelling (Naclerio et al., 2010). Cold-dry-air led to significantly higher osmolarity than methacholine or histamine among cold-dry-air responders than non-responders. This was confirmed by higher osmolarity in nasal secretions after a cold-dry-air challenge (Naclerio et al., 2007). Further, hyperosmolar challenge may cause histamine and leukotriene (C_4) release, probably caused by hyperosmolar stimuli in mast cells; the release is more pronounced among cold-dry-air (e.g., asthmatics) responders than among healthy non-responders.

3.2.3.3. Effect on the vocal cord. "Laryngeal desiccation challenges by oral breathing led to surface dehydration, which had significant negative effects on several acoustic parameters such as, jitter, shimmer, noise-to-harmonics ratio, phonation threshold pressure, and perceived phonatory effort." Systemic hydration appears the most effective way to improve voice quality (Alves et al., 2019). Further literature to be found in Wolkoff (2018a).

3.2.4. *Stress*

Heart rate variability was measured in office workers over three consecutive days. The office workers that were exposed to RH between 30 and 60% were more likely to experience 25% less stress (measured by lower heart rate variability as proxy) than those exposed in much of their time to drier conditions (Razjouyan et al., 2020). The finding is important, because the elevated stress in dry IAH conditions might be initiated by reactions from desiccation of the ocular surface and mucous membranes in the airways, and subsequent initiation of dry eyes and upper airways. However, further research is needed to clarify the direct causality.

3.2.5. *Work performance*

Table 2b summarizes experimental studies about the influence of IAH on work performance. It appears that at least one major factor causing deteriorated cognitive work performance relates to dry eye-like symptoms. This can partially be associated with low IAH conditions. This is more common among elderly people (Wolkoff, 2020a), while the effect of dry air exposure appears less pronounced among younger subjects like students (Wyon et al., 2006). The dry air conditions cause instability of the precorneal tear film leading to hyperosmolarity, and further initiation of a cascade of inflammatory reactions (Wolkoff, 2018b, 2020a). For instance, common visual complaints like dry eye symptoms are generally associated with inter alia eye fatigue (Koh, 2016). Many office workers feel eye fatigue during intensive near and visually cognitive demanding work, like visual display work, and inadequate light condition; this may be further exacerbated among people with dry eye diseases (Ayaki et al., 2019). For instance, it has been speculated that eye fatigue is the outcome of "dry eye struggle" to visualize during conditions of visual disturbance (blurred vision) (Koh, 2016), i.e., low visual acuity, to be associated with an aggravated precorneal tear film. Thus, a stable precorneal tear film is considered important for uncompromised work performance, especially among elderly female workers, cf. Wolkoff (2020a).

The interaction between IRT, IAH, and VR and work performance is complex and depends on many other factors (Horr et al., 2016) including occupational and personal factors (Wolkoff, 2020a); however, as indicated in the experimental study with subjects by Wu et al. (2020), elevated IAH, in general, impacts the work performance positively.

It has also been found that elevated water loss from the body by extended dry IAH conditions, which are uncompensated by adequate water intake, can compromise cognitive performance (Benton et al., 2016). It is known that that young subjects lose weight during dry air conditions (Andersen et al., 1974) and the transdermal water loss appears to be fast within a few hours and larger in low IAH conditions (Egawa et al., 2002).

3.2.6. *Infectious diseases*

Comparison of viability, transmission, and infectivity of influenza virus has shown the importance of the IAH; thus, both dry air (RH$<$ 40%) and extremely humid air (RH$>$ 90%) appear to favor their viability (Lin and Marr, 2020). For instance, seasonality, as cold temperature, and low RH has been associated with increased occurrence of airway infections, as well as rainy seasons. This is in line with an increase of influenza virus viability and transmission efficiency, e.g., from coughing, breathing, and talking (Asadi et al., 2020; Morawska er al., 2009). For example, for many influenza viruses their infectivity is greatly reduced at RH $>$ 40% (Dietz et al., 2020; Moriyama et al., 2020; Wolkoff, 2018a).

Modeling studies indicate that low temperature and low AH prevent disruption of some influenza virus as opposed to higher temperature and humidity. Several studies indicate favorable viability conditions for some influenza viruses at cold temperature and low RH as reviewed by Ahlawat et al. (2020; Dietz et al. (2020); Lauc et al. (2020); Moriyama et al. (2020) and Wolkoff (2018a). The lower IAH increases the formation of smaller droplets (aerosols) from evaporation of larger droplets, and thus being suspended in the indoor air for longer time and travel further away from the source. Furthermore, it was demonstrated in a mice model that dry air conditions impaired the mucociliary clearance and further the innated antiviral defense and tissue repair, which indicates a reduction of the host antiviral defense (Kudo et al., 2019). Thus, decreased ability to fight against virus and microorganisms due to ulceration of the respiratory mucosa (Ference et al., 2020). However, the experimental inadequacy of such animal studies should be considered carefully together with the overall complexity of transmission and viability, and associated mechanisms of infection and defense mechanism at the host. For instance, elevated vulnerability of the eyes and airways in low IAH conditions (Moriyama et al., 2020; Wolkoff, 2018b).

The elevated infectivity at low RH in schools is elegantly demonstrated in an intervention study where manipulation of the humidity in preschool classrooms in the cold season to about 45% RH significantly reduced total influenza virus and viral genome copies in the air compared with control classrooms. Furthermore, pupils exposed to the elevated humidity classrooms showed lower absence rate (Reiman et al., 2018). Many other intervention studies have shown that an increase of the IAH reduced respiratory infection rates (Arundel et al., 1986).

How the IAH influences the virus-droplet viability and infectivity indoors depends on the physical and chemical properties of the virus envelope (lipid versus non-lipid), associated droplet dynamics, and the interplay with the IRT, IAH, and VR, cf. Morawska (2006). The mechanisms of viability, transmission, and infectivity of virus and bacteria in human generated droplets associated with IAH and temperature is complex, but crucial for understanding the spread of virus, both within the microclimate and regionally, and far from completely understood (Ahlawat et al., 2020; Moriyama et al., 2020; Wolkoff, 2018a). Modeling studies do indicate that elevated IAH can hinder evaporation and contribute to the deposition of more exhaled droplets, e.g., Ahlawat et al. (2020) and Liu et al. (2021).

The hygienic aspect of the viability of deposited virus droplets and fomites on surfaces is also an important source of infection by hand-face contact. Thus, Casanova et al. (2010) demonstrated that Corona virus at 20% and 80% RH at 20 °C remain viable for more than a week on steel plates, while 50% RH reduced the viable virus to less than 1% after two days. Similar results have been found for other material surfaces by increase of the AH or temperature showing more decay of SARS-CoV-2 (Biryukov et al., 2020).

Many studies indicate that cold and low IAH conditions favor viability and transmission for some influenza virus, but the opposite has also been observed for other virus types, e.g., Ijaz et al. (1985). Thus, their viability and infectivity should be dealt with virus-by-virus (Moriyama et al., 2020; Wolkoff, 2018a) and generalizations to humans based on animal findings and use of artificial saliva should be considered cautiously. Important factors to consider is the combined viability and transmission efficiency, in part influenced by both indoor and outdoor climatic conditions and reflected in the seasonal dependence for some virus. For instance, Dabisch et al. (2021) concluded that indoor air humidity, temperature, and sunlight interact and influence the viability of COVID-19 with a particle size about 2 μm.

The robustness of the airways, inter alia the viscosity of the mucous and the mucociliary clearance efficiency, is essential to consider, i.e., the host vulnerability. The clearance rate is lower in dry IAH conditions, especially among elderly people (Moriyama et al., 2020; Wolkoff, 2018b), and so is the immune response capacity (Lauc et al., 2020; Moriyama et al., 2020), as elegantly demonstrated in the mice study by Kudo et al. (2019). It has even been speculated that the elevated air humidity in the inspired air wearing a face mask might be an additional benefit by hydration of the respiratory epithelium enhancing the mucociliary clearance (Courtney and Bax, 2020).

3.2.7. *Positive and negative effects by indoor air humidification (from low indoor air humidity conditions)*

Positive and some negative effects are summarized below. It is relevant, however, in context of indoor humidification, to distinguish between the well-known adverse effects of mold exposure from moisture damaged construction products and associated respiratory effects (Hurraβ et al., 2017) versus elevation of the IAH from dry air conditions. Some of the identified effects are suggestive indicating more research is needed for substantiation.

Positive effects by elevation of indoor air humidity from dry indoor air conditions:

- Elevation of the IAH may increase the deposition rate of airborne particles onto surfaces and thus decrease their air concentration.
- Elevation of the IAH may reduce the resuspension of deposited particles from certain surfaces.
- The re-emission of inhalable microbiological particles (mold species) from moisture-damaged building surfaces may be reduced.
- Elevation of the IAH may reduce complaints about dry air and possibly also stale air, especially among elderly people.
- Elevation of the IAH increases the stability of precorneal tear film and reduces the risk of dry and tired eyes, especially among elderly people.
- Elevation of the IAH increases the mucociliary clearance providing more robust upper airways, especially among elderly people.
- The stress level may be lower among those working in offices at 40–60% RH, then among those working in dry air conditions.
- Elevation of the IAH may increase the work performance, as symptoms of dry and tired eyes are reduced.
- Elevation of the IAH hinders droplet evaporation to smaller size droplets.
- Elevation of the IAH generally reduces the viability and transmission capability of influenza virus.
- Elevation of the IAH reduces the viability of influenza virus droplets on surfaces.

Negative effects by elevation of the indoor air humidity:

- The immediately perceived IAQ may change by altered emission of certain VOCs from material surfaces. The odor emission profile changes, usually in an unpredictable way, and may result in a less acceptable IAQ.
- Elevation of the IAH above 60% increases the risk of mold growth on cold and poorly ventilated surfaces.
- Elevation of the IAH above 80% increases the viability of influenza virus on steel surfaces.

3.3. *Ventilation*

3.3.1. *General comments*

Current information on the association between ventilation and health is mainly based on epidemiological studies (Seppänen and Fisk, 2004; Sundell et al., 2011; Wargocki, 2013). However, many of the studies lack important details about ventilation rates and their measurements. Nearly all studies suffer from lack of information about measurements of pollutants that potentially may affect health, comfort, or mental/work performance. Special measures to reduce the emission rates of VOCs from building materials, furnishing and equipment, have not been carried out, e.g., by dedicated source control. Few studies provide information on the quality of the outdoor air and/or the air supplied by the ventilation system downstream the air-handling unit, implicitly assuming clean outdoor air. The wide range of reported VRs at which different outcomes were reported are probably due to the complex relationship between VRs, air pollutant levels and health. Strictly speaking this is because ventilation is merely an intermediate and indirect proxy rather than the main causative factor for the underlying relationship. This section summarizes recent evidence on the association between ventilation and health effects and performance in offices, see Tables 3a, 3b and 3c.

3.3.2. *Health effects*

3.3.2.1. *Acute effects.* Increasing ventilation has often been observed to reduce several health outcomes, since increased VRs are expected to reduce the indoor exposures that may cause these effects; see Tables 3a and 3b for additional information. However, there have also been studies without any association or even a negative association (Carrer et al., 2015; Lu et al., 2015; Maula et al., 2017).

Ventilation rates from 6 to 7 L/s per person were the lowest rates at which no effects on any acute health outcomes have been observed in field studies. However, other studies have suggested up to 25–40 L/s per person as the lowest indoor VR at which no health effect outcomes were observed (Carrer et al., 2015). Recently, it was concluded that numerous epidemiological studies indicate an association between low-level exposure to CO_2 as a proxy of IAQ and ventilation, beginning at 700 ppm, and negative effects on office workers. However, other indoor comorbid pollutants may be involved in such effects (Azuma et al., 2018b).

In a study performed in five office buildings in the Netherlands, personal control of ventilation was the most significant factor that influenced the satisfaction of the thermal comfort due to its physical and positive psychological impacts (Kwon et al., 2019).

3.3.2.2. *Chronic effects.* None of the reviewed studies assessed the impact of building VRs on chronic health effects, such as respiratory and cardiovascular diseases, or cancer. The reason is the complexity and extended periods that would be needed to run such experiments, which seems unrealistic in view of the occupant mobility and the variability in indoor pollution and VRs across different indoor environments. However, regarding the association between ventilation and chronic acute health effects modeling studies were carried out in Europe (Asikainen et al., 2016) and in US (Chan et al., 2016; Logue et al., 2012). Chronic health effects were estimated using disability adjusted life years (DALYs) accounting for asthma, cardiovascular diseases, acute toxicities, respiratory infections, lung cancer, and chronic obstructive pulmonary disease. The health risks were driven primarily by exposures to particulate matter ($PM_{2.5}$). The increase of ventilation alone is ineffective at reducing the chronic health burden and can cause negative effects. In such cases, filtration of outdoor air is necessary for prevention of an elevated health risk(s).

3.3.3. *Ventilation and health guidance*

Ventilation is not the direct causal factor of health and comfort effects. Ventilation simply modifies the underlying relationship between exposure and health outcome (or between exposure and perceived IAQ and exposure and cognitive performance). The level of exposure depends not only on the VR, but also on the strength of indoor emitting sources.

When the pollution source strength of indoor sources is high, higher VRs are required for reduction of the exposure. In context of the HealthVent project, the “health-based VR” for a specific building is defined as the VR that is required to meet WHO’s air quality guidelines

Table 3a

Summary of reviews on ventilation and health in offices.

Study	Main conclusions
Azuma et al. (2018b)	- Human experimental studies suggested that short-term CO_2 exposure beginning at 1000 ppm affects cognitive performances including decision making and problem resolution. - Numerous epidemiological studies indicate an association between low-level exposure to CO_2 beginning at 700 ppm and building-related symptoms and respiratory symptoms have been indicated in children exposed to indoor CO_2 concentrations higher than 1000 ppm, however, other indoor comorbid pollutants are possibly involved in such effects.
Carrer et al. (2015)	- Ventilation rates from 6 to 7 L/s per person were the lowest VRs at which no effects on any health outcomes were observed in field studies, up to 25–40 L/s per person, which were in some studies the lowest VRs at which no effects on health outcomes were seen. - These data show that, in general, higher VRs in many cases will reduce health outcomes, and that there are the minimum rates, at which some health outcomes can be avoided.
Carrer et al. (2018)	- Carbon dioxide is used as a marker of numerous pollutants emitted by humans. - The “health-based VR” for a specific building is defined through an integrated approach combining source control measures and health-based ventilation practices, where priority is given first to source control measures and then to ventilation. - Based on CO_2 modeling, for metabolic rates, activities and occupation densities that are typically found in residences, offices, schools and other buildings of similar typology, the VR of 4 L/s per person assures that the CO_2 concentration stays, on average, below the 1500 ppm level, at which no harmful health effects have been reported in the literature (except for the isolated effects on the decision-making performance). It is the “baseline value” below which no VRs can be allowed. - If the WHO air quality guidelines are not met after all options of outdoor and indoor source control measures have been exploited, then the “actual health-based VR” should be higher and calculated by selecting a multiplying factor (>1) of the base VR.

IAH = indoor air humidity. VR = ventilation rate.

Table 3b
Summary of studies on ventilation and acute health effects and environmental comfort in offices.

Type of study Literature	Subjects	Exposure	Health Effects	Main conclusions
Controlled office room:				
Lu et al. (2015)	417 employees in 87 office rooms of eight high-rise buildings	CO_2, temperature, humidity and TVOCs for 8 office hours using portable monitors. The mean 8-hour CO_2 levels at the surveyed offices in high-rise buildings, to near 2800 ppm in an office with 25 persons at work. The hourly mean CO_2 concentration of indoor (1160 ppm, SD = 604 ppm) was 2.6 times higher than that outdoors (mean = 434 ppm, SD = 60 ppm	After controlling for personal and environmental variables, per 100 ppm increase in dCO_2 had significant associations with dry throat (OR = 1.10; 95% CI = 1.00–1.22), tiredness (OR = 1.16; 95% CI = 1.07–1.26), dizziness (OR = 1.22; 95% CI = 1.08–1.37) and non-specific syndrome (OR = 1.16; 95% CI = 1.04–1.29) but had a protective association with eye irritation (OR = 0.81; 95% CI = 0.67–0.98).	After controlling for personal and environmental variables, increase in dCO_2 had significant associations with dry throat, tiredness, dizziness, and non-specific syndrome, but had a protective association with eye irritation.
Zhang et al. (2017b)	25 subjects exposed to different levels of CO_2 and bioeffluents	Five exposures were examined: a reference exposure with CO_2 at 500 ppm, exposure to CO_2 at 1000 ppm and 3000 ppm, achieved by adding CO_2 to the supply air, and exposure to metabolically generated CO_2 at 1000 ppm and 3000 ppm	Heart rate, blood pressure, end-tidal CO_2 ($ETCO_2$), oxygen saturation of blood (SPO_2), respiration rate, nasal peak flow, and forced expiration, and the levels of salivary α-amylase and cortisol. Exposures to CO_2 at 3000 ppm when pure CO_2 was added caused $ETCO_2$ to increase to a higher level and heart rate to decrease less than in the reference exposure in which the CO_2 concentration was 500 ppm. No other physiological reactions were observed during exposure to added CO_2 at levels below 3000 ppm.	- Exposure to human bioeffluents when metabolically generated CO_2 is at 3000 ppm may elevate arousal/stress or lead to physiological effects that cause health symptoms and either mechanism would be expected to reduce cognitive performance. - No clear indication that such effects might occur because of exposure to pure CO_2.
Cohort study:				
Kwon et al. (2019)	Office workers from 5 offices in the Netherlands. A total of 579 (90.9%) completed respondents.	Four buildings were energy-retrofitted offices and one a conventional office in normally work conditions	Questionnaires about: satisfaction with the indoor environmental quality and the degree of personal control for individuals' thermal and visual comfort during summer, winter, and mid-season.	Personal control of ventilation was the most significant factor influencing the satisfaction with thermal comfort. The results showed that a higher controllability leads to more satisfaction in terms of thermal and visual comfort.

(WHO, 2010) and at the same time dilute human bio-effluent emissions to reach an acceptable perceived IAQ (Carrer et al., 2018). In this project it has been calculated that the "base VR" of 4 L/s per person assures that the CO_2 concentration emitted by occupants stays, on average, below the 1500 ppm level (it is the "baseline value" below which no VRs can be accepted). If the WHO air quality guidelines are not met after exploitation of all control measures of outdoor and indoor pollution sources, then the "actual health-based VR" should be higher and calculated by selecting a multiplying factor (>1) of the base VR.

Scientific and technical literature shows that operation and maintenance of systems that provide air from ventilation (particularly mechanical ventilation systems with humidity control and cooling) have not always been fully adequate; this can result in systems becoming strong sources of pollution, which are caused by elevated exposures and consequently increased health risks (Mendell et al., 2008; Seppänen and Fisk, 2002; Wargocki et al., 2002). Some studies show that ozone- and nitrogen dioxide-initiated processes on the surface of particle filters employed in buildings lead to the formation of secondary byproducts (Destaillats et al., 2011); for a risk assessment, see Wolkoff (2020b).

3.3.4. *Work performance*

Human experimental studies have suggested that short-term CO_2 exposure from 1000 to 1500 ppm, indicating low VR, may affect cognitive performance including decision-making and problem solving (Allen et al., 2016; Azuma et al., 2018b; Hong et al., 2018; Satish et al., 2012), even when symptoms and perceived air quality are unaffected (Maddalena et al., 2015) see Table 3c for further information. The results, however, are often contradictory with large variations and uncertainties (Du et al., 2020; Fisk et al., 2019). For instance, odorous VOCs like 2-propanol and heptane dominated the office at the high CO_2 concentration in the study by Allen et al. (2016), thus biasing the outcome. In another example, mixing ventilation and passive displacement ventilation by lowering of CO_2 and an increase of RH improved work performance by reduction of dry eye symptoms (Shan et al., 2016), and these symptoms are strongly associated with deteriorated work performance (Wolkoff, 2020a).

Exposure to human bioeffluents, when metabolically generated CO_2 is at 3000 ppm, may elevate arousal/stress or lead to physiological effects that cause health symptoms and either mechanism would be expected to reduce cognitive performance (Zhang et al., 2017b). However, there is no clear indication that such effects might occur by exposure to pure CO_2 (Fisk et al., 2019; Snow et al., 2019; Zhang et al., 2017b). Thus, other environmental causes may deteriorate the work performance as discussed by Azuma et al. (2018b) and Wolkoff (2020a). For instance, high CO_2 is proxy of annoyed IAQ, which may cause mental distraction, possibly by odorous VOCs, either as human bioeffluents or emitted from building materials or consumer products.

3.3.5. *Infectious diseases*

The infectivity mechanisms are complex, and it is difficult to quantify the source strength of infections and the resulting population exposure. In general, the outbreak of infectious disease depends on many factors that can contribute to the transmission of infection, both indoors and outdoors (Dietz et al., 2020; Moriyama et al., 2020). The major factors are size and lifetime of the virus droplets, the viability of the virus, and the vulnerability of the airways.

In general, poor ventilation in crowded confined indoor spaces is associated with increased risk of transmission of respiratory infections but such relationship is complex and still unclear. For example, air flow generated by air-conditioning units may facilitate the spread of virus droplets and aerosols, which are excreted by infected people, at longer distances within indoor spaces (European Centre for Disease, 2020; Li et al., 2007). Furthermore, the recirculation of air is a measure for saving energy, but care must be taken, as it can transport airborne contaminants (including infectious viruses) from one space and distribute them to other spaces connected to the same system (e.g., in cruise ships,

Table 3c
Summary of controlled chamber/room studies on ventilation and cognitive/performances effects in offices.

Literature	Subjects	Exposure	Effects	Main conclusions
Allen et al. (2016)	24 participants in 6 full workdays in offices (09.00–17.00)	CO_2 exposure levels: Conventional: 921–969 ppm (high TVOC) Moderate CO_2: 906–962 ppm High CO_2: 1400–1420 ppm Green: 716–726 ppm Green+: 486–609 ppm	Cognitive assessment using the Strategic Management Simulation software tool.	- Cognitive scores 61% and 101% higher in green buildings than on conventional building with one order of magnitude higher TVOC, dominated by odorous VOCs. - VOCs and CO_2 were independently associated with cognitive scores. - Office workers had significantly improved cognitive function scores when working in Green and Green+ environments compared with scores obtained when working in a conventional environment.
Maddalena et al. (2015)	Sixteen adult subjects in a controlled environment designed to simulate a recently renovated open-plan office	Groups of four subjects were exposed to specific test conditions during two 4 h sessions conducted during the same day. CO_2 average concentrations for the final 3 h were about 900 ppm in condition 1 and 1800 ppm in condition 2. The overall average temperature and relative humidity during the full study were 22.5 °C and 40.4%, respectively. Average TVOC concentrations were not constant and in conditions 3 and 4, with low and high VRs per floor area, were 29 and 176 $\mu g/m^3$, respectively	Three times during each session, a web-based survey instrument was used to assess perceived air quality and intensity of SBS symptoms.	Neither changing the VR per person nor changing the VR per floor area, had consistent statistically significant effects on perceived air quality or SBS symptoms. Reductions in either occupant-based VR or floor-area-based VR had a significant and independent negative impact on most decision-making measures. However, in the present study, VOC concentrations increased while CO_2 concentrations increased.
Maula et al. (2017)	36 undergraduate university students (21 female and 15 male), non-smokers, healthy, native Finnish speakers and aged between 19 and 35 years (Median = 25)	CO_2 concentration level used as an indicator of bioeffluents: - Condition A: outdoor air flow rate 28.2 l/s person CO_2 level 540 ppm - Condition B: outdoor air flow rate 2.3 l/s person CO_2 level 2260 ppm	- Performance results: Condition B had a negative effect on performance in the information retrieval task and nearly significant negative effect on performance in the operation span task. Experimental condition had no effect on performance in N-back, creative thinking, attention, psychomotor, or long-term memory tasks. - Questionnaire results: workload increased with exposure time in both experimental conditions, but it was slightly higher at the end of session in Condition B. Experimental condition had no effect on other factors of subjective workload (perceived frustration, exertion, and performance). - Experimental condition influenced perception of fatigue in two out of three factors: Lack of energy and lack of motivation were slightly higher in Condition B. No effect was found on tiredness. - No effect of experimental condition on symptoms was found. - Experimental condition influenced perceived air quality and observed odor intensity in the beginning of the session. No effect of experimental condition was found in other exposure times.	- No effects on health symptoms. - The experimental condition influenced perceived air quality and observed odor intensity only in the beginning of the session.
Satish et al. (2012)	Twenty-two participants in an office-like chamber	Subjects were exposed to CO_2 at 600, 1,000, and 2,500 ppm in an office-like chamber, in six groups. Each group was exposed to these conditions in three 2.5-hr sessions, all on 1 day, with exposure order balanced across groups. Ventilation rate and temperature were constant.	Participants completed a computer-based test of decision-making performance as well as questionnaires on health symptoms and perceived air quality.	At 1,000 ppm CO_2, compared with 600 ppm, performance was significantly diminished on six of nine metrics of decision-making performance. At 2,500 ppm CO_2, compared with 600 ppm, performance was significantly reduced in seven of nine metrics of performance.

(*continued on next page*)

Table 3c (*continued*)

Literature	Subjects	Exposure	Effects	Main conclusions
Hong et al. (2018)	22 building occupants in office room	Three scenarios simulating IEQ conditions during an 8-hour working period. CO_2 low (around 1000 ppm) and high (around 2400 ppm)	Six cognitive tasks.	The building occupant's task performance can be improved under cold and low CO_2 concentrations.
Snow et al. (2019)	31 participants in 5 office buildings	Three environmental loggers measured temperature, relative humidity, and CO_2 concentration Short exposures (<60 min) to normal CO_2 (830 ppm) and high CO_2 (2700 ppm), raised by introducing pure CO_2 alongside the occupant generated CO_2	Physiological measurements: - Skin temperature (middle finger, non-dominant hand). - Pulse rate (finger clip, non-dominant hand). - Respiration rate (abdominal belt). - Electroencephalogram (EEG) measurements: a neuroelectric dry electrode wearable wireless EEG cap was used. EEG was gathered continuously, throughout each of the EEG sessions.	- Lack of an expected performance, improvement in executive function and cognitive flexibility parameters when CO_2 is artificially raised. - This lack of expected improvement can occur without changes to SBS symptoms, or perceived air quality, can occur after only short duration exposures to the higher CO_2 conditions, and cannot be explained by physiological, neurophysiological, or subjective factors. Individuals already lacking sleep may be more susceptible to the effects of CO_2 in enclosed spaces.

hospitals), potentially increasing the risk of airborne infection in areas that otherwise would not have been contaminated (Horve et al., 2020; Knibbs et al., 2012). Recently, discussion about how to prevent airborne transmission of SARS-CoV-2 indoors has underlined the benefits of an effective ventilation system, possibly enhanced by particle filtration and air disinfection, for contributing to an overall reduction in the SARS-CoV-2 indoor airborne infection risk (Morawska and et al., 2020). This, however, without considering the potential of IRT and IAH control and the beneficial effects in reduction of the viability and infectivity of virus, and elevated robustness of the airways, see sections 3.1.4 and 3.2.5. For instance, the ventilation of cold dry outdoor air in the cold season and subsequently heated indoors will result in exceptionally low IAH, ideal for the viability and transmission of virus droplets and their viability on surfaces, see 3.2.5.

The viability of SARS-CoV-2 could be mitigated not only via ventilation, but also by strategic heating, ventilation, and air conditioning systems maintaining thermodynamic conditions possibly deactivating the virus (Spena et al., 2020). Ventilation should be considered a modifying, but salient factor, and the transmission by other routes, that are not controlled by ventilation, cannot be ruled out, i.e., not a stand-alone parameter. Thus, the ventilation should be integrated in a strategic joint control of both the IRT and IAH (Spena et al., 2020), which both influence the viability and infectivity of the virus.

3.3.6. *Positive and negative effects of ventilation*

Positive effects.

- Increasing the VR has often been observed to reduce some health outcomes, including infectious diseases, and to improve work performance.
- Installation of mechanical ventilation system would usually increase the VR and thus reduce exposure to indoor air pollutants by dilution and removal; consequently, leading to the reduction of discomfort and health risks. The ventilation can also to some extent reduce exposures to ambient particles (size dependent) if efficient filtration and/or air cleaning systems are installed.
- Personal control of the ventilation is a significant factor influencing the overall satisfaction with the indoor microenvironment.

Negative effects.

- Natural ventilation or improperly designed, operated, and maintained ventilation systems can become sources of pollutants and allergens of outdoor or indoor origin. This elevates rather than decreases the exposures (incl pathogens), causing an increase in the health risk. Improper maintained systems will also elevate ozone surface-initiated reactions leading to new reaction products, which might deteriorate the perceived IAQ and elevate the risk of exposure to new chemicals.
- Increase of the VR from outdoor may increase exposures to some pollutants that originate outdoors (e.g., combustion products and particles) and efficient filtration and/or air cleaning systems are needed (Asikainen et al., 2016).
- Increase of the VR without humidification in the cold season of dry outdoor air may facilitate viability of virus droplets and virus on surfaces and elevate the risk of infection.

4. Conclusion

Epidemiological and human experimental studies have revealed the effects of temperature on human health, work, and cognitive performance. The dose-effect curves are described as a concave shape. Decreased temperature increases the risk of cardiovascular and respiratory diseases. Elevated temperature increases the risk of acute non-specific symptoms and respiratory symptoms. The virus viability generally decreases at elevated temperatures. Cognitive and work performance was optimal at 22 °C–24 °C for regions with temperate or cold climate, and deteriorated performances and learning efficiency may deteriorate at both higher and lower temperatures. However, people are acclimatized to different temperatures in different climate regions; thus, optimal temperature range depends on the specific region.

Epidemiological, experimental, and clinical studies have demonstrated the beneficial effects of elevating the indoor air humidity from dry indoor air conditions. These effects are alleviation of dry eye and fatigue symptoms, less complaints about dry air, and less compromised work performance. Furthermore, intervention by elevation of the indoor air humidity may be considered as a non-pharmaceutical treatment of influenza risk, and further, maintain the airway mucociliary clearance rate. Thus, it should be emphasized that indoor air humidity is a thermal parameter as important as room temperature and ventilation in controlling the indoor air quality, health, comfort, and working performance. Thus, relative humidity between 40 and 60% is recommended.

Ventilation will reduce both acute and chronic health outcomes and improve work performance since elevated ventilation rates generally reduce the indoor air exposure. Personal control of ventilation appears to be a significant factor that influences the satisfaction of the thermal comfort due to its physical and positive psychological impacts. However, natural ventilation or mechanical ventilation can become sources of air pollutants, allergens, and pathogens of outdoor or indoor origin and thus potentially cause an increase in exposure. Poor ventilation in crowded confined indoor spaces is associated with increased risk of transmission of respiratory infections but increase of ventilation and recirculation of air without efficient particle filtration and air disinfection may facilitate the spread of virus droplets. It has been proposed that ventilation rates in buildings should not be lower than 4 L/s per person. The “health-based ventilation rate” in a building should be determined to meet WHO’s air quality guidelines and dilute human bio-effluent emissions to reach an acceptable perceived indoor air quality. Ventilation, however, is not a panacea, but should be considered a modifying, but salient factor.

A joint and concerted control strategy of the indoor air humidity, the room temperature, and ventilation is essential, not only in offices and public buildings, but also in residences to satisfy the requirements for optimal perceived indoor air quality, health, work performance, and deactivation and removal of virus.

5. Future perspective and research needs

Research should be stratified to improve our understand and optimize the casual relationships between ventilation, indoor air humidity and temperature. Studies are required to determine the optimum temperature range in different climate regions. For instance, an extremely narrow optimum range of temperature may require high energy consumption in a building.

Our understanding is still limited about particle dynamics and resuspension, virus droplet transmission dynamics, droplet size dynamics away from source, and surface viability on surfaces as function of temperature and indoor air humidity. Thus, further research is recommended in five segments: First, (dry) particle dynamics and resuspension from various surfaces. Second, virus droplet evaporation dynamics, that includes viability and transmission kinetics in the air, and the viability of deposited virus droplets on various surfaces. The outbreak of the novel coronavirus has focused the attention on how the elevation of the indoor air humidity from dry air conditions potentially can diminish the viability and infectivity and improve the airway robustness and immune system. Thus, research should be initiated towards the interplay and identification of optimal conditions for a combined control strategy of the indoor air humidity jointly with the room temperature and the ventilation, as recommended by Ching and Kajino (2020) and WHO (2018). This should be combined with an analysis of risk-benefit and cost-effectiveness of the relative importance of the different actions of the interplay between temperature, indoor air humidity, and ventilation, e.g., to combat virus infection more efficiently. Third, research should initially be carried out in controlled realistic chamber conditions, preferably with mannikins to measure the particle and virus exposure from breathing, speaking, and coughing (different airflows) in realistic indoor environmental conditions to reconfirm laboratory findings and modeling studies. Fourth, the airway robustness should be explored further by studying the mucociliary clearance rate and the immune response in the airways in elderlies by elevated indoor air humidity in realistic indoor settings; further to this is the need to study how aggressive outdoor and indoor air pollution might aggravate the robustness of the airways. Furthermore, the potential impact of a high humidity regime in the nose region by wearing face masks should also be explored. Fifth, high ventilation rates for infection control may cause low indoor temperature and dry air in cold season and high indoor temperature in hot season. Optimal ventilation condition for infection control jointly with keeping optimal temperature and air humidity for human health should be explored.

Work performance research has so far focused on temperature, ventilation (CO_2), and emission sources as the mediating factors. Clearly, the influence of the indoor air humidity should be explored and the potential benefit on work performance jointly with the temperature and different ventilation scenario and different odor characteristics.

Author responsibilities

PW conceptualized and edited the manuscript. KA, PW, and PC were leading authors for the section of temperature, air humidity, and ventilation, respectively. All authors have reviewed and accepted the final version.

Declaration of competing interest

The authors declare no financial conflict of interest.

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Modelling faecal pathogen flows and health risks in urban Bangladesh: Implications for sanitation decision making

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ABSTRACT

Faecal-oral infections are a major component of the disease burden in low-income contexts, with inadequate sanitation seen as a contributing factor. However, demonstrating health effects of sanitation interventions – particularly in urban areas – has proved challenging and there is limited empirical evidence to support sanitation decisions that maximise health gains. This study aimed to develop, apply and validate a systems modelling approach to inform sanitation infrastructure and service decision-making in urban environments by examining enteric pathogen inputs, transport and reduction by various sanitation systems, and estimating corresponding exposure and public health impacts. The health effects of eight sanitation options were assessed in a low-income area in Dhaka, Bangladesh, with a focus on five target pathogens (*Shigella*, *Vibrio cholerae*, *Salmonella* Typhi, norovirus GII and *Giardia*). Relative to the sanitation base case in the study site (24% septic tanks, 5% holding tanks and 71% toilets discharging directly to open drains), comprehensive coverage of septic tanks was estimated to reduce the disease burden in disability-adjusted life years (DALYs) by 48–72%, while complete coverage of communal scale anaerobic baffled reactors was estimated to reduce DALYs by 67–81%. Despite these improvements, a concerning health risk persists with these systems as a result of effluent discharge to open drains, particularly when the systems are poorly managed. Other sanitation options, including use of constructed wetlands and small bore sewerage, demonstrated further reductions in local health risk, though several still exported pathogens into neighbouring areas, simply transferring risk to downstream communities. The study revealed sensitivity to and a requirement for further evidence on log reduction values for different sanitation systems under varying performance conditions, pathogen flows under flooding conditions as well as pathogen shedding and human exposure in typical low-income urban settings. Notwithstanding variability and uncertainties in input parameters, systems modelling can be a feasible and customisable approach to consider the relative health impact of different sanitation options across various contexts, and stands as a valuable tool to guide urban sanitation decision-making.

1. Introduction

Faecal-oral infections are a major component of disease burden in low-income contexts. Diarrhoeal disease linked to inadequate sanitation constitutes one percent of the total global disease burden and results in more than 400,000 deaths each year (Prüss-Ustün et al., 2019). Accordingly, sanitation investments by governments and development partners are primarily justified by health improvements. Despite strong theoretical grounds for supposing that sanitation improvements are necessary for health (Cumming et al., 2019), recent major studies

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evaluating the health effects of sanitation interventions have produced inconsistent results (Null et al., 2018; Luby et al., 2018; Humphrey et al., 2019). Concomitantly, in low-income urban contexts there is limited empirical evidence on how best to design interventions and direct available resources to maximise health gains (Mills et al., 2018). This situation compromises the effectiveness of sanitation programming. Significant funds are currently invested to install on-site sanitation systems and to improve emptying and sludge management services in densely populated low-income areas, however the fate and transport of liquid effluent discharging from these systems is often overlooked, despite the related potential health risk (Mitchell et al., 2016). There is therefore a growing recognition of the need to better understand and compare the health impacts of different sanitation options (WHO, 2018), particularly on-site systems (such as septic tanks or small-scale systems), which are given an important place in the emerging city-wide inclusive sanitation (CWIS) approach (Schrecongost et al., 2020).

The imperative to ensure sanitation decisions minimise public health risks in low-income urban settlements will only grow in importance. Globally, more than 600 million people living in urban areas still lack even basic sanitation, and the total urban population is expanding by around 80 million every year (WHO/UNICEF 2019), making it challenging to keep up with sanitation infrastructure requirements. Moreover, the Sustainable Development Goal target that seeks ‘universal access to safely-managed sanitation services’ represents an elevated ambition compared with previous global targets, and necessitates safe management of excreta along the entire sanitation chain from containment to final re-use or disposal (WHO/UNICEF 2018).

The sanitation challenges in urban Bangladesh are emblematic of those faced by many large cities in low- and middle-income countries. Dhaka, the focus of the study described in this paper, has all but eliminated open defecation, including from slums and informal settlements (BBS, 2015). Yet, despite significant investment in sanitation infrastructure, it is estimated that more than 99% of the city’s wastewater is discharged without treatment into drains and waterways (Ross et al., 2016). Around one-third of Dhaka’s population use pour-flush toilets that discharge directly to drains, with this number increasing to 40–50% amongst the poorest two quintiles (WSUP 2018). A further 20% use on-site septic tanks, which commonly discharge effluent into drains and surface water bodies, since dense clay soils prevent infiltration (DWASA, 2011). This situation poses a concerning health risk, as signified by high levels of faecal indicator bacteria in Dhaka’s open drains (Amin et al., 2019), as well as country-level disease burden estimates that attribute more than 23,000 deaths each year to inadequate water, sanitation and hygiene (Prüss-Ustün et al., 2019).

Global efforts to understand health effects of sanitation interventions have largely been in the form of impact evaluations. While on the whole such studies suggest sanitation improvements can reduce the risk of diarrhoeal disease (Norman et al., 2010; Wolf et al., 2018), individual study results vary. Randomized control trials (RCTs) and other quasi-experimental approaches applied to assess sanitation impacts have robust internal validity, but also come with limitations, particularly for densely populated urban areas. They produce results that may not be generalisable, are costly and struggle to disentangle complex urban sanitation contexts, in which people come into contact with excreta from multiple sources in multiple ways (Wang et al., 2017; Amin et al., 2019). Most recently, the inconsistent results produced by rigorous RCTs in rural Bangladesh, Kenya and Zimbabwe raised questions about the effect of sanitation investments, even when made alongside improvements in water supply and hygiene behaviours (Stewart et al., 2018; Luby et al., 2018; Humphrey et al., 2019). The equivocal results to date have been attributed to a range of factors, one of which is the importance of multiple and context-dependent pathways for the transmission of faecal pathogens (Cumming et al., 2019), calling our attention to examine these pathways in greater depth.

Various tools and approaches have emerged in recent years that characterise how excreta and its associated microorganisms move through the urban environment, though they do not estimate resultant health risks. Shit Flow Diagrams (SFDs) are increasingly used to illustrate the flow of both safely and unsafely managed faecal sludge and wastewater effluent in urban areas for advocacy purposes (Peal et al., 2014). SFDs highlight the scale of potential exposure risks at a city-wide scale. Limited understanding of pathogen removal by on-site systems – which are widespread in low-income urban areas – makes it difficult to move from a SFD to a more detailed risk-based sanitation planning process. The extensive variation in on-site sanitation technology, construction, management, discharge arrangements, and local context (e.g. soil type, groundwater depth etc.) results in different measured and predicted performance outcomes, and the potential for pathogen transmission and exposure via multiple pathways is not well understood. The recent SaniPath studies and exposure assessment tool examined a range of exposure pathways, but this approach did not extend to estimating health impacts of different sanitation interventions (Robb et al., 2017; Wang et al., 2017; Raj et al., 2020). Other urban sanitation planning tools exist, but a recent review noted their limitations in addressing this complexity, with some tools omitting health considerations altogether (Mills et al., 2018). What has been lacking, therefore, is an approach that can link sanitation options and scenarios with resultant health risks.

Systems modelling presents an alternative, but complementary, method for examining and predicting the context-specific health impacts of sanitation interventions (Mills et al., 2018). Systems modelling has been widely used to analyse and understand a range of complex cause-effect systems, including in fields of environmental health, public health and water management (Benedetti et al., 2013; Carey et al., 2015; Currie et al., 2018). Applying a systems modelling approach to sanitation interventions has the potential to link understanding of the magnitude of pathogen containment or release into the environment by various sanitation systems with potential for exposure and likelihood of illness, which in turn can better inform sanitation investments. Modelling the transport and fate of pathogens in water bodies and waterways has been carried out in a variety of contexts and scales (Haydon and Deletic 2006; Whitehead et al., 2016; Kroeze et al., 2016). Likewise, there is an emerging body of literature assessing exposure and risks associated with faecal pathogens in low-income urban areas, particularly through quantitative microbial risk assessment (QMRA) (Labite et al., 2010; Yapo et al., 2014; Katukiza et al., 2014). However, the extent to which these assessments have measured enteric pathogen concentrations in the environment has been limited. Combining these two approaches with sufficient, high-quality primary data, has been identified as a key priority for understanding health risks associated with faecal pathogens (Hofstra et al., 2019). Such systems modelling has the potential to support analysis of complexity, characterise causal pathways that might otherwise be difficult or costly to measure, identify key inter-relationships and evidence gaps, and evaluate multiple scenarios for sanitation service provision – including those that are novel or counter-intuitive (Mills et al., 2018).

In the context of a low-income neighbourhood in Dhaka, this paper applies a systems modelling approach to understand the local sanitation situation and its impact on health risks in relation to exposure to open drains. The specific objectives of this case study were to: (a) develop, apply and validate a systems modelling approach to inform sanitation infrastructure and management decision-making that weighs public health impacts; and (b) identify key gaps in the evidence base required to model pathogen flows and related health risks in urban environments. In so doing, the study presents a site-specific application of a conceptual approach outlined by Mills et al. (2018),[1] and seeks to address the lack of available tools that link sanitation options with health risks. The modelling focused on the flow of, and exposure to, five faecal pathogens and a faecal indicator bacteria in a bounded case study site, and explored a range of sanitation options and management scenarios. The intention of the work was to provide a health-based metric that can be used alongside other considerations – such as cost, environmental impacts, and potential for resource recovery – in a multi-criteria decision support tool.

2. Methods

2.1. Study site

The study focussed on a low-income neighbourhood in Mirpur, Dhaka. The site selection was based on five key criteria. Three criteria (high population density, low-income status, likely high exposure via open drains and surface water) were applied to ensure the study site was broadly representative of settings commonly found in low-income urban neighbourhoods in low- and middle-income countries. Two criteria (variation in sanitation technologies, and relatively uncomplicated hydraulic/drainage characteristics) were applied so the modelling could generate and compare results across different sanitation technologies, whilst simplifying hydraulic aspects of the modelling.

The chosen study site – which consisted of four parallel roads – was a contained catchment with no (or very limited) inflows of wastewater or excreta from elsewhere (Fig. 1). The eastern side was bounded by a main road, which represented the uppermost part of the catchment, while the western side of the site was bounded by a canal, which received all the wastewater via open drains from the four roads. The site's four roads were configured in an east-west direction (160–250m in length), with open drains running parallel along both sides of each road (average drain width: 30 cm). In two of the roads (Road B and Road D), the parallel drains converged into a single drain before the point of discharge into the receiving canal. Although slightly separated from the other roads, Road A was included in the study site due to its high coverage of septic tanks, which allowed for a useful point of comparison to Roads B, C and D. The road immediately north of Road D was initially included in the study due to the presence of two anaerobic baffled reactors (ABRs); however, this road had to be excluded because the ABRs were decommissioned just prior to the commencement of sampling. Instead, data collection for ABRs was conducted at a separate site (see Amin et al., 2020 for further information).

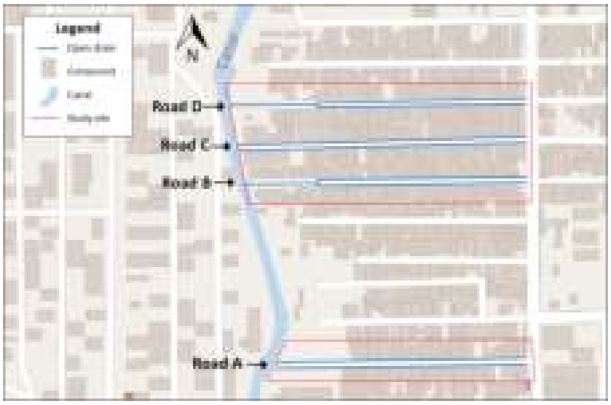

Fig. 1. Layout of four roads in the study site (bounded by dotted red perimeter). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The study site had a population of 4792 people living in 1493 households, which in turn were grouped into 176 compounds (Table 1) (80% government-owned compounds, 20% privately-owned). Most compounds were situated within 1 m of an open drain. Each compound included a sanitation facility. Pour-flush toilets discharging directly to drain (with no containment) were the most common sanitation facility, used by 71% of the population. One quarter of the population used pour-flush toilets with a septic tank[2] (all of which then discharged effluent into the drain), with road-wide coverage of septic tanks[3] ranging from 3% to 79% of the population. Almost all compounds had a metered water supply from Dhaka's municipal utility.

2.2. Infrastructure assessment and household survey

A household survey and infrastructure census were conducted to capture data for key modelling inputs. The infrastructure census identified and mapped all sanitation, water, and wastewater infrastructure in the study site, included a comprehensive enumeration of compounds and population, captured water meter data, and measured flowrates in each open drain. The household survey covered 350 households (approximately 30% of the population in the study site) and collected information about water and sanitation facilities and practices, exposure behaviours, and prevalence of diarrhoea. To estimate exposure frequency, each respondent was asked how many times they and their children came into contact with a drain in the previous week. This allowed calculation of separate exposure event distributions for adults and children (see Fig. S3 in Supplementary Material).

Table 1
Characteristics of study site.

	Road A	Road B	Road C	Road D	Total
Population	970	1194	1277	1351	4792
Number of households	357	344	404	388	1493
Number of compounds	34	43	48	51	176
Average household size (persons)	2.7	3.5	3.2	3.5	3.2
Population by age group					
Adults (>18 years) (%)	62	62	62	62	62
Children (5–17 years) (%)	24	25	24	24	24
Children (<5 years) (%)	14	14	14	14	14
Sanitation facilities					
Septic tanks (tank only, effluent to drain) (%)	79	11	3	15	24
Toilet direct to drain (%)	17	89	88	79	71
Other (%)[a]	4	0	9	6	5
Drinking water piped to compound (%)	100	89	98	100	97
% of compounds within 1m of open drain (%)	93	65	85	62	75
Avg. drain width (cm)	28	31	30	31	30

Source: Household survey and infrastructure census (described below). [a]'Other' sanitation facilities were single-chamber holding tanks or tanks of unknown type.

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[1] Although it is possible to define a tolerable health risk and then work backwards to identify acceptable sanitation solutions, the purpose of this study was to compare the predicted impact of different technologies and management strategies in a low-income urban context where physical, financial and social constraints present a range of trade-offs and require incremental improvements.

[2] These septic tanks were constructed by non-governmental organisations and consisted of two chambers with a baffle between the chambers.

[3] 'Road-wide' coverage of septic tanks refers to the percentage of the population in a particular road using sanitation facilities with a septic tank.

2.3. Choice of pathogens and transmission pathways

After reviewing enteric infection literature focussed on Dhaka and consulting an expert advisory panel of sanitation and public health specialists (see Acknowledgements), five reference pathogens were chosen: three bacterial pathogens (*Shigella, Vibrio cholerae, Salmonella* Typhi), one virus (norovirus GII), and one protozoa (*Giardia*).[4] Additionally, *E. coli* were selected as faecal indicator bacteria (FIB). Given the different patterns of removal, inactivation and survival of different pathogen types in sanitation systems and environmental compartments, representatives from each of the three pathogen groups were sought. When selecting reference pathogens, consideration was given to local infection prevalence, data availability to support modelling (including fate and transport, and dose-response), availability of sensitive and specific methods for detection in environmental samples and the likely importance of sanitation for control. Studies of diarrhoea patients in Dhaka have found a prevalence of infection of around 16% for Norovirus GII (Rahman et al., 2016), 12% for *V. cholerae* (Das et al., 2013), 8% for *Giardia* (Haque et al., 2005), and 3% for *Shigella* (Das et al., 2013); while the annual incidence rate for typhoid has been estimated at around 2 per 1000 persons (Naheed et al., 2010).

The study focussed on exposure to faecal pathogens via open drain water as a primary transmission pathway, as this was a key pathway relevant to sanitation in the study site, as in other low-income areas of Dhaka (Amin et al., 2019). Open drains were ubiquitous in the study neighbourhood, and young children were frequently observed to be sitting and playing near the drains. Ingestion of open drain water was modelled assuming hand contact with the drain water (either directly or via an object) would result in hand contamination and subsequent hand-to-mouth transfer of microorganisms attached to the hand (Wang et al., 2017). Pathways via groundwater contamination were not relevant because groundwater in Mirpur is deep (Akhter and Hossain 2017), and households are served by a municipal piped water supply. This study did not examine additional pathways for faecal-oral transmission of enteric pathogens (e.g. water supply, food hygiene, soil, person-to-person), although we recognize their importance and the need for wider multi-sectoral interventions and environmental modification to control transmission of faecal pathogens (Robb et al., 2017; Cumming et al., 2019).

2.4. Modelling approach

The model consisted of two connected sub-models following the logic previously outlined by Mills et al. (2018): (i) pathogen fate-and-transport sub-model to estimate reference pathogen and indicator concentrations at specific locations, and (ii) exposure-and-risk sub-model (Fig. 2). Model inputs comprised a combination of estimates based on relevant scientific literature as well as primary data collected from the study site (household survey and infrastructure census). Eight sanitation options were tested in the model to predict their expected effect on concentrations of microbes in wastewater and subsequent health risks from exposure. The model also tested the effects of different scenarios relating to climate, disease prevalence, and faecal sludge management.

2.4.1. Pathogen fate and transport sub-model structure and approach

The stochastic fate and transport sub-model was written in Python 3 and consisted of 165 nodes (representing compounds, drains and sanitation systems) to model wastewater volume and pathogens (see Fig. S1 in Supplementary Material). Conceptually, the model started with the households (or residents) as the source for pathogens, with pathogens flowing through and/or being removed by, various infrastructure (sanitation systems and drains) across the study site. Household survey results indicated that for 96% of households, faeces of young children were disposed of via the same sanitation system used by adult members of the household, and hence when assigning pathogen inputs by sanitation type the model did not differentiate between adults and children. Pathogen inputs from animals were not included in the model because of the small animal population in the study site, combined with the fact that four of the six target organisms were human specific.[5] The model did not consider possible pathogen inputs via greywater as the purpose was to examine relative outcomes across different sanitation options.

Model input variables included household water and toilet usage by time of day (based on household survey data), faecal mass excretion per person per day (point value = 243g) (Rose et al., 2015), and pathogen-specific prevalence of infection (Table 2). To account for the diurnal distribution in water usage, the model was run for three days with a 10-min time step. Stochastic inputs were modelled using random sampling (1000 Monte Carlo simulations). Pathogens and FIB were assumed to be uniformly mixed within each node. Concentrations from the final 24-h period (144 steps, allowing the first 2 days for burn-in) were pooled to create one random sample across the study site. A zero-inflated skewed normal distribution was then fitted to the random sample. In order to understand the impact on populations 'downstream' from the study site, the model also calculated the quantity of pathogens/FIB discharged into the canal.

Pathogens were removed from the system in three ways:

i) A log reduction value (LRV) was applied for the relevant sanitation system (Table 2 and Tables S6–S9 in Supplementary Material) at each time step, based on its expected performance in removing pathogens.
ii) A quantity of pathogens was removed at each time step according to literature-based assumptions on pathogen die-off in surface waters (see Table S10 in Supplementary material).
iii) A quantity of pathogens was removed at each time step according to literature-based assumptions on pathogen settling (see Table S11 in Supplementary material). Estimates for pathogen settling in drains considered the proportion of pathogens that might attach to particulate matter and the proportion in a free phase, with settling velocities applied to each fraction (Cizek et al., 2008).

In order to evaluate the plausibility of the estimated concentrations and the usefulness of the modelling approach for filling in gaps in environmental data, the random sample of estimated pathogen/indicator concentrations was compared with results from an environmental monitoring program conducted at the same site (Amin et al., 2020).

2.4.2. Exposure and risk sub-model structure and approach

The exposure-and-risk sub-model started with the predicted pathogen concentrations (from the fate-and-transport sub-model) and applied a QMRA with input parameters for exposure (contact frequency, ingestion volume), dose-response and probability of illness, to estimate the number of cases of illness and overall disease burden in terms of disability-adjusted life years (DALYs). Model inputs are summarised in Table 2 and described more fully in Supplementary Material. The model was focused on the impact of sanitation via exposure to open drains (with ingestion associated with either direct contact with drain water or contact with objects submerged in drains). Ingestion volume was estimated based on a methodology applied in previous SaniPath studies (Gretsch et al., 2016), which considered exposure frequency (based on data from the household survey) and range of variables influencing the degree to which drain water might be ingested via hands (see Tables S13

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[4] Resource limitations prevented inclusion of a helminth.

[5] In total, compounds in the study site housed 12 cows, 1 goat, 1 cat, 94 chickens and 64 pigeons. Of the six target organisms, only *E. coli* and *Giardia* are not human specific.

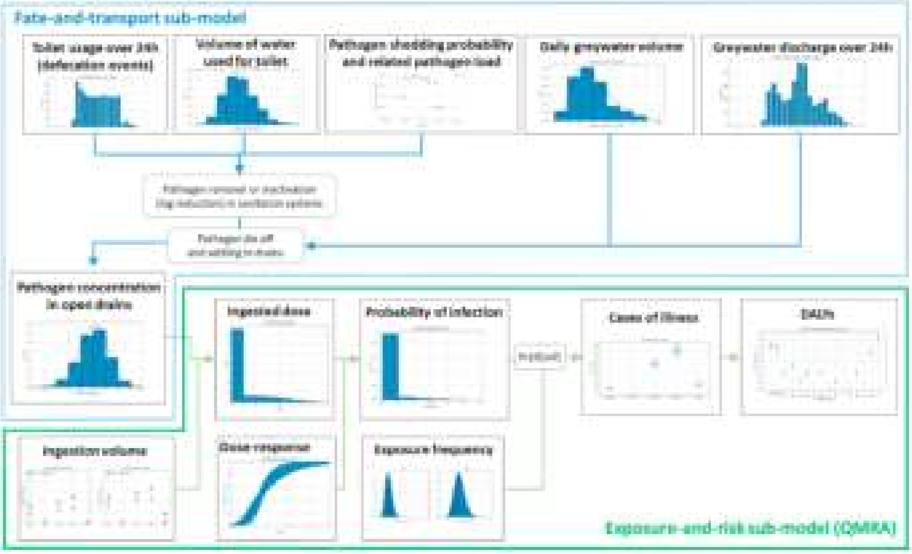


Fig. 2. Schematic of modelling approach and sub-models.

and S14). Exposure frequencies were inputted as a negative binomial distribution based on how many times survey respondents reported that they and their children had come into contact with an open drain in the previous week (see Fig. S3). Converting cases of illness to disability-adjusted life years (DALYs) was done by calculating the sum of years lived with disability (YLD) and the years of life lost (YLL) due to premature mortality, drawing on Global Burden of Disease studies for estimating disability weight, duration and distribution of cases across different levels of severity (Troeger et al., 2018; Stanaway et al., 2019) as well as Dhaka-based studies for case fatality estimates and the associated years of life lost (Tables S15 and S16) (Paul et al., 2016; Yu et al., 2018) The scope for examining health impact was contained to the study site population, and the risks to the wider population could only be characterised by quantifying pathogens exported (outflow) into the nearby waterway, to which other downstream populations may be exposed.

2.4.3. Sanitation options

The sanitation options assessed are outlined in Table 3 and illustrated in Fig. 3. Two key considerations informed the choice of these options: (i) realistic constraints in a low-income Dhaka context, and (ii) options representing a variety of scales. The realistic constraints included cost and complexity (leading to exclusion of high-tech options and inclusion of interim solutions such as deepening and covering drains); soil type (e.g. dense, clay soils that prevent infiltration of on-site effluent (DWASA, 2011)); and cultural appropriateness (e.g. preference for water-based sanitation). The options were drawn from sanitation technologies already present throughout Dhaka. Exceptions were Options 3 and 4 which involved decentralised constructed wetlands, solutions that are increasingly adopted in urban environments (ElZein et al., 2016; Russo et al., 2019; Stefanakis 2019); and Option 7 comprising sealed vaults, associated with container-based sanitation, which is also increasingly being adopted elsewhere (Russo et al., 2019). Variety in technology scale was intended to reveal differences in pathogen transmission via open drains, and included household, communal (up to ~400 households) and whole road (~1200 households) systems, as well as wastewater piped to centralised wastewater treatment beyond the study site. The options were selected in consultation with both local stakeholders and the expert advisory panel. 'Managed' and 'unmanaged' variants of each option were proposed based on the level of faecal sludge management (FSM) and other common management issues such as blockages and overflows that occur in practice. Detailed assumptions underpinning managed and unmanaged cases (and their associated LRVs) are described in Tables S6–S9 in Supplementary Material.

2.4.4. Scenarios and sensitivity analysis

The effects of six scenarios were examined: four climate-related scenarios (dry season, wet season but not raining, wet season and raining, wet season and flooding), a short-term sudden increase in infection/disease prevalence (outbreak), and the dumping of septic tank sludge in a drain (sludge dumping). In addition, sensitivity analysis was conducted to assess the effect of key parameters on the predicted impacts of different sanitation options. Plausible maximum and/or minimum values were inputted for: (i) disease prevalence, (ii) shedding load, (iii) immunity, (iv) ingestion volume, (v) exposure frequency (vi) LRVs of sanitation systems. The details of the scenarios and maximum/minimum values tested for each parameter are presented in Tables S4, S5 and S9 in Supplementary Material.

2.5. Environmental microbiology

In order to validate the transport and fate component of the model (see Section 2.4.1), faecal pathogen and FIB concentrations in drain water were measured at various locations in the study site. Samples were also collected from flood waters, drain sediments, the canal receiving all drain water, as well as septic tanks and ABRs (sludge, supernatant and effluent) to assess the plausibility of LRV assumptions for sanitation systems. Because the ABRs in the study site were decommissioned just prior to data collection, sampling of ABR sludge, supernatant and effluent took place in a neighbouring area (Amin et al., 2020). In total, 150 environmental samples were collected and both faecal pathogen and indicator concentrations were measured. *E. coli* concentrations were assessed using IDEXX Quanti-tray 2000 (IDEXX Laboratories, Westbrook, Seattle, WA), a method which quantifies the most probable number (MPN) of *E. coli* per 100 ml, while pathogens were detected and quantified using singleplex quantitative PCR. In-depth descriptions of the environmental sampling and laboratory methods can be found in an accompanying paper (Amin et al., 2020)).

3. Results

3.1. Environmental microbiology findings

The detailed findings from all the environmental samples are presented elsewhere by Amin et al. (2020), however the summarised results are presented in Table 4. Pathogens of all types were detected in almost

Table 2
Parameters included in model.

Variable	Parameter	Source(s)
Prevalence of diarrhoea (in previous week)	7.5%	Household survey
Infection state of each individual (1 = infected, 0 = not infected)[a]		
V. cholerae	Bernoulli ($p = 0.0043$)	Weil et al. (2009, 2014); Das et al. (2013)
S. Typhi	Bernoulli ($p = 0.0003$)	Ames and Robins (1943); Naheed et al. (2010); Gunn et al. (2014); Darton et al. (2016); Gauld et al. (2018)
Shigella	Bernoulli ($p = 0.0030$)	Das et al. (2013); George et al. (2015)
Norovirus GII	Bernoulli ($p = 0.0149$)	Partridge et al. (2012); Milbrath et al. (2013); Rahman et al. (2016); Wu et al. (2019)
Giardia	Bernoulli ($p = 0.040$)	Karim et al. (2018)
Shedding load ($\log_{10}$ per gram of faeces)[b]		
E. coli	Normal ($\mu = 8, \sigma = 0.5$)	Wright (1982); Mara and Oragui (1985)
V. cholerae	Normal ($\mu = 8, \sigma = 0.5$)	Uddin et al. (2013)
S. Typhi	Normal ($\mu = 6, \sigma = 0.5$)	Expert opinion
Shigella	Normal ($\mu = 8, \sigma = 0.5$)	Assumption
Norovirus GII	Normal ($\mu = 7.5, \sigma = 0.5$)	Kirby et al. (2014); Teunis et al. (2015); Sabrià et al. (2016)
Giardia	Normal ($\mu = 5.5, \sigma = 0.5$)	Danciger and Lopez (1975)
Probability of illness given infection		
V. cholerae	0.53	Weil et al. (2014)
S. Typhi	0.70	Darton et al. (2016)
Shigella	0.19	George et al. (2015)
Norovirus GII	0.55	Teunis et al. (2008); Kirby et al. (2014)
Giardia	0.40	Ortega and Adam (1997); Platts-Mills et al. (2015)
Faecal mass (grams per day)	243	Rose et al. (2015)
Water usage (litres per day)	Road A: Skew normal ($\mu = 56.8, \sigma = 121.3, \alpha = 4.9$) Road B: Skew normal ($\mu = 25.4, \sigma = 99.2, \alpha = 5.0$) Road C: Skew normal ($\mu = 53.6, \sigma = 106.1, \alpha = 4.8$) Road D: Skew normal ($\mu = 41.4, \sigma = 120.0, \alpha = 4.6$)	Water meter data
Blackwater as proportion of water use	Normal ($\mu = 0.061, \sigma = 0.0072$)	Household survey
Sanitation system LRVs [managed, unmanaged]		
Holding tank	Bacteria [0.5,0.25], Virus [0.25,0.125], Protozoa [1,0.5]	See Tables S6–S9 in Supplementary Material
Septic tank	Bacteria [1,0.5], Virus [0.5,0.25], Protozoa [2,1]	
ABR	Bacteria [1,0.5], Virus [0.5,0.25], Protozoa [2,1]	
Constructed wetland	Bacteria [2,1], Virus [1.5,0.75], Protozoa [1.5,0.75]	
Waste stabilisation pond	Bacteria [6], Virus [4], Protozoa [4]	
Exposure frequency		
Adults	Negative binomial ($N = 3, P = 0.958$)	Household survey
Children	Negative binomial ($N = 1, P = 0.795$)	Household survey
Ingestion	Various (see Tables S13–S14 in Supplementary Material)	Various
Dose-response		
V. cholerae	Beta-Poisson ($\alpha = 2.5 \times 10^{-1}$, $N_{50} = 2.43 \times 10^{2}$)	Hornick et al. (1971)
S. Typhi	Beta-Poisson ($\alpha = 1.75 \times 10^{-1}$, $N_{50} = 1.11 \times 10^{6}$)	Hornick et al. (1966, 1970)
Shigella	Beta-Poisson ($\alpha = 2.65 \times 10^{-1}$, $N_{50} = 1.48 \times 10^{3}$)	DuPont et al. (1972)
Norovirus GII	Fractional Poisson ($P = 0.722$, $\mu = 1106$)	Messner et al. (2014)
Giardia	Exponential ($k = 1.99 \times 10^{-2}$)	Rendtorff (1954)
DALYs – diarrhoeal pathogens		
Distribution of cases by severity	Mild (0.243), Moderate (0.617), Severe (0.14)	Troeger et al. (2017)
Duration by severity (years)	Mild (0.0115), Moderate (0.0115), Severe (0.0115)	Troeger et al. (2017)
Disability weight by severity	Mild (0.074), Moderate (0.188), Severe (0.247)	Troeger et al. (2017)
Case fatality	0.001%	Paul et al. (2016)
Years of life lost per fatality	55	Paul et al. (2016)
DALYs – typhoid		
Distribution of cases by severity	Moderate (0.35), Severe (0.43), Severe with GI bleeding (0.05), Severe with other abdominal complications (0.17)	Stanaway et al. (2019)
Duration by severity (years)	Moderate (0.038), Severe (0.079), Severe with GI bleeding (0.076), Severe with other abdominal complications (0.079)	Stanaway et al. (2019)
Disability weight by severity	Moderate (0.051), Severe (0.133), Severe with GI bleeding (0.133), Severe with other abdominal complications (0.324)	Stanaway et al. (2019)
Case fatality	0.3%	Yu et al. (2018)
Years of life lost per fatality	32	Yu et al. (2018)

[a] Point prevalence of infection for *V. cholerae*, *shigella* and norovirus GII estimated by multiplying prevalence of infection among diarrhoeal patients visiting medical facilities in Dhaka by the proportion of population with diarrhoea, adjusting for duration of symptoms, duration of shedding, and probability of illness given infection. Point prevalence of infection for *S.* Typhi was based on an estimate of typhoid incidence in Dhaka, adjusting for duration of shedding, chronic carriage, and probability of illness given infection. Point prevalence of infection for *Giardia* based on a cross-sectional assessment of stools in Dhaka.[b] Applied equally to the whole population. [c]*Salmonella typhimurium* used as a proxy for *S.* Typhi.

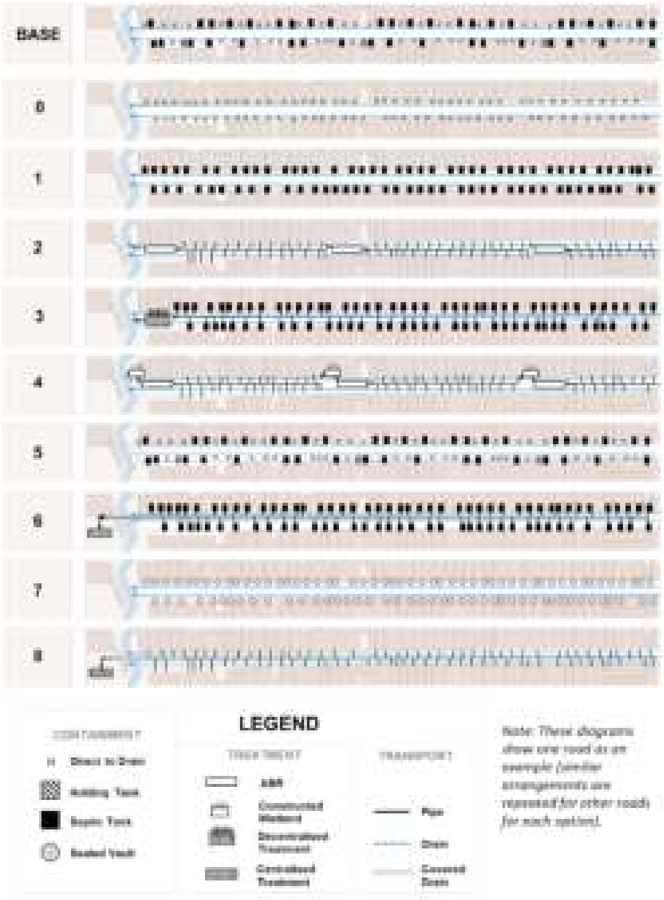
all sample types. *Shigella* and *V. cholerae* were the most commonly detected pathogens in drain samples (100% of samples), followed by norovirus GII (67%), *Giardia* (50%) and *S.* Typhi (27%). *Giardia* and *S.* Typhi were more prevalent in the wet season, though the converse was true for norovirus. *E. coli* had the highest geometric mean concentration in drain water, followed by *Shigella*, *V. cholerae*, *Giardia*, norovirus GII, and *S.* Typhi.

3.2. Comparison of sanitation options

Modelled disease burden associated with faecal pathogen exposure

Table 3
Sanitation options examined by the model.

Option	Description	Managed	Unmanaged
Base case	**Base case**: Represents the current sanitation infrastructure in the study site (combination of septic tanks, holding tanks and toilets discharging directly to drains).	Optimally managed holding tanks and septic tanks (regularly emptied and maintained)	Holding tanks and septic tank systems overloaded, unmaintained and not emptied. (represents the current situation).
Option 0	**No containment**: Hypothetically remove all sanitation systems (so all toilets discharge to drains) (included as a reference point)	NA	NA
Option 1	**Septic tanks**: Full septic tank coverage for all household compounds (two-chamber tank only without soak-away infiltration), septic tank effluent flows direct to drains	Optimally managed septic tanks (regularly emptied and maintained)	Septic tank systems overloaded, unmaintained and not emptied.
Option 2	**Communal primary treatment**: All toilets discharge to closed sewer and piped to decentralised primary treatment in anaerobic baffled reactors (ABRs) (three ABRs per road, approximately 400hh per ABR) which then discharge to the drain	Optimally managed ABR (regularly emptied and maintained)	ABR overloaded, unmaintained and not emptied.
Option 3	**Septic tanks with secondary treatment**: Full septic tanks coverage for all household compounds. All septic effluent collected and piped through small bore sewers to decentralised secondary treatment (constructed wetland) at the end of each road (for approx. 1200hh) discharging into adjacent canal	Optimally managed septic tanks (regularly emptied and maintained) and constructed wetland (proactively maintained)	Septic tanks overloaded, unmaintained and not emptied. Constructed wetland unmaintained, with clogged filter media, blocked or overflowing, plants unattended.
Option 4	**Communal primary and secondary treatment**: All toilets discharge to closed sewer and piped to a decentralised primary and secondary treatment (three ABR and constructed wetlands per road, approximately 400hh per system), which then discharge to drain	Optimally managed ABR (regularly emptied and maintained) and constructed wetland (proactively maintained)	ABR may be overloaded, unmaintained and not emptied. Constructed wetland unmaintained, with clogged filter media, blocked or overflowing, plants unattended.
Option 5	**Deepen and cover drains**: Sanitation systems remain as per base case but the open drains are all deepened and covered	Regularly maintained and flushed drains	Blockages (e.g. with solid waste and faecal waste) create overflows into the road as well as breakage of covers
Option 6	**Septic tanks with small-bore pipe to centralised tertiary treatment**: Full septic tank coverage with effluent piped through shallow small-bore sewer to centralised secondary and tertiary treatment (beyond the study boundary)	Optimally managed septic tanks and well-maintained small-bore sewer.	Septic tanks overloaded, unmaintained and not emptied, and small-bore sewer with broken pipes or overflowing into drains or road.
Option 7	**Fully sealed vaults**: All toilets discharge to fully sealed vaults or containers (with contents tankered to centralised faecal sludge treatment)	Optimally managed and emptied vaults (frequently safely emptied)	Poor emptying practices and broken tanks leading to some direct discharge into the open drains
Option 8	**Sewer system to centralised tertiary treatment**: Toilets discharge to a closed sewer and conveyed to centralised secondary and tertiary treatment (beyond the study boundary)	Optimally managed and maintained sewerage system	Poor maintenance and blockages result in local sewerage overflows into open drains or road



Note: These diagrams show one road as an example (similar arrangements are repeated for other roads for each option).

Fig. 3. Schematic of sanitation options.

via open drains varied widely under the different sanitation options (Fig. 4). Under the base case ('Base-UM'), the model estimated an annual disease burden associated with the five target pathogens to be 1.3 DALYs per 1000 people (540 cases of illness per 1000 persons per year). As a point of comparison, reverting all households to toilets that discharge

Table 4

Prevalence and mean $\log_{10}$ concentration per 100 ml for faecal pathogens and faecal indicator bacteria (*E. coli*) by sample type.

Sample type	n	FIB (*E. coli*)		Norovirus GII		*V. cholerae*		*Shigella*		*S.* Typhi		*Giardia*	
		% +ve	Mean	% +ve	Mean	% +ve	Mean	% +ve	Mean	% +ve	Mean	% +ve	Mean
Drain water	30	100	7.2	67	3.5	100	4.8	100	4.9	27	2.5	50	4.0
Canal water	4	100	6.9	0	–	75	3.6	100	4.0	50	2.8	0	–
Flood water	6	100	5.0	33	4.7	67	4.5	67	4.3	17	–	50	3.3
Septic sludge	10	100	6.1	90	6.5	0	–	70	5.3	10	4.7	0	–
Septic supernatant	8	100	5.9	25	2.5	0	–	13	3.5	0	–	0	–
Septic effluent	22	100	6.8	64	4.6	45	3.4	95	3.3	0	–	18	3.5
ABR sludge	8	100	8.0	100	7.1	63	5.9	100	6.9	0	–	25	7.1
ABR supernatant	7	100	7.9	71	4.2	57	3.7	100	4.5	0	–	29	3.3
ABR effluent	7	100	8.0	100	5.1	86	4.2	100	5.0	29	2.7	57	3.8

Note: Mean values represent the geometric mean and are based only on the positive samples.

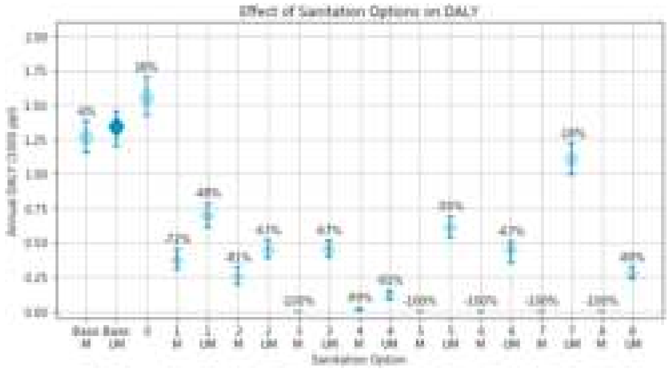


Fig. 4. Modelled effect of sanitation options on annual DALYs (relative to base case unmanaged – base-UM).

Note: Numbers above violin plots refer to percentage change in DALYs relative to the *unmanaged* base case. Base = sanitation status quo in study site; Option 0 = no containment (direct to drain); Option 1 = septic tanks; Option 2 = communal treatment in ABRs; Option 3 = septic tanks with effluent treated in constructed wetlands; Option 4 = communal ABRs and constructed wetlands; Option 5 = deepen and cover drains; Option 6 = septic tanks with centralised tertiary treatment offsite; Option 7 = fully sealed vaults (contents regularly removed by tanker and treated offsite); Option 8 = sewerage to centralised treatment offsite.

directly to drain ('0') was estimated to increase DALYs by 16% compared with the base case. Improving the management of existing septic tank infrastructure through regular emptying ('Base-M') was predicted to have only a 6% reduction in the disease burden for the population within the study site. This minimal impact is because under this scenario more than 70% of the population would still be using toilets discharging directly to the drain. Relative to the base case, comprehensive coverage of septic tanks was associated with a 72% reduction in DALYs when well-managed ('1-M'), and a 48% reduction when poorly managed ('1-UM'). Complete coverage of communal scale ABRs was predicted to have a greater impact of 81% and 67% for managed ('2-M') and unmanaged ('2-UM') situations respectively, since it also reduced exposure through closed pipe conveyance. An option with comprehensive septic tank coverage, with all effluent piped through small bore sewers to decentralised secondary treatment at the end of the roads, eliminated all of the disease burden for the study site population when well managed ('3-M'), since it prevents entry of all pathogens to the drain. However, when the septic tanks were unmanaged ('3-UM'), this option had some residual health risk, albeit still 67% lower than the base case. Communal ABRs installed alongside secondary treatment reduced the disease burden by 99% when well managed ('4-M'), and by 91% when unmanaged ('4-UM'). Deepening and covering all open drains ('5M') and fully-sealed containment systems ('7-M') also reduced the local disease burden associated with poor sanitation to zero when well-managed, though the former option exported high numbers of pathogens to 'downstream' neighbourhoods. Both of these options posed a significant health risk if unmanaged ('5-UM', '7-UM'). Conveyance to centralised treatment ('6M' and '8M') also reduced the local disease burden to zero when well-managed, and by 67% (for '6M') and 80% (for '8UM') when unmanaged.

The results for all sanitation options need to also be considered in light of the exported pathogen load to 'downstream' neighbourhoods (see Fig. 5). Pathogens discharged to the open canal at the boundary of the study site could adversely affect other populations; though it was beyond the scope of this study to quantify those health risks. When well-managed, Options 6, 7, and 8 resulted in the lowest pathogen concentrations in exported wastewater since they avoid any local discharge. This was followed by: (i) Options 3 and 4, which include secondary on-site treatment in constructed wetlands; (ii) Options 1 and 2 comprising primary on-site treatment in septic tanks and ABR respectively; and finally (iii) Option 5, Option 0 and Base Case, which all exported drain water containing high pathogen concentrations (for example, concentration of greater than 5 $\log_{10}$ per 100 mL for *V. cholerae)*. However, when Options 6, 3 and 4 were unmanaged, pathogen concentrations in exported wastewaters were similar to those for unmanaged Options 1 and 2.

The relative contribution of each pathogen to DALYs for each sanitation option is shown in Fig. 6. Under the base case, norovirus GII was predicted to contribute 36% of the disease burden associated with the five target pathogens, followed by *V. cholerae* (35%), *Giardia* (25%), *Shigella* (5%) and *S. Typhi* (<1%). There was little variation in the percentage contribution of *V. cholera*, *Shigella* and *S.* Typhi across different sanitation options, though for a number of sanitation options (1, 2, 3-UM, 4 and 6-UM) the percentage contribution of *Giardia* to the disease burden was reduced, while the contribution of norovirus increased.

Ranges of predicted pathogen concentrations were generally wide – even on the $\log_{10}$ scale – yet predicted cases of illness fell within a relatively narrow band (Fig. 7). In terms of percentage reduction in cases of illness, the pathogen-specific impact of sanitation improvements tended to mirror the sanitation LRVs assigned to each pathogen type. Sanitation improvements had the greatest effect on Giardiasis, reflective of the sanitation system LRVs which were highest for *Giardia*. Cholera and Shigellosis exhibited similar percentage reductions in cases of illness across different sanitation options. The percentage reduction in cases of illness associated with sanitation improvements was lowest for norovirus. The effect of sanitation options on cases of typhoid was difficult to characterise, which is likely an artefact of the lower probability of *S.* Typhi being shed at any particular point in time.

3.3. Model validation

The model predicted a wide range of concentrations for all pathogens and *E. coli*, which generally agreed with empirical observations (Fig. 8). The model estimated concentrations that spanned the majority of observed concentrations for three of five pathogens (*Shigella*, *S.* Typhi, *V. cholerae*) as well as *E. coli*. When norovirus and *Giardia* were detected

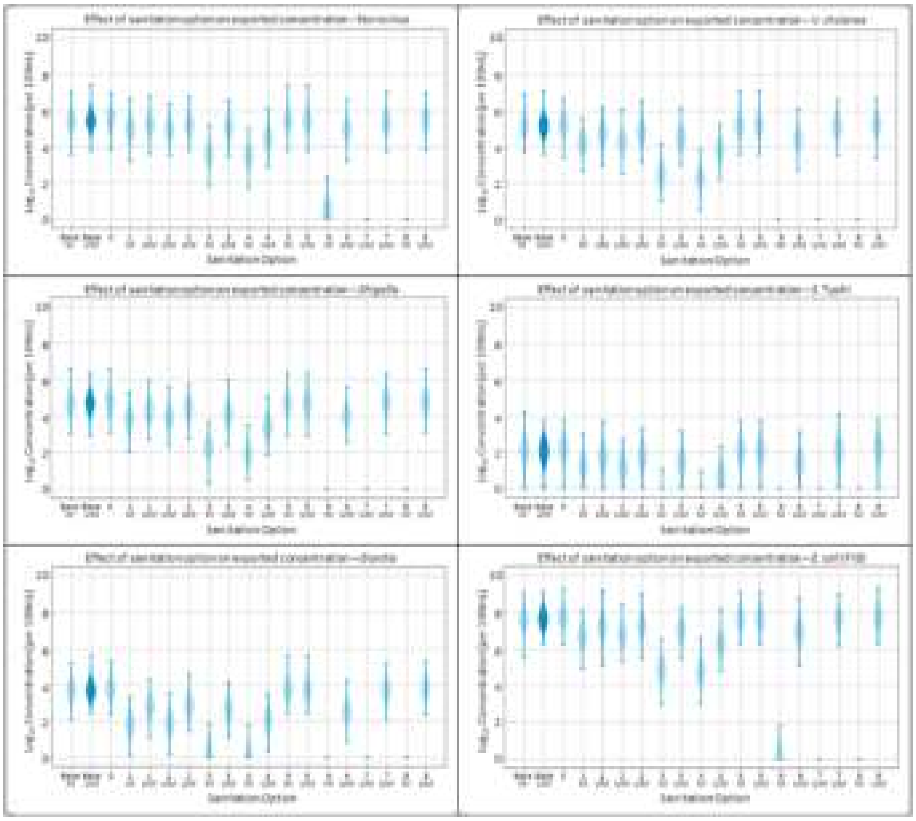


Fig. 5. Predicted concentrations of exported pathogens and FIB in wastewater discharged to canal by pathogen and sanitation option.

Note: Exported pathogen concentrations are in relation to ‘downstream’ communities nearby to the canal, hence Option 8M (well managed sewer system to centralised tertiary treatment) is assigned exported pathogen concentrations of zero, on the assumption that tertiary treatment (and its residual health risk) would occur elsewhere.

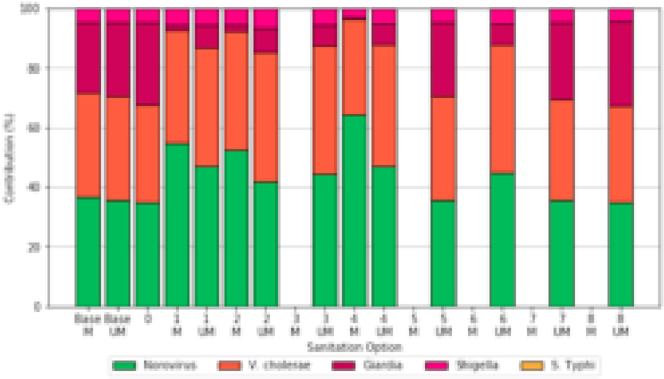


Fig. 6. Relative contribution of each pathogen to DALYs by sanitation option.

in drain water, the observed concentrations for these pathogens fell within modelled distributions. However, the sampling results had a high number of non-detects for *Giardia* and for norovirus that the model failed to reproduce. Conversely, *S.* Typhi was detected more frequently than the model predicted, although the observed concentrations (2–4 $\log_{10}$ concentration per 100 mL) were still within the range the model anticipated. Those pathogens with lower prevalence of shedding among the population but higher shedding load per gram of faeces (*V. cholerae*, *Shigella*) had the widest modelled ranges (0-7 $\log_{10}$ concentration per 100 mL), while the more prevalent microorganisms had narrower modelled ranges (e.g. *E. coli*, norovirus and *Giardia*).

Given the limited literature on LRVs for sanitation systems, it was important to review the chosen LRV assumptions against empirical data. On average, measured pathogen and FIB concentrations in ABR effluent were similar to modelled concentrations, but for septic tanks the measured effluent concentrations were discernibly lower than what the model predicted for three pathogens (those being norovirus, *V. cholerae* and *S.* typhi) (Fig. S4). Measured concentrations in septic tank effluent were lower than in ABR effluent for all five pathogens and for the FIB. While this may indicate differential LRVs, it could also relate to the smaller catchment population represented in septic tank samples (as compared with ABRs), which in turn may lower the probability of infected individuals being within the user population.

The predicted numbers of cases of infection for each pathogen are shown in Fig. S5. Among the five pathogens, norovirus was predicted to cause the highest number of infections annually (927, 36%), followed by *V. cholerae* (904, 35%), *Giardia* (637, 25%), *Shigella* (120, 5%), and *S.* Typhi (<1, <1%). Estimated case numbers for all pathogens were below the total case numbers one would expect from all transmission routes based on the prevalence inputs. Overall, predicted cases of illness from exposure to drains amounted to 30% of the estimated total cases of illness based on prevalence inputs. In other words, the model estimated that 30% of illnesses from the five target pathogens were attributable to exposure via open drains, while the rest of the cases were due to transmission via other exposure pathways. Pathogen-specific ratios were 25% (norovirus GII), 46% (*V. cholerae*), 25% (*Giardia*), 24% (*Shigella*), and <1% for *S.* Typhi. Children under 5 years were predicted to experience a disproportionately high disease burden, accounting for 39% of cases of illness despite constituting only 14% of the population. The proportion of estimated illnesses borne by children under 5 years was relatively similar for norovirus (40%), shigellosis (38%) and cholera (36%), but slightly higher for giardiasis (43%).

3.4. Scenarios and sensitivity analysis

Analysis of six scenarios and sensitivity analysis revealed the importance of several key input parameters in determining the disease burden, though generally speaking the relative effectiveness (rank order) of different sanitation options was not sensitive to changes in input parameters, except for the LRV input parameter.

Among the six scenarios tested, a flooding scenario – which reduces

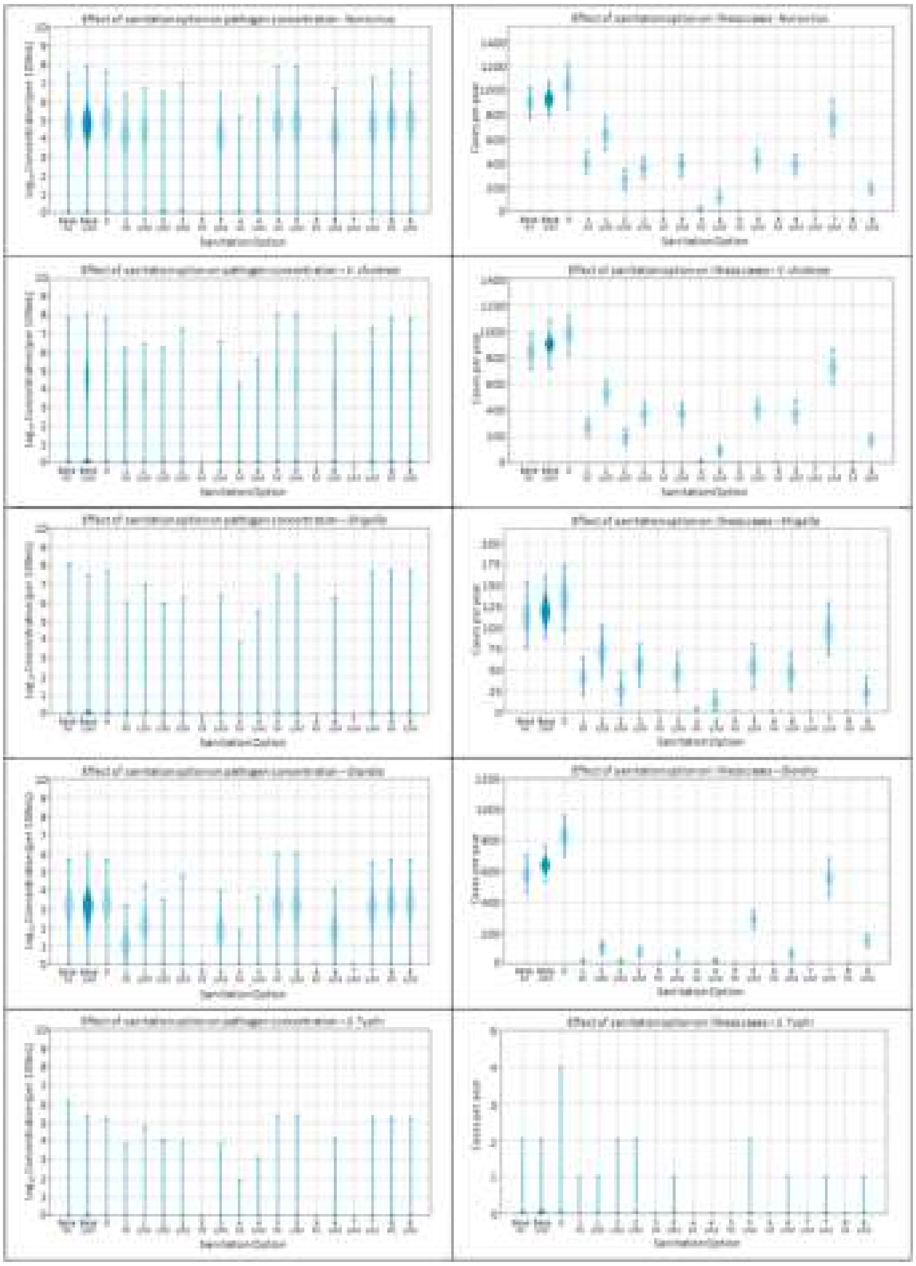


Fig. 7. Modelled impact of sanitation options on pathogen concentration in drains and associated cases of illness per year.

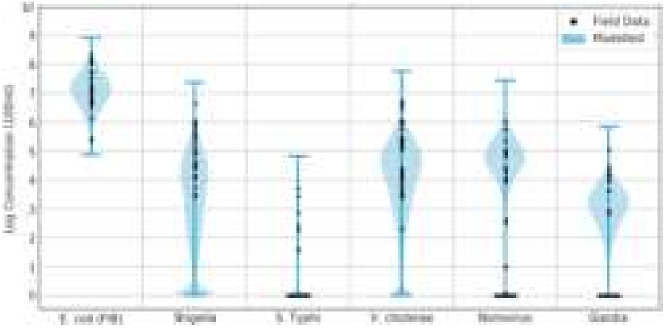


Fig. 8. Faecal pathogen and faecal indicator concentrations in drain water: Modelled vs Observed.

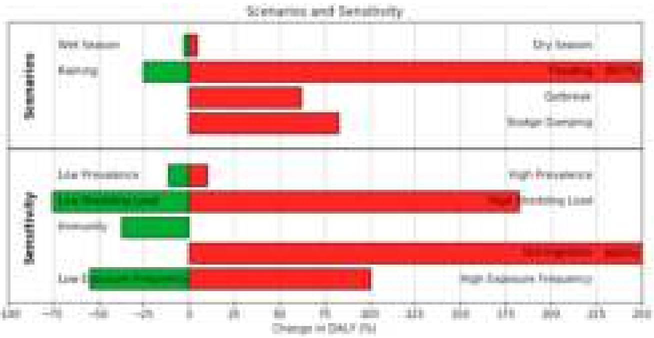


Fig. 9. Relative change in disease burden estimates for selected scenarios and sensitivity analyses for the base case (UM).

the pathogen concentration through dilution, but increases local exposure – had a major effect on disease burden, with base case DALYs increasing by an order of magnitude (Fig. 9). This effect was similar across all sanitation options. Inclusion of sludge dumping in the base case (as typically occurs in relation to on-site options) increased the estimated disease burden by 83%. The health risk associated with open drains under the base case was predicted to increase by 62% during an outbreak scenario when more infected people in the population would be excreting pathogens into the septic tanks and drains; conversely the overall disease burden was predicted to decrease during wet season, especially with moderate raining that did not result in flooding (increased dilution but no change in exposure). The reduced disease burden in wet season is linked to the predominance of norovirus, which was the only pathogen with assumptions suggesting prevalence decreased during this time.

Among the parameters for which sensitivity analysis was conducted, ingestion volume and shedding load emerged as the most influential in terms of impact on disease burden (Fig. 9). Modifying the ingestion volume from a distribution averaging 0.1 mL (base case assumption) to a fixed value of 1 mL (a typical value applied in QMRA studies) (WHO 2016) had a considerable effect on predicted disease burden, increasing the base case DALYs by 664%. However, increasing the ingestion volume in this way did not change the rank order of sanitation options. A one $\log_{10}$ increase in the shedding loads increased the disease burden under the base case by 182%. It should be noted that the effect for shedding may be exaggerated due the deterministic nature of the sensitivity analysis: shedding variables for all pathogens were modified simultaneously, so the figure shows the combined impact of all five shedding variables. In contrast, prevalence changes had a more moderate impact. High prevalence assumptions increased the base case DALYs by 10%. The model results were less sensitive to changes in assumptions about pathogen survival and settling, with maximum and minimum inputs having little impact on modelled concentrations in drains or disease burden.

The rank order of sanitation options in terms of health risk varied little across different scenarios and when substituting key inputs with maximum and minimum values. In other words, the prioritisation of sanitation options in terms of health risk was not sensitive to changes in most input parameters. There was one exception, however: the relative effectiveness of different sanitation options did change when applying different LRV assumptions to reflect how well or poorly systems were managed (Fig. 10).

4. Discussion

The discussion covers three main areas: 1) the feasibility of the systems modelling approach; 2) implications for sanitation interventions and decision-making; and 3) key gaps in evidence, including important areas for further research and development.

Feasibility of the systems modelling approach: This study demonstrates the value and feasibility of a systems modelling approach for comparing sanitation options and estimating associated health risks. Modelled concentrations for most pathogens were relatively consistent with empirical observations, suggesting the fate and transport submodel generates realistic results. Full validation of the exposure and risk component of the model was not possible, though disease burden outputs in terms of number of cases and DALYs appeared plausible when compared alongside two key benchmarks. First, for the base case, the model predicted total DALYs of 1.3 per 1000 persons, which is equivalent to 25% of the WASH-attributable diarrhoeal disease burden in Bangladesh generally (5.3 DALYs per 1000 people) (Prüss-Ustün et al., 2019). This is what one might expect given exposure to drains represents just one of numerous possible exposure/transmission pathways and that the target pathogens constitute only a proportion of the total disease burden. Second, the number of cases of illness predicted for each pathogen was lower than the input prevalence, which is what one would expect for the same reason (i.e. exposure to open drains being one of multiple possible transmission pathways). Nonetheless, while the model produced plausible results, it is important to emphasise the outputs are theoretical and premised upon numerous assumptions and uncertainties.

The main deviation between modelled and observed pathogen concentrations was the proportion of samples with no detection of norovirus GII or *Giardia*. There are a number of possible explanations for this discrepancy. First, either the prevalence or shedding load may have been overestimated. By contrast, *S.* Typhi had a significantly lower prevalence input than both *Giardia* and norovirus, and the model successfully predicted a high proportion of samples with no detection. Other plausible contributors may be pathogen loss during sample processing, PCR inhibition, and limit of detection issues. Another important factor is that when pathogens enter the drainage system, the model assumes an instantaneous uniform distribution within a 'node' (drain section of ~45m). It is reasonable to expect significant dispersion of pathogens by the time they reach the end of a drain, but they may not be uniformly distributed. Hence, a grab sample of 400 mL may not contain the target pathogen even if the overall concentration within a drain section is quite high.

Implications for sanitation interventions and planning: The results have important implications for reliance on on-site sanitation in low-income urban contexts. Even with the highest possible removal in septic tanks and ABRs, there is still significant residual risk, and this worsens under poor management. For example, a quarter of the health

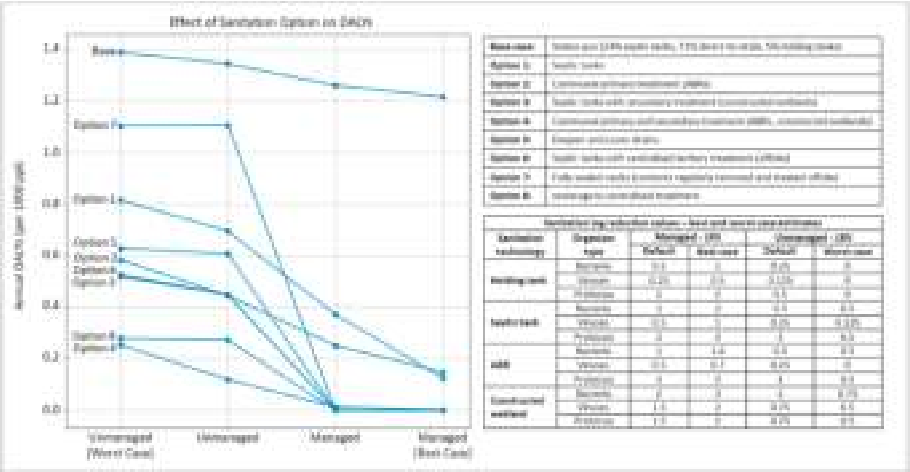


Fig. 10. Estimated disease burden by sanitation option and level of management.

risk remains unaddressed when shifting away from all toilets discharging directly to drains to universal coverage of well-managed septic tanks. Likewise, analyses of the environmental samples from the northern drain of Road A, where 90% of the population's excreta was contained in septic tanks, indicated that *V. cholerae* and *Shigella* were still detected in all drain samples. Septic tanks systems should comprise a two-part system including a soak-away or drainfield with infiltration to soil to provide further pathogen removal and inactivation. However, in Dhaka the clay soil and space limitations prevent such a design. These findings may be widely relevant as recent research has reported that tanks connected to open drains are commonplace in Dhaka and in many other cities (Peal et al., 2020), and high levels of faecal contamination have been observed in open drains in many urban areas (Yapo et al., 2014; Katukiza et al., 2014; Gretsch et al., 2016; Berendes et al., 2018, 2020).

Although both ABRs and septic tanks were assigned the same LRVs, the disease burden associated with full coverage of ABRs was 30–40% less than the disease burden associated with full coverage of septic tanks. This result reflects differences in exposure rather than a differential effect on pathogen removal. A key design feature of the ABR systems is that the black water is conveyed from households in enclosed pipes, and so pathogens do not enter the drain until after the liquid effluent is discharged (at a location some distance 'downstream' from the user households). As a result, the modelling demonstrated how the reduced local exposure served to reduce the disease burden in the immediate area served by ABRs. This is in contrast to septic tanks, which in the study site discharged effluent to drains immediately outside user compounds. This indicates the potential for ABRs to serve as a first step on a ladder towards sewerage and a potential option for contexts such as Dhaka where effluent infiltration is not possible, so long as adequate management can be provided. Use of constructed wetlands further reduced the disease burden as compared with ABRs alone, but in practice requires both land area and proactive, dedicated management and hence may only be a viable option in certain contexts. A related solution is, over time and as it becomes available, to link ABR effluent to a wider sewerage network. An interim option of deepening and covering drains should be approached with caution; unless hydraulically designed to carry faecal matter during heavy rainfall, this could exacerbate local flooding and pathogen exposure.

Although the modelling produced outputs relating to localised disease burden, this overlooks the negative externality and downstream health risk created when pathogens are simply exported elsewhere rather than removed. Illustrating this is Sanitation Option 5 ("deepen and cover drains"); although it prevents exposure locally, wastewater with high pathogen content is still discharged into a receiving waterway at the western perimeter of the site. Most of the other options also include a residual pathogen load that enters that receiving waterway. Quantifying the health risk associated with pathogen export is not straightforward as it requires an increase in the spatial scale of modelling and associated inputs. Nonetheless, conducting modelling at a city-scale, such as in the hypothetical example presented in Mills et al. (2018), is an important next step, and could also support the inclusion of additional exposed populations such as sanitation workers.

In considering the implications of the results for on-going sanitation planning and investments in Dhaka, which include both off-site and on-site sanitation options, the following points need to be made. First, further implementation of septic tanks and ABRs to treat blackwater must include subsequent effluent treatment to reduce the pathogen load (given inability to infiltrate effluent) and should deliver comprehensive rather than piecemeal sanitation coverage. In addition, in other contexts such as Japan and the US, UV treatment or other disinfection steps are implemented before discharge of the effluent (US EPA, 2003; Gaulke 2006), and this provides a further option for consideration, noting that it introduces additional operation and maintenance requirements. Second, this study demonstrates that the use of on-site systems in Dhaka or elsewhere requires appropriate and robust management (such as overcoming inadequate emptying practices that result in sludge wash-out and short-circuiting, and avoiding sludge dumping in drains) – otherwise these systems fail to adequately protect public health. This is particularly true in locations that flood, as this scenario exhibited the potential for significant increase in disease burden during such times. To protect public health, strong institutionally-based management systems are required, including for decentralised systems such as ABRs, as has been demonstrated elsewhere (Willetts et al., 2020). Third, an important complement to consideration of health risks is weighing up the costs of different sanitation options as well as other criteria such as environmental considerations (Willetts et al., 2020).

Key evidence gaps: There is a need for more robust data on how on-site sanitation systems, as actually constructed and operated in low-income settings, perform under different conditions and management regimes. The sensitivity analysis revealed LRV as the key input parameter for differentiating between the effect of the various sanitation options. Yet, robustly determined LRVs for different types of pathogens (bacteria, viruses, protozoa and helminths) in septic tanks and ABRs are lacking, despite the ubiquity of these technologies in urban settings and the key role of on-site sanitation in city-wide inclusive sanitation strategies (Schrecongost et al., 2020). Although the LRV inputs were largely based on literature, available data points for septic tanks and ABRs are very limited and rarely presented consistently or with sufficient information. For example, some sources do not clarify whether the quoted LRVs refer to just a septic tank, or its use in combination with a soak-away for infiltration (and related treatment in the soil) (Adegoke and Stenstrom, 2019). Estimating LRVs for small-scale or on-site sanitation systems is fraught with methodological challenges. It is challenging to measure the 'influent' to a septic tank, given the periodic nature of that influent and because it contains a mixture of solid and liquid. Nonetheless, addressing this knowledge gap is an urgent priority, including examining the potential effects of different management regimes, as well as modifications to septic tank designs such as an effluent filter or addition of disinfection processes.

The sensitivity analysis also highlighted other key areas of uncertainty that have a significant impact on estimated pathogen concentrations and disease burden. Chief among those were shedding load for each pathogen – for which evidence remains relatively scant – and ingestion volume of drain water. This study followed the SaniPath approach to estimate ingestion volume (Gretsch et al., 2016; Robb et al., 2017) and extended it to incorporate adults and children >12 years. This resulted in ingestion volumes of approximately 0.1 mL, well below the 1–5 mL fixed estimates used in other studies. Nonetheless, the rank order of the sanitation options (in terms of their predicted impact on disease burden) remained unaffected by substitution of these and other key parameters with minimum/maximum estimates. Another evidence gap concerns exposure assessment. Data on exposure of children and adults to open drains and via other contamination pathways is limited (Gretsch et al., 2016), and yet essential for furthering systems modelling of this kind. Structured observation, rather than self-reporting (as undertaken in this study), is likely to generate more robust data for the purposes of characterising exposure behaviours.

4.1. Limitations

The study has a number limitations related to both the modelling and processes for detecting and quantifying pathogens.

Model parameters. While we sought to base model parameters on empirical evidence from the Dhaka context, this was not always possible. Estimates for shedding load were based on few empirical data points, and generally related to adults. For some pathogens (*V. cholerae*, *Shigella* and norovirus GII), we assumed that prevalence of infection did not differ between diarrhoea patients seeking medical care and those not seeking medical care. These estimates also relied on self-reported diarrhoea which may be subject to recall bias (Zafar et al., 2010),[6] and we applied estimates for duration of shedding and duration of symptoms that were not always Dhaka-specific. The estimates also did not fully reflect the complexities of co-infection with multiple pathogens, intermittent shedding or immunity due to previous infection. Exposure estimates were based on self-reported contact with drains with no structured observation, as would be preferable. Dose-response relationships were generally based on challenge studies involving adults from high-income countries, so it is uncertain how applicable they may be to children or to a low-income area of Dhaka more generally, where longer term impacts of repeated enteric infection may also play a role. Standardising DALY assumptions across all diarrhoeal pathogens also belies the differential impact of pathogen-specific diarrhoea cases. Moreover, the DALY calculations only consider acute impacts, and did not account for childhood growth impairment and other sequelae associated with repeated enteric infections (Troeger et al., 2018).

Model validation. Only partial validation of the model was possible based on an assessment of faecal pathogen and indicator concentrations in drain water. While we could check the plausibility of disease burden outputs, this only confirmed that results were within credible ranges. The microbiological methods underpinning the validation of pathogen and indicator concentrations also had a number of caveats, including uncertain limits of detection and the assumption that what was detected and quantified in the environmental samples was 100% infective. While most of the target organisms were human specific, animals are potential additional sources for *Giardia* and *E. coli*; however, the animal population in the study site was relatively small.

Generalizability of findings. The model set-up and its application had a localised focus, and hence there is a question around wider relevance of the findings. We chose a study site that was a relatively 'simple' catchment with limited inflows of wastewater and pathogens, but recognize that many urban environments in Dhaka and other large cities are significantly more complex. Hence, the complexity of modelling will increase when attempted in other contexts. The results produced by the model may be quite specific to the study site. Different contexts will vary in infrastructure, exposure behaviours, epidemiology and climate. Nonetheless, one of the strengths of a systems modelling approach is that it possesses flexibility to be applied to different contexts so long as the assumptions and inputs are tailored accordingly.

Additional transmission routes. By virtue of the study site, the modelling focused just on local transmission of faecal pathogens from sanitation systems via open drains. In Dhaka – as in other urban centres – high numbers of faecal pathogens and indicators have been detected in drinking water, on fresh produce, and soils (Amin et al., 2019), while person-to-person transmission also represents an important route for infection for some of these pathogens. These transmission pathways may well be impacted by local sanitation interventions. In the study site, rubbish and sediment were frequently removed from the drain and piled up on the roadside, and the pathogen content in drain sediment samples indicate that these could be an important exposure pathway (Amin et al., 2020). Similarly, throughout the study site, overflowing or backed-up toilets were observed, and visibly damaged water supply pipes were submerged in drains. Underground storage tanks for municipal water were also observed and likely provided sites for contamination. However, in many cases the place at which contamination of food or water occurs may be geographically distant to the point of exposure, making it difficult to evaluate with a localised modelling of sanitation options. Similarly, a localised focus means exported pathogens cannot be easily converted into a health risk to populations outside of the study site. For the same reason, safe management along the whole sanitation chain could not be fully studied and incorporated. Comprehensively incorporating these additional considerations and transmission routes will help build a fuller understanding of faecal pathogens in the urban environment, but will also require more data, more extensive validation and application of modelling to a larger geographic scale.

5. Conclusion

Systems modelling can help build a more complete and evidence-based picture of urban sanitation outcomes in specific contexts and more generally. In this paper, we have applied a systems modelling approach to investigate pathogen flows in a low-income urban area in Dhaka, Bangladesh. The study demonstrated that it was feasible to compare the impact of different sanitation options by modelling expected outcomes, despite the extensive variability and uncertainties associated with many of the parameters involved. This approach can therefore complement other planning and decision tools used to weigh sanitation options and understand how excreta and its associated microorganisms move through the urban environment. Using QMRA to compare the relative effect on annual DALYs of eight sanitation options, our results demonstrated that some options that reduce exposure (for example, blackwater piped directly to ABRs) may provide slightly greater reduction in health risk than septic tanks, and options that include constructed wetlands for effluent treatment can further reduce health risk. However, when poorly managed, such as through inadequate sludge emptying (leading to short-circuiting and wash-out of sludge) or sludge dumping, all of the sanitation options we examined provide inadequate pathogen removal to protect public health.

The modelling approach developed and applied in this study could be strengthened in a number of ways. As this study focused on a bounded area, an important consideration was export of wastewater with high pathogen concentrations to 'downstream' neighbouring areas, pointing to the need to conduct modelling at a city rather than neighbourhood scale, and to include a larger number of transmission pathways. Further research is critically needed to fill the multiple evidence gaps we identified, including: 1) more robust LRVs for sanitation systems of different types and under different management regimes; 2) pathogen flows under flooding conditions; and 3) pathogen shedding and exposure assessments in typical low-income urban environments. Such improved evidence will assist in furthering the potential for systems modelling to provide practical guidance on how sanitation interventions can best be designed and managed to protect the health of urban populations.

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[6] The self-reported prevalence of diarrhoea based on a one-week recall was estimated to be 7.5% across all ages, which aligns with previous surveys based on a 48 h recall (Najnin et al., 2019).

(independent consultant), Sean Tyrrel (Cranfield University), Alexandria Boehm (Stanford University), Nynke Hofstra (Wageningen University), Nick Ashbolt (University of Alberta), Khairul Islam (WaterAid) and Tim Julian (EAWAG).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2020.113669.

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Ethics

Ethical approval was provided by the University of Technology Sydney (UTS HREC REF NO. ETH18-2599). The study protocol was also approved by the International Centre for Diarrhoeal Diseases Research, Bangladesh (icddr,b) scientific and ethical review committees (protocol number 19011).

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Normal variability of 22 elements in 24-hour urine samples – Results from a biobank from healthy non-smoking adults

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ABSTRACT

Background: Urine is often used for biomonitoring the exposure to elements. However, most studies report concentrations in spot urine samples, which may not accurately mirror the "gold standard" of complete 24-h (24 h) urine samples. There are relatively few data published for 24 h samples, and little information on the within- and between person variability.

Objectives: The present study aimed at assessing variability within and between individuals in 24 h excretion for a number of elements in adults from the general population and the typical 24 h excretion of these elements. In addition, we assessed concentrations adjusted for creatinine and specific gravity (SG), and associations between elements.

Methods: 60 healthy non-smokers (31 women and 29 men) from Sweden, aged 21–64 years, collected all urine during 24 h (split into six separate samples) on two occasions, about one week apart. Concentrations of As, Br, Cd, Co, Cr, Cu, Fe, Hg, Li, Mn, Mo, Ni, P, Pb, S, Sb, Se, Sn, U, V, W, and Zn in urine were analyzed by inductively coupled plasma sector-field mass spectrometry (ICP-SF-MS) and 24 h excretion rates were calculated for each day. The ratio of between-individual variance and the total variance, the intra-class correlation (ICC) was calculated based on natural log-transformed 24 h excretion. Correlation coefficients were calculated between excretion rates (mass/24 h), and concentrations adjusted for creatinine and SG.

Results: Geometric means (GM), and 90-percentiles are presented for each element. The 24 h excretion was higher in men than in women for most elements, and the difference was statistically significant for Cr, Cu, Fe, Li, P, Pb, S, Se, U, V, and Zn. However, for Cd and Co, the excretion was higher in women. Variability between days was low for Cd, Co, Hg, Pb, Sn, Se, V, and Zn (ICC 0.75–0.90), highest for Cr (ICC = 0.3) and Sb (ICC = 0.18), and moderate for the other elements. Spearman's rank correlation coefficients were about 0.8–0.9 for 17 elements, and 0.3–0.7 for Br, Cu, P, S, Se. Excretion of P and S were highly correlated, and also associated with excretion of most of the other elements, especially Cu, Se, V, and Zn. A high correlation was also found between As and Hg, between Mo and W, as well as between Cr, Fe and Mn.

Conclusions: These data present normal variability of 24 h excretion of a number of elements, and can also be used as updated reference levels for elements with no or limited previous literature available. Information on variability within- and between individuals is important to know when designing studies with urine levels of elements used as exposure biomarker in studies of associations with health outcomes.

Abbreviations: SG, specific gravity; BMI, body mass index; GM, Geometric mean; ICP-SF-MS, inductively coupled plasma sector-field mass spectrometry; DL, detection limit; ICC, intra-class correlation.

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1. Introduction

Urine is often used for biomonitoring the exposure to metals and metalloids in occupational and environmental health surveillance and scientific studies. In contrast to blood sampling, urine collection has the advantage of being a non-invasive method. However, most studies in the literature report results for concentrations of elements in spot urine samples, which may not accurately mirror the "gold standard" of concentration in complete 24-h (24 h) urine samples, and there are relatively few data published for 24 h samples (Smolders et al., 2014). Some studies on multiple elements in 24 h urine have focused on occupationally exposed groups, and some on samples from the patients or general population samples, e.g. in Japan (Araki et al., 1986), US (Komaromy-Hiller et al., 2000), the UK (Sieniawska et al., 2012), Belgium (Smolders et al., 2014), and China (Wang et al., 2016). In addition, there are some studies on 24 h urine excretion of single elements such as zinc (Henderson et al., 1996; Ilich et al., 2009), cadmium (Hotz et al., 1999; Uno et al., 2005; Lampe et al., 2008; Akerstrom et al., 2013, 2014), mercury (Akerstrom et al., 2017), chromium (Nomiyama et al., 1980), sulphur (Magee et al., 2004) and phosphorus (Palomino et al., 2013). Older studies may have used analytical methods with limited sensitivity.

There is normal variability between days in 24 h excretion of elements, but few studies did repeated sampling, so there is little information on the relation between within- and between person variability for 24 h excretion. We identified only two studies using repeated sampling of normal excretion in 24 h urine in a limited number of individuals. Four male-female couples in Belgium were examined over six consecutive days (Smolders et al., 2014), and 11 men in China were examined on eight separate days over a 3-month period (Wang et al., 2016, 2019; Chen et al., 2019).

Adjustment for urine dilution is often performed using urinary creatinine or specific gravity (SG) when using spot samples, and it has been discussed which best reflects the long-term excretion (Barber and Wallis, 1986; Suwazono et al., 2005; Smolders et al., 2014; Hoet et al., 2016; Hsieh et al., 2019). There is, however, limited data on impact of adjustment in 24 h urine samples (Sienawska et al., 2012; Wang et al., 2016, 2019; Chen et al., 2019).

The present study aimed at assessing variability within (between days) and between individuals in 24 h urine samples for a number of elements in adults from the general population. In addition typical 24 h excretion, and concentrations adjusted for creatinine and SG are presented, as well as associations between elements. We selected nutritional elements and well recognized toxic elements for analysis, taking into account also the experience of the laboratory with analysis of the respective elements, and other analytical issues.

2. Methods

2.1. Subjects and urinary sampling

A description of the study population and sample collection has been described elsewhere (Sallsten and Barregard, submitted). Briefly, the study was performed in a convenience sample of 60 healthy non-smokers (31 women and 29 men) from Gothenburg, Sweden, not occupationally exposed to metals (Table 1). They were 21–64 years of age (mean 34 years), 52 were never smokers and eight were former smokers. The mean body mass index (BMI) was 24, and 63% (n = 38) were born in Sweden. The frequency of certain food items are shown in Table 1. Only one person was vegetarian. The participants collected all urine (in six separate consecutive samples) during 24 h on two separate days, about one week apart. The mean urinary volume (mean of two days) was 1.7 L (range 0.84–3.7), and the mean creatinine concentration in the 24 h urine samples was 1.1 g/L (0.8 g/L for women and 1.3 g/L for men). The study was approved by the Ethics Review Board at the University of Gothenburg, and all participants signed a written informed consent to participate in the study. The biobank is open for researchers examining normal variability of their favorite biomarker(s).

Table 1
Background data in the 60 individuals providing samples for the varfiability biobank.

	Mean or %	Range
Age	34	21–64
Sex, % women	52%	
Born in Sweden	63%	
Body mass index	24	19–44
Exercise, at least 2 × 30 min/week	78%	
Amalgam fillings	20%[a]	
Meat, meals per week	4.7	0–14
Fish, meals per week	1.8	0–7
Rice, meals per week	2.3	0–10

[a] The percentage for amalgam fillings are based on N=50 (missing data for 10 individuals).

2.2. Analyses of elements in urine

Trace elements analyses in urine were performed at the National Institute of Occupational Health in Oslo, Norway (NIOH). Urine specimens were heated for 1 h at 80 °C prior to analysis in order to prevent laboratory acquired infections and to dissolve urine precipitates. One hundred μL of an internal standard solution containing 2.0 μg mL^{-1} of gallium, germanium, indium and thallium were added to 1 mL of urine in a 15 mL polypropylene tube before dilution to 5 mL with deionized water. The DI water used was prepared by a Milli Q System (18.2 MΩ cm, Millipore Corp., Billerica, USA). The prepared solutions were analyzed by inductively coupled plasma sector-field mass spectrometry (ICP-SF-MS) using an Element 2 mass spectrometer (Thermo Electron, Bremen, Germany) calibrated with urine matrix matched standard solutions. Seronorm™ (Sero AS, Billingstad, Norway)Trace Elements human urine quality control materials were used for quality assurance (Seronorm L1 (LOT 1403080), Seronorm L2 (LOT 1403081). The range (due to more than one analytical run) of the obtained detection limits (DLs) and number of samples below DL for trace elements in urine are shown in supplemental Table S1. The detection limits were calculated daily as three times the standard deviation of "water blank" (see supplemental material) concentrations.

The laboratory is regularly taking part in external quality assurance schemes, which include: Proficiency Testing Program for Blood Lead, EP and Trace Elements organized by Wadsworth Center, New York State Department of Health; German External Quality Assessment Scheme organized by Institute and Outpatient Clinic for Occupational-, Social- and Environmental Medicine, Friedrich-Alexander University Erlangen-Nuremberg; PCI: Interlaboratory Comparison Program for Metals in Biological Matrices organized by The Centre de toxicologie du Québec.

Details on blanks used and operation conditions of the ICP-SF-MS equipment are described in the supplemental material (text and table S2 and S3).

2.3. Data analysis

From the six spot samples the 24 h excretion rates (mass/time) were calculated (one for each day and participant) by adding element masses (obtained from concentrations and volumes) for each spot sample. For one person, two spot samples were erroneously merged, leading to a total number of 719 analyzed samples. For all elements, the detection limit (DL) was determined for each individual measurement. Values below the detection limits were replaced by $DL/\sqrt{2}$, as the geometric standard deviation was always <3 (Hornung and Reed, 1990). For each element, the range of DLs and the number of samples below DL are shown in Table S1.

Concentrations of elements in 24 h urine adjusted for creatinine were calculated by dividing the 24 h mass of each element by the 24 h mass of creatinine. Concentrations in 24 h urine were also adjusted to a specific gravity of 1.015 (close to the median SG of 1.016 in the present study). The SG of the 24 h urine sample was calculated from the SGs in the spot samples, weighted for urine volumes of the six separate samples.

Differences in the 24 h excretion rates between men and women were tested with the Mann-Whitney-Wilcoxon test, and significance was assumed for a p-value <0.05.

Between- and within-individual (inter-day) variability was calculated based on natural log-transformed 24 h excretion rates. Individual variance components were estimated using the PROC MIXED procedure in SAS. Sex was first included in the models as a fixed effect.

Three different variance structures were compared: common between- and within-person variances for men and women, distinct between-person but common within-individual variances, and distinct between- and within-individual variances, using a likelihood ratio test (significance level; $p < 0.05$) where the difference in -2loglikelihood follows a chi square distribution (Rappaport and Kupper, 2008).

The estimated ratio of the between-individual variance to total observed variance, the intra-class correlation (ICC) for the two 24 h urine samples was calculated. If either within- or between-individual variance or both was significantly different in men and women, separate estimates by sex were calculated for ICC. If common variances could be used, they were calculated without sex in the models.

Spearman's rank correlation coefficients were calculated between excretion rates (mass/24 h), and concentrations adjusted for creatinine and SG. In addition, rank correlations between 24 h excretion rates for the 22 elements were calculated.

Calculations were carried out with R version 3.3.1 (R Core Team, 2016) or SAS, version 9.4 (SAS institute, Cary, NC, USA).

3. Results

The 24 h excretions of 22 elements are listed in Table 2. Since the distribution was skewed for many elements, results are presented as GM, 90-percentile, minimum and maximum. As shown in the table, for most elements the difference in GMs for day 1 and 2 was <5%. On the individual level, day-to-day variation was, however substantial for several elements, see below.

The geometric mean 24 h excretion was higher in men than in women for most elements, with a statistically significant difference for Cr, Cu, Fe, Li, P, Pb, S, Se, U, V, and Zn. However, for Cd and Co, the excretion was significantly higher in women. These differences were the same in Day 1 and 2 (data not shown).

Adjustment for urinary creatinine or specific gravity is usually performed, to adjust for urinary dilution in spot samples. Concentrations of the 22 elements in 24 h urine samples adjusted for creatinine and specific gravity are shown in Tables 3 and 4. Since urinary creatinine excretion is lower in women than in men, concentrations adjusted for creatinine are higher in women than in men for most elements, statistically significant for Br, Cd, Co, Cu, Ni, P, and Se (Table 3). When concentrations instead were adjusted for specific gravity (normalized to SG = 1.015) they were higher in women for Cd, and Co, but higher in men for S, V, and Zn (Table 4).

Variability between days was low for Cd, Co, Hg, Pb, Sn, Se, V, and Zn, having within-person (inter-day) variabilities of only 10–25% of total variability (intra-class coefficients 0.75–0.90). It was moderate for As, Br, Cu, Fe, Li, Mn, Mo, Ni, P, S, U, and W (ICC 0.35–0.75), and highest for Cr (ICC = 0.31) and Sb (ICC = 0.18), for details see Table 5 and example plots in Figures S1 – S8. For Co, Fe and U the likelihood ratio test showed that distinct between- and within-person (inter-day) variance should be used and for Cd distinct between-person but common within-person variance. For all other elements the test showed a common variance structure.

The 24 h concentrations of elements adjusted for creatinine or specific gravity, or unadjusted concentrations were highly correlated with the 24 h excretion, as could be expected. Spearman's rank correlation coefficients were about 0.8–0.9 for all elements except for Br (0.53–0.77), Cu (0.34–0.69), P (0.46–0.71), S (0.48–0.75), and Se (0.52–0.78). In the total study population correlations after adjustment for SG were slightly higher than after creatinine adjustment, but the reverse was true after stratification for sex, which removed the impact of higher creatinine excretion in men.

There were many significant associations between the 24 h excretion of the various elements (Figure S9). Excretion of P and S were highly correlated, and also associated with excretion of most of the other elements, especially Cu, Se, V, and Zn. A high correlation was also found between As and Hg, between Mo and W, as well as between Cr, Fe and

Table 2

Excretion of 22 elements in 60 healthy non-smokers in 24 h urine collected on two different days, one week apart. The units are µg/24 h, apart from Br, P, and S with the units are mg/24 h and U where it is ng/24 h. Significant differences (5% level) between men or women are marked in bold.

	Mean of two days							Day 1				Day 2			
	All (N = 60)		Men (N = 29)		Women (N = 31)		P-value men vs. women	All (N = 60)				All (N = 60)			
Element	GM	90%	GM	90%	GM	90%		GM	90%	Min	Max	GM	90%	Min	Max
As	48.1	244	47.9	246	48.3	203	0.76	41.0	199	4.64	935	39.4	234	4.21	1301
Br	3.27	5.04	3.56	5.57	3.03	4.62	0.18	3.20	4.84	0.83	8.50	3.25	5.48	0.92	8.31
Cd	0.12	0.34	0.087	0.28	**0.16**	0.40	0.011	0.12	0.33	0.012	0.49	0.12	0.33	0.012	0.48
Co	0.38	1.20	0.30	1.34	**0.47**	1.02	0.019	0.36	1.16	0.059	2.90	0.38	1.37	0.11	2.99
Cr	0.11	0.19	**0.13**	0.24	0.097	0.16	0.012	0.12	0.24	0.021	0.74	0.097	0.18	0.036	0.38
Cu	8.76	11.9	**10.2**	15.4	7.62	9.81	<0.001	8.67	12.9	3.58	16.4	8.71	12.4	4.65	20.6
Fe	4.36	11.8	**5.42**	11.9	3.55	8.35	0.011	4.34	12.9	1.19	56.0	3.76	10.5	1.08	37.8
Hg	0.23	0.49	0.24	0.48	0.22	0.49	0.67	0.22	0.53	0.068	1.99	0.23	0.46	0.055	1.25
Li	17.5	36.2	**22.2**	37.3	14.0	20.6	<0.001	16.9	38.5	3.57	107	16.6	31.9	4.35	161
Mn	0.18	0.39	0.20	0.39	0.16	0.37	0.086	0.18	0.44	0.027	1.35	0.15	0.39	0.046	0.64
Mo	54.2	101	62.6	104	47.3	101	0.081	50.8	130	10.1	236	53.0	100	12.0	248
Ni	1.47	2.88	1.58	2.98	1.38	2.13	0.31	1.46	3.28	0.35	5.21	1.38	2.66	0.53	8.06
P	867	1286	**1008**	1327	753	1084	<0.001	840	1277	242	2135	871	1281	507	2993
Pb	0.50	0.83	**0.60**	0.96	0.43	0.63	0.001	0.50	0.98	0.15	1.26	0.50	0.76	0.14	1.53
S	744	1146	**903**	1467	620	864	<0.001	756	1157	195	1836	715	1176	323	3245
Sb	0.080	0.28	0.082	0.28	0.079	0.23	0.58	0.068	0.21	0.0098	0.64	0.072	0.24	0.018	14.8
Se	22.6	31.9	**26.3**	50.4	19.7	25.1	<0.001	22.6	36.1	8.81	89.7	22.2	30.2	12.8	123
Sn	0.36	0.90	0.39	1.26	0.33	0.69	0.47	0.36	1.08	0.042	9.49	0.33	0.78	0.084	5.11
U	3.01	5.17	**3.64**	5.42	2.52	4.65	0.007	2.93	5.21	0.46	15.1	2.94	5.60	0.86	9.53
V	0.023	0.042	**0.032**	0.054	0.017	0.025	<0.001	0.023	0.043	0.0036	0.16	0.022	0.043	0.0063	0.20
W	0.079	0.18	0.087	0.14	0.071	0.26	0.23	0.072	0.19	0.015	0.58	0.072	0.19	0.015	0.61
Zn	352	727	**493**	881	258	438	<0.001	335	782	54.8	1143	357	717	83.8	1820

Table 3
Concentrations adjusted for creatinine of 22 elements in 60 healthy non-smokers in 24 h urine collected on two different days, about one week apart. Units are μg/g creatinine, apart from Br, P, and S (mg/g) and U (ng/g). Significant differences between men and women are marked in bold.

	Mean of two days							Day 1				Day 2			
	All (N = 60)		Men (N = 29)		Women (N = 31)		P-value men vs. women	All (N = 60)				All (N = 60)			
Element	GM	90%	GM	90%	GM	90%		GM	90%	Min	Max	GM	90%	Min	Max
As	31.6	143	24.7	130	39.7	143	0.12	26.8	130	3.25	543	25.9	144	2.33	867
Br	2.14	3.24	1.84	2.64	**2.47**	3.92	<0001	2.09	3.10	0.60	5.37	2.14	3.47	0.62	4.80
Cd	0.079	0.25	0.045	0.11	**0.13**	0.28	<0001	0.078	0.23	0.0055	0.45	0.077	0.22	0.0073	0.40
Co	0.25	0.75	0.16	0.64	**0.38**	0.87	<0001	0.24	0.84	0.056	1.40	0.25	0.74	0.067	1.30
Cr	0.073	0.11	0.068	0.12	0.079	0.11	0.10	0.077	0.13	0.026	0.45	0.064	0.12	0.021	0.25
Cu	5.72	7.59	5.26	7.30	**6.18**	7.62	0.008	5.67	7.81	3.20	9.64	5.24	7.54	3.47	10.7
Fe	2.85	5.71	2.83	5.78	2.87	5.45	0.85	2.84	7.73	1.15	27.6	2.48	5.60	0.72	18.8
Hg	0.15	0.33	0.12	0.24	0.18	0.46	0.052	0.15	0.31	0.041	1.25	0.15	0.40	0.034	0.83
Li	11.4	19.8	11.5	20.9	11.4	19.1	0.75	11.1	19.7	3.61	75.8	10.9	18.2	3.8	80.7
Mn	0.11	0.25	0.10	0.21	0.13	0.25	0.23	0.12	0.31	0.019	0.77	0.097	0.23	0.028	0.51
Mo	35.4	70.2	32.6	50.2	38.3	71.9	0.19	33.2	72.1	8.5	128	34.9	59.9	10.5	131
Ni	0.96	1.71	0.81	1.54	**1.12**	1.87	0.027	0.96	1.80	0.25	5.26	0.91	1.65	0.24	3.85
P	567	750	522	649	**612**	832	0.014	549	760	131	1031	574	729	325	1032
Pb	0.33	0.53	0.31	0.51	0.35	0.53	0.49	0.32	0.56	0.093	0.94	0.33	0.55	0.11	0.67
S	485	636	466	595	503	662	0.092	494	649	259	905	471	647	281	855
Sb	0.052	0.17	0.042	0.17	0.064	0.16	0.086	0.044	0.15	0.013	0.35	0.048	0.16	0.012	11.5
Se	14.8	20.7	13.6	22.7	**16.0**	19.7	0.009	14.8	20.5	7.77	50.5	14.6	22.0	8.34	40.6
Sn	0.23	0.58	0.20	0.69	0.27	0.54	0.11	0.23	0.72	0.056	8.34	0.22	0.56	0.049	3.97
U	1.97	3.30	1.89	3.31	2.05	3.29	0.28	1.91	3.26	0.51	7.93	1.93	3.61	0.63	7.13
V	0.015	0.025	0.017	0.028	0.014	0.019	0.34	0.015	0.026	0.0059	0.079	0.014	0.023	0.0063	0.11
W	0.051	0.12	0.045	0.067	0.058	0.17	0.23	0.047	0.12	0.012	0.36	0.047	0.10	0.013	0.53
Zn	231	417	255	442	210	367	0.10	219	414	35.0	564	235	416	62.8	661

Table 4
Concentrations adjusted for specific gravity of 22 elements in 60 healthy non-smokers in 24 h urine collected on two different days, about one week apart. Units are in μg/L, apart from Br, P, and S (in mg/L) and U (in ng/L). Significant differences between men and women are marked in bold.

	Mean of two days							Day 1				Day 2			
	All (N = 60)		Men (N = 29)		Women (N = 31)		P-value men vs. women	All (N = 60)				All (N = 60)			
Element	GM	90%	GM	90%	GM	90%		GM	90%	Min	Max	GM	90%	Min	Max
As	28.3	124	24.6	124	32.2	123	0.26	23.7	114	2.43	472	23.4	146	1.37	734
Br	1.91	2.56	1.81	2.40	2.00	2.56	0.27	1.85	2.53	0.62	5.20	1.93	2.72	0.66	3.45
Cd	0.071	0.22	0.045	0.12	**0.11**	0.26	<0.001	0.069	0.22	0.0062	0.35	0.069	0.21	0.0094	0.36
Co	0.22	0.69	0.15	0.69	**0.31**	0.69	<0.001	0.21	0.78	0.057	1.65	0.23	0.69	0.048	1.52
Cr	0.066	0.11	0.067	0.11	0.064	0.10	0.86	0.068	0.12	0.022	0.46	0.058	0.11	0.020	0.19
Cu	5.13	7.26	5.21	6.79	5.06	7.25	0.86	5.01	6.87	2.40	9.76	5.18	7.66	3.09	9.35
Fe	2.55	5.69	2.78	5.71	2.34	5.14	0.26	2.51	6.67	0.74	24.0	2.24	4.95	0.67	15.5
Hg	0.13	0.28	0.12	0.25	0.15	0.29	0.35	0.13	0.31	0.040	1.17	0.13	0.29	0.032	0.71
Li	10.2	17.2	11.3	19.5	9.22	16.1	0.084	9.77	21.3	3.14	51.6	9.85	17.9	2.49	85.7
Mn	0.10	0.24	0.10	0.24	0.10	0.25	0.81	0.10	0.26	0.023	0.58	0.088	0.21	0.024	0.41
Mo	31.8	59.7	32.3	55.9	31.3	63.4	0.94	29.4	60.7	8.09	114	31.5	64.2	11.7	118
Ni	0.86	1.52	0.81	1.43	0.91	1.57	0.51	0.84	1.72	0.18	4.24	0.82	1.47	0.14	4.08
P	506	632	514	632	498	618	0.42	485	620	152	753	518	659	328	807
Pb	0.29	0.45	0.30	0.49	0.28	0.43	0.35	0.29	0.48	0.085	0.72	0.30	0.44	0.12	0.77
S	432	508	**459**	534	409	472	0.002	437	503	201	787	425	506	236	715
Sb	0.047	0.15	0.042	0.16	0.053	0.14	0.39	0.039	0.11	0.010	0.32	0.043	0.15	0.0096	9.15
Se	13.2	18.3	13.4	17.8	13.1	18.3	0.51	13.1	19.0	8.20	50.1	13.2	17.5	6.95	35.5
Sn	0.21	0.51	0.20	0.57	0.22	0.46	0.94	0.21	0.62	0.044	7.85	0.20	0.52	0.054	3.17
U	1.76	2.84	1.86	2.72	1.67	2.82	0.69	1.69	2.60	0.45	10.4	1.75	3.45	0.53	7.09
V	0.013	0.022	**0.016**	0.030	0.011	0.018	0.006	0.013	0.023	0.0037	0.072	0.013	0.023	0.0047	0.11
W	0.046	0.098	0.045	0.073	0.047	0.14	0.94	0.042	0.11	0.0098	0.25	0.043	0.099	0.013	0.49
Zn	207	402	**251**	423	172	316	0.003	193	391	28.0	549	212	365	43.9	623

Mn.

4. Discussion

The present study presents results for excretion of 22 elements in repeated full 24 h samples in 60 adult non-smokers from the general population. For several elements there are few previous data in the literature, and for some of them such data are lacking completely.

4.1. 24 h excretion of 22 elements and differences between men and women

This section compares our results with previous studies, with some comments on sources and differences between men and women. Elements for which urinary elimination is not important, as well as sulphur and phosphorous are discussed together in the end of the section.

4.1.1. Antimony

Sb is a non-essential element with a short half-life in urine. Milk and seafood are examples of dietary sources (Tylenda et al., 2015). The 24 h GM excretion was only about 0.08 μg, similar in men and women. This is

Table 5
Intra-class correlation (ICC; ratio between-individual variance/total variance) for 24 h excretion of 22 elements in 60 healthy non-smokers. Samples were collected on two separate days, about one week apart. All data were log-transformed before calculation of ICC. If either within-or between-individual variance was significantly different in men and women, Separate estimates of ICC are presented.

Element	ICC	ICC women	ICC men
As	0.52		
Br	0.63		
Cd		0.81	0.91
Co		0.82	0.95
Cr	0.31		
Cu	0.66		
Fe		0.22	0.69
Hg	0.91		
Li	0.39		
Mn	0.38		
Mo	0.56		
Ni	0.55		
P	0.56		
Pb	0.81		
S	0.71		
Sb	0.18		
Se	0.76		
Sn	0.83		
U		0.59	0.66
V	0.75		
W	0.43		
Zn	0.81		

lower than the median of 0.29 μg/24 h reported from a renal stones clinic in the UK by Sienawska et al. (2012) and 0.15 μg/24 h in Chinese young men (Wang et al., 2019).

4.1.2. *Arsenic*

The GM amount of total As was 48.1 μg/24 h with no significant difference between men and women. This is higher than previously reported medians of 36 μg/24 h (Sieniawska et al., 2012) and 20 μg/24 h (Wang et al., 2016). The urinary concentration of total As is strongly related to the consumption of seafood (Smolders et al., 2014). This may explain the differences in 24 h urinary As excretion. It has also been shown that the As concentration in fish muscle differs substantially between species (Sobolev et al., 2019). Only a minor part of the As exposure in the general population is inorganic As. For example, Hinwood et al. (2002) found that 70% of Australian adults had a concentration of inorganic As in 24 h urine samples below the detection limit, which was 2 μg/L. On the individual level it is not possible to assess inorganic As without speciation.

4.1.3. *Bromine*

The GM in the present study was 3.3 mg, with no difference between men and women. We found only one previous report in the literature on Br in 24 h urine. Wester (1974) reported a mean of 3.2 mg/24 h in six hypertensive adults.

4.1.4. *Cadmium*

For Cd, smoking is a strong predictor of exposure, and the mean level in the present study of non-smokers was only 0.12 μg/24 h. We found few studies reporting 24-h excretion of Cd in in non-smokers. The 24 h urinary Cd was reported to be 0.4 μg in elderly US non-smokers in the 1990s (Lampe et al., 2008), and 0.17 μg in 40-year old non-smokers in Sweden in the 2000s (Akerstrom et al., 2014). In combined groups of smokers and non-smokers the median Cd level was about 1 μg/24 h in Japan (Uno et al., 2005), 0.9 μg/24 h in UK patients (Sienawska et al., 2012), and 0.8 μg/24 h in the Belgian Pheecad population where one third were smokers (Hotz et al., 1999). Urinary Cd levels are known to be higher in Japan than in Europe and the US due to rice consumption (Nordberg et al., 2015), and also high in Belgium due to contamination from zinc smelters (Hotz et al., 1999). The excretion of Cd was about two-fold higher in women than in men. This difference between non-smoking women and men has been shown previously (Akerstrom et al., 2014) and is considered a result of higher gastrointestinal absorption of cadmium in women due to lower iron stores (Nordberg et al., 2015; Berglund et al., 1994; Meltzer et al., 2010).

4.1.5. *Chromium*

The GM urinary content of Cr was 0.11 μg/24 h, slightly higher in men than in women. This is somewhat lower than the median amount of 0.25 μg/24 h reported previously (Sieniawska et al., 2012) and much lower than the median of 2.6 μg/24 h reported by Komaromy-Hiller et al. (2000) in US patients, and by Chen et al. (2019) in eleven Chinese men.

4.1.6. *Cobalt*

The Co excretion was 0.38 μg/24 h, and significantly higher in women than in men. This may be due to higher prevalence of iron deficiency in women, as iron deficiency may substantially increase the uptake of Co (Meltzer et al., 2010). The 24 h Co excretion reported by Sieniawska et al. (2012) was higher, 1.4 μg/24 h, while Komarory-Hiller et al. found 0.7 μg/24 h, and Wang et al. (2016) 0.24 μg Co/24 h, results which are more in agreement with ours.

4.1.7. *Lead*

The geometric mean 24 h excretion of Pb was 0.5 μg which is much lower than reported in some previous studies in non-occupationally exposed adults after year 2000; 2.0 μg in the US (Komaromy-Hiller et al., 2000), 2.4 μg in the UK (Sienawska et al., 2012), and 3.1 μg in China (Wang et al., 2016). Likely explanations are that Pb exposure has decreased substantially in the last couple of decades, that levels still differ between countries, and that the present study included only non-smokers. Studies of U–Pb in spot urine samples from adults in Germany (Heitland et al., 2006), Sweden (Sommar et al., 2014), and the US (Buser et al., 2016), have shown levels consistent with the 24 h excretion in the present study. The 24 h excretion was somewhat higher in men than in women.

4.1.8. *Lithium*

Li is a non-essential metal used in the manufacturing of batteries, ceramics, glass, and medicines. Environmental exposure occurs mainly through food and drinking water. The average dietary exposure to lithium in a recent study from New Zealand was estimated to be between 0.14 and 0.31 μg/kg body weight/day among adult male and female, with the highest concentrations in fruits, vegetables, crustaceans and shellfish (Pearson et al., 2020). Elevated lithium exposure (>1,000 μg/L) through drinking water has been reported in some areas in Austria and South America (Kapusta et al., 2011; Zaldivar, 1980; Concha et al., 2010). In Sweden, Li concentrations in well water are generally low (median 6.7 μg/L; Harari et al., 2017). Bottled water may contribute to elevated Li exposure as certain brands have shown to contain lithium concentrations of up to 5,000–10,000 μg/L (Krachler and Shotyk, 2009). The daily dose of Li, prescribed for mood disorders ranges between 300 and 1,300 mg. The GM Li excretion in this study was 18 μg/24 h and statistically significantly higher among men (22.2 vs 14.0 μg/24 h among women). Our results are very similar to the median of 19 μg/24 h in UK patients (Sienawska et al., 2012). Li is readily absorbed from the intestinal tract, and at high intake it is mainly excreted in urine (95%) with a half-life of 1–4 days (Davanzo et al., 2011). Toxicokinetics at low-dose Li from environmental sources are, however, largely unknown.

4.1.9. *Nickel*

The GM excretion of the essential element Ni was 1.5 μg/24 h, similar in men and women. This is lower than 5.1 μg/24 h reported in patients from the UK (Sieniawska et al., 2012) and 3.3 μg/24 h from US patients (Komary-Hiller et al., 2000), but similar to the median of 1.9

μg/24 h in Chinese men (Wang et al., 2016). Urine is the major elimination pathway of Ni, and the half-life of U–Ni is about one day (Klein and Costa, 2015).

4.1.10. Mercury

The 24 h excretion of Hg was 0.23 μg and very similar in men and women. This is lower than reported in a few previous studies. Sienawska et al. (2012) found a median U–Hg of 0.7 μg/24 h in UK adults, Komaromy-Hiller et al. (2000) 1.0 μg/24 h in US adults, and Akerstrom et al. (2017) 1.9 μg (mean) in Swedish adults. The number of dental amalgam fillings has, however, a strong impact on U–Hg, and in the study by Akerstrom et al. (2017) >90% had dental amalgam fillings, while that was the case in a minority of the individuals in the present study.

4.1.11. Selenium

The excretion of Se was 26.3 and 19.7 μg/24 h in men and women, respectively. These levels are very similar to the results of around 26 and 18 μg/24 h in men and women reported from UK patients by Sieniawska et al. (2012). They are, however, much lower than the median levels of 128 and 109 μg/24 h reported in men and women from Japan (Yoneyama et al., 2008), and around 162 μg/24 h reported in an American population (Longnecker et al., 1996). Chen et al. (2019) found a low median of 9.4 μg/24 h in eleven Chinese men. Substantial differences in urinary Se levels were observed in an experimental study of subjects on a diet high in Se (114 μg/24 h) compared to low (14.9 μg/24 h) (Hawkes et al., 2003). The dietary intake of Se from food is dependent on the soil from where crops for human and animal consumption are grown (Alexander, 2015), which is the likely explanation of differences between countries.

4.1.12. Tungsten

The GM 24 h urinary excretion of W was only 0.08 μg, similar in men and women. This is slightly lower than the median reported in Chinese men (Wang et al., 2019) and substantially lower than the GM of around 9 μg/24 h reported in UK patients (Sieniawska et al., 2012). Recent studies of spot urine samples have reported median concentrations of 0.04 μg/g creatinine and 0.07 μg/L in occupationally unexposed populations (De Palma et al., 2010; Ellingsen et al., 2017). Moreover, Alimonti et al. (2005) found a GM of 0.05 μg/L in spot samples from 50 Italian individuals. This suggests that the W levels reported by Sieniawska et al. (2012) are too high.

4.1.13. Uranium

Urine is the major elimination pathway for U, but human exposure is normally low. Therefore 24 h U levels were below the detection limits in previous studies from the UK and the US (Sieniawska et al., 2012; Komary-Hiller et al., 2000). Uranium in diet often originates from dirt contaminating potatoes or certain vegetables (Keith et al., 2015). Table salt is another source, and in areas with high U content in rock and soil, drinking water levels of U may be high (Kurttio et al., 2002). In the present study the GM of U was 3 ng/24 h. This is consistent with reports from the US of U levels of 7–8 ng/gC in spot samples (Keith et al., 2015), but much lower than the median of 55 ng/24 h reported by Wang et al. (2019) in eleven Chinese men. A study in a Finnish population consuming drinking water from drilled wells in granite bedrock showed a median U level in overnight urine samples of 78 μg/L (Kurttio et al., 2002), i.e. >10 000 times higher than in the present study.

4.1.14. Vanadium

The GM urinary V excretion of 0.02 μg/24 h is substantially lower than the median amount of 1.9 μg/24 h reported in a previous study (Sieniawska et al., 2012). As for W, there is little information published on 24 h urinary excretion of V. However, spot urine samples of non-occupationally exposed individuals have shown concentrations of 0.05 μg/g creatinine (Ellingsen et al., 2017) or around 0.1–0.2 μg/L (Barceloux, 1999; Gruzewska et al., 2014). This may indicate that also the V levels reported by Sieniawska et al. (2012) are too high.

4.1.15. Iron, manganese, tin, copper, zinc and molybdenum

For the essential elements Fe, Mn, Sn, Cu, Zn and Mo, excretion in feces (mainly via bile) is more important than elimination in urine (Lucchini et al., 2015; Ellingsen et al., 2015; Ostrakhovitch, 2015; Sandstead 2015; Tallkvist et al., 2015). This limits the importance of urine biomonitoring for these elements. However, increased levels of Cu in urine are found in Wilson's disease, and in other conditions with disturbed copper transporters. The GM 24 h excretion of Fe (4.4 μg), Mn (0.18 μg), Sn (0.36 μg), and Cu (8.8 μg) were lower than reported in UK patients (Fe: 12 μg, Mn: 0.7 μg, Sn: 2.3 μg, Cu: 22 μg) by Sieniawska et al. (2012) and in Chinese men (Fe: 38 μg, Mn: 1.9 μg, Cu 11 μg) by Chen et al. (2019) and Wang et al. (2019). The GM excretion of Zn was 352 μg/24 h, and higher in men than in women. The results for Zn are similar to those found in the UK (Sieniawska et al., 2012), in the US (Komary-Hiller et al., 2000), as well as in Chinese men (Chen et al., 2019). Homeostasis of Zn is maintained by regulating gastrointestinal absorption as well as urinary excretion. For Mo, the GM in the present study was 54 μg/24 h, with no difference between men and women. Similar results were found in UK patients (66 μg/24 h) (Sieniawska et al., 2012) and in Chinese men (96 μg/24 h) (Wang et al., 2016). Mo excretion in bile is more important than excretion in urine. Cereals and dairy products are the most important sources (Swedish National Food Agency, 2012).

4.1.16. Sulphur and phosphorous

The 24 h excretions of S (GM 744 mg) and P (GM 867 mg) are in agreement with previous literature (Magee et al., 2004; Palomino et al., 2013). Dietary intake of S and P is mainly derived from protein, but for S also inorganic sulfates and sulfites contribute (Magee et al., 2004). Urine is the major elimination route for both elements.

4.2. Variability within and between individuals

Urinary excretion of elements varies over the day (Smolders et al., 2014; Wang et al., 2016, 2019) and therefore the within-person variance is reduced in 24 h urine samples compared to spot samples. In spite of this we found considerable within-person variability in 24 h samples for many elements. This was, however, not the case for Pb, Cd and Hg, for which the low within-person (inter-day) variability and high ICCs reflect the long half-lives of these elements. For Cd this is in agreement with previous findings by Akerstrom et al. (2014) and Wang et al. (2016). For Pb, Wang et al. (2016) found high within-person variability in Chinese men, and a very low ICC of 0.01. In the present study ICC was high (≥0.75) also for Co, Se, Sn, V, and Zn. This is in agreement with the study in Chinese men for Co (Wang et al., 2016) and Zn (Chen et al., 2019), while the ICC for Se was much lower in that study (Chen et al., 2019). For Sn and V we found no published studies on ICC. ICC values approaching or exceeding 0.75 are desirable for good to excellent reliability in exposure classification, while an ICC below 0.4 indicates that a single sample (in our case a 24 h urine sample) will not provide reliable exposure classification (Rosner, 2015).

We found low ICC (<0.4) for Sb, Cr and Mn in agreement with the study in Chinese men (Wang et al., 2016, 2019; Chen et al., 2019). For Li we found no previous published study on ICC. For Mo, Ni, U, W and P) the ICCs were around 0.5 in our study, which is much higher than the ICCs presented for Mo, Ni, U, and W in the Chinese study (Wang et al., 2016, 2019). ICC around 0.5 indicate fair to good reproducibility (Rosner, 2015).

There seem to be very disparate results for some of the elements, especially for Pb and Se but also for Cu, Mo, Ni and U. Further investigations on variability of metals in urine for 24 h samples, first morning samples as well as for spot samples from different time of the day are needed in order to provide reliable exposure assessment in epidemiological studies on health effects. For elements with long half-life the associations between concentrations adjusted for creatinine or specific gravity can be expected to be quite strong. This has been demonstrated in some studies, which include both first morning urine and 24 h urine samples, e.g. Pearson correlation coefficients of 0.75 for cadmium (Akerstrom et al., 2013), and 0.84 for mercury (Akerstrom et al., 2017). We hope to be able to present such data also for other elements and other day-time sampling times.

4.3. Impact of adjustment for creatinine or SG

It is not surprising that excretion of elements in mass/24 h was highly correlated with concentrations adjusted for creatinine or specific gravity, or unadjusted concentrations. Such adjustment is mainly done to take into account variability in urinary flow rate, which is less relevant in 24 h samples. The fact that creatinine-adjusted 24 h concentrations for some metals are higher in women is a natural result of the lower average 24 h excretion of creatinine in women.

4.4. Associations between elements – common sources

The most important route of exposure for all elements examined is diet. Excretion of S and P is largely affected by intake of protein, with meat, fish and dairy products a s important sources. This likely explains the high correlation between excretion of S, P, and Se, and also moderate associations between these elements and Fe, Cu, Zn, and V (Swedish National Food Agency, 2012). For Cu, Zn, Fe and Mn, also cereals are important dietary contributors (Swedish National Food Agency, 2012), contributing to intercorrelations. The high correlation between As and Hg is likely due to fish consumption (Swedish National Food Agency, 2012).

4.5. Strengths and limitations

The present study is moderately sized (N = 60) and limited to Sweden. On the other hand, the individuals had mixed ethnic origin. The study included only non-smokers, which is a strength if impact of dietary sources is examined, but a limitation if there is a focus on the impact of smoking. It adds to the knowledge of levels and variability in 24 h excretion of many elements, since for most of the elements the only prior data on ICC was derived from repeated samples in 11 young Chinese men (Wang et al., 2016, 2019; Chen et al., 2019).

4.6. Implications and conclusions

Information on variability within- (inter-day) and between individuals is important when designing studies where urine levels of elements are used as exposure biomarker in studies of associations with health outcomes. A high ICC is necessary in such studies if only a single 24 h sample is available since otherwise the true exposure-response associations will be attenuated (Rappaport and Kupper, 2008). These data on 24 h excretion of a large number of elements can also be used as updated reference levels, especially for a number of elements with no or limited previous data available.

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Ethics approval

The study was approved by the Ethics Review Board at the University of Gothenburg, and all participants signed a written informed consent to participate in the study.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2021.113693.

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The mediating role of lung function on air pollution-induced cardiopulmonary mortality in elderly women: The SALIA cohort study with 22-year mortality follow-up

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ABSTRACT

Background: Air pollution exposure is associated with reduced lung function and increased cardio-pulmonary mortality (CPM).

Objectives: We analyzed the potential mediating effect of reduced lung function on the association between air pollution exposure and CPM.

Methods: We used data from the German SALIA cohort including 2527 elderly women (aged 51–56 years at baseline 1985–1994) with 22-year follow-up to CPM. Exposures to PM_{10}, $PM_{2.5}$, $PM_{2.5}$ absorbance, NO_2 and NO_x were assessed by land-use regression modelling and back-extrapolated to estimate exposures at baseline. Lung function (FVC, FEV_1) was measured by spirometry and transformed to GLI z-scores. Adjusted Cox proportional hazards and causal proportional hazards mediation analysis models were fitted.

Results: The survival analysis showed that reduced lung function (z-scores of FVC or FEV_1 below 5% predicted) reflected significantly lower survival probability from CPM ($p < 0.0001$). Longterm exposures to NO_x and NO_2 were associated with increased risks of CPM (eg. HR = 1.215; 95%CI: 1.017–1.452 for IQR increase in NO_x and HR = 1.209; 95%CI: 1.011–1.445 for IQR increase in NO_2) after adjusting for reduced lung function and additional covariates. The associations of $PM_{2.5}$ absorbance and CPM remained significant in models adjusted for FEV_1/FVC, but the associations with PM_{10} and $PM_{2.5}$ were not significant. The mediation analysis showed significant indirect effects of NO_2 and NO_x on CPM mediated through reduced FEV_1 and FVC. The largest indirect effects were found for exposures to NO_2 (HR = 1.037; 95%CI: 1.005–1.070) and NO_x (HR = 1.028; 95%CI: 1.004–1.052) mediated through reduced FVC. The mediated proportion effect ranged from 13.9% to 19.6% in fully adjusted models.

Discussion: This study provides insights into the mechanism of reduced lung function in association between long-term air pollution exposure and CPM. The mediated effect was substantial for exposure to nitrogen oxides (NO_x and NO_2), but less pronounced for PM_{10} and $PM_{2.5}$.

1. Introduction

According to the Global Burden of Disease studies, the long-term exposure to ambient air pollution is responsible for increasing morbidity and mortality, especially in low-income and middle-income countries (Cohen et al., 2017). In 2012, ambient particulate matter caused about 85 million disability-adjusted life years (DALYs) (World Health Organization, 2018). The latest study applied on a global scale

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indicated that outdoor air pollution caused significant excess mortality and loss of life expectancy, particularly through ischaemic heart disease, followed by low respiratory infections, chronic obstructive pulmonary disease (COPD) and lung cancer (LC) (Lelieveld et al., 2020). These estimated effects, jointly called cardiopulmonary diseases, seem to be the most crucial according to recent rigorous epidemiological studies.

The most substantial associations have been seen between long-term exposures and mortality due to cardiovascular diseases (CVD), COPD and LC in large studies of Asian populations (Chen et al., 2016; Yang et al., 2018; Yin et al., 2017). The results of 22 European Cohorts (within the multi-center European Study of Cohorts for Air Pollution Effects - ESCAPE project) have shown only borderline hazard ratios of cardiovascular mortality for nitrogen oxides (NO_x) or nitrogenic dioxide (NO_2) and particulate matter with an aerodynamic diameters of $\leq$10 μm (PM_{10}) or $\leq$2.5 μm ($PM_{2.5}$) (Beelen et al., 2014b). The significant association of long-term NO_2 and $PM_{2.5}$ exposures on mortality for ischaemic heart disease was found in an Italian cohort of more than a million adults (Cesaroni et al., 2013). Besides this, a nationwide cohort of U.S. adults documented significant evidence that long-term $PM_{2.5}$ exposure contributed to cardiopulmonary mortality (CPM) risk (Dockery et al., 1993; Pope et al., 2019).

Spirometric measures of lung function, specifically forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), are considered to be sensitive indicators of both respiratory and cardiovascular health (Gan et al., 2004; Götschi et al., 2008; Silvestre et al., 2018). Causality is supported by biologic mechanisms of promoting oxidative stress and respiratory inflammatory responses as a consequence of exposures to ambient air pollution. Pulmonary responses may subsequently lead to sub-clinical systemic inflammation resulting in endothelial dysfunction and cardiovascular diseases (Künzli and Tager, 2005). The effect of air pollution is well established for respiratory outcomes. According to the ESCAPE study of 5 European cohorts, increases in NO_2 and PM_{10} were associated with a lower level of FEV_1 and FVC (Adam et al., 2015). In addition, another European cohort study documented reduced decline in FEV_1 during a reduction of PM_{10} over 11 years (Downs et al., 2007).

Nevertheless, very few studies have reported the effect of lung function in air pollution-induced cardiopulmonary mortality in elderly. The results of German cohort study SALIA (**S**tudy on the influence of **A**ir pollution on **L**ung function, **I**nflammation and **A**geing) previously demonstrated a link between long-term traffic-related air pollution and chronic obstructive pulmonary disease (COPD) (Schikowski et al., 2005). Moreover, this study focused on investigation whether respiratory health contributed to cardiovascular mortality due to the negative effect of long-term exposure. Despite the fact that a significant association of impaired lung function on mortality in survival analysis has been shown, no interaction between long-term exposure to pollutants and respiratory health was observed (Schikowski et al., 2007).

Therefore, the SALIA study provided an opportunity to investigate longitudinal mediated effect of reduced lung function on the association between air pollution and cardiopulmonary mortality in elderly women after 22 years of observation. The underlying hypothesis was that exposure to air pollutants could induce lung impairment through a local inflammatory response, especially in susceptible populations, which could promote systemic inflammatory response and subsequently lead to cardiopulmonary mortality (van Eeden et al., 2005).

2. Methods

2.1. Study design and population

Data were used from the SALIA German prospective cohort study with 22-year mortality follow-up. The investigators recruited 4874 participants between 1985 and 1994 from seven different study areas in a highly industrialized district (Ruhr area) and two nearby non-industrial towns. This analysis focused on women (aged 51–56 years at baseline) whose addresses were available and could be merged with geographical coordinates (Schikowski et al., 2005). In 2008, a follow-up was conducted, providing mortality data for 4756 women. The survival and mediation analysis presented here was based on 53% of the participants, for whom also lung function measurements were available at baseline. From the whole sample of participants recruited, every second woman was invited for lung function testing. Afterwards, 91 participants with missing exposure data were excluded, resulting in a sample of 2527 women. Written informed consent from all study participants was collected. The study was approved by the ethics committee of the Ruhr University in Bochum (Germany).

2.2. Air pollution exposure assessment

We applied a Geographical Information System for the exposure assessment. Annual average concentrations of NO_x, NO_2, PM_{10}, $PM_{2.5}$ as well as $PM_{2.5}$ absorbance (absorbance of particulate matter with an aerodynamic diameter $\leq$ 2.5 μm or less, determined as the reflectance of $PM_{2.5}$ filters) were assigned to each participant. First, five-year (2003–2007) means of PM_{10} and NO_2 from routine monitoring sites located nearest to the women's home addresses were used to define long-term air pollution background exposure. Second, air pollution was monitored in three 2-week periods (cold, warm and intermediate seasons) over the measurement campaign (2008–2009) in the 40 sites for NO_2 and 20 sites for particulate matter of the study area in frame of the ESCAPE project. Afterwards, validated Land-use regression (LUR) models were used to assign the individual long-term exposure to air pollutants of each participant's home address. Predictor variables on population/household density, nearby traffic and land use were applied to control spatial variations (Beelen et al., 2014a; Eeftens et al., 2012). To estimate exposures during the baseline investigation (1985–1994), back-extrapolation was conducted by multiplying the modelled ESCAPE annual mean concentration with the ratio between average annual concentrations derived from eight routine monitoring sites for the period in the past and for the ESCAPE measurement period time (Beelen et al., 2013; Hüls et al., 2017). By implementing this technique, the implicit spatial contrasts over time were validated. The models achieved moderate to high adjusted R^2 of 0.85 for $PM_{2.5}$ mass, 0.66 for PM_{10} mass and 0.88 for NO_2 (Hüls et al., 2019). The air pollution exposures are standardized in interquartile ranges (IQR).

2.3. Health outcomes

Mortality data (cause and date of death) were obtained from official death certificates collected until 23rd December 2008. The causes of death were coded according to the International Classification of Diseases, ninth (ICD-9) or tenth revision (ICD-10). The main outcome of interest was cardiopulmonary mortality defined as causes of death from cardiovascular diseases (ICD-9 codes 400–440 or ICD-10 codes I10 – I70) as well as from lung cancer (ICD-9162/ICD-10 C33, C34) and from respiratory diseases (ICD-9460–519/ICD-10 J00 – J99). The limited number of deaths in the sample required combining mortality outcomes. Participants dying from natural causes as well as all other causes were censored at time of death.

2.4. Pulmonary function

Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured according to American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations (Miller et al., 2005) during the baseline investigation. Descriptions of measurement techniques and strategies have been provided in a previous publication (Hüls et al., 2019). Lung function (FEV_1, FVC and their ratio FEV_1/FVC) was transformed to z-scores according to the reference values from the Global Lung Initiative (Quanjer et al., 2013) to control for age and height-dependency. Reduced lung function was defined using $z < -1.64$ (5% quantile of the standard normal distribution) as lower limit of normal (LLN) for the z-score values of FEV_1, of FVC and of FEV_1/FVC.

2.5. *Assessment of potential confounders for cardiopulmonary mortality*

As a part of the SALIA study, all participants completed a self-administered questionnaire focused on education, current symptoms or diseases, medications, smoking and occupational exposures. The potential confounders were defined according to American and Dutch cohort studies (Dockery et al., 1993; Hoek et al., 2002) and were also used in several previous studies conducted on SALIA cohort (Gehring et al., 2006; Schikowski et al., 2007). Potential risk factors such as age, socio-economic status (SES), body mass index (BMI), current or former smoking and second-hand smoking were assessed at the baseline investigation. SES was subdivided into three categories according to the highest educational level of the woman and her spouse (<10; $= 10$ or $>$ 10 school years). Passive smoking was considered as second-hand tobacco smoke exposure at home or the workplace for nonsmoking women.

2.6. *Statistical methods*

The Spearman (r_s) correlations between pollutants (NO_x and NO_2, PM_{10} and $PM_{2.5}$) were estimated. Survival time was calculated as the interval from the time of a participant's recruitment to death or censoring (in years). Kaplan-Meier estimates were used for survival curves in subgroups with reduced vs. normal lung function. Log-rank tests were performed to test for differences in survival probability from cardiopulmonary mortality between these two groups.

Multivariable Cox proportional hazards (PH) models (Cox, 1972) were fitted to determine the association between long-term air pollution exposures (PM_{10}, $PM_{2.5}$, $PM_{2.5}$ absorbance, NO_2 and NO_x) and cardiopulmonary mortality. Crude models for each pollutant adjusted for reduced lung function (FVC, FEV_1 or FEV_1/FVC) were fitted. Other models were fitted additionally adjusting for age, socioeconomic status, BMI, current smoking, former smoking and second-hand smoking. Hazard ratios (HRs) with corresponding 95% confidence interval (CIs) were estimated for these models.

Furthermore, mediation analysis of air pollution through reduced lung function on cardiopulmonary mortality was conducted. The causal mediation analysis was performed from a counterfactual perspective and a semiparametric Cox PH model was applied to analyze the time-to-event data (Yu et al., 2014; Yu and Li, 2017). Since a rare outcome (occurring in less than 10% of subjects) was expected, the proportional hazard model was appropriate (VanderWeele, 2011). The results of the analysis are presented as hazard ratios (HR) transferred from Cox PH regression coefficients with corresponding 95% confidence interval for indirect, direct and total effects, as well as the proportion of effect through the mediator (Burgos Ochoa et al., 2020). To conclude a mediation effect, the indirect and total effect must be significant. The direct effect describes the effect of the independent variable (exposure to each air pollutant) on the time-to-event outcome (cardiopulmonary mortality). Whereas the indirect effect describes the effect of the independent variable on the time-to-event outcome when changing the value of the mediator (reduced lung function). The total effect is estimated as the summation of the direct and indirect effect. The proportion (in %) of indirect effect in the total effect describes the range to which the association between air pollution and cardiopulmonary mortality is mediated through reduced lung function (Valeri and Vanderweele, 2013). The direct, indirect and total effects were estimated additionally for a multiple mediators model combining the effect of the reduced FVC, FEV_1 and FEV_1/FVC. All models were adjusted for potential confounders described above.

As sensitivity analyses for Cox PH models, we included interactions of long-term air pollution exposures of several pollutants and reduced lung function when modelling cardiopulmonary mortality. Additionally, we refitted the Cox PH models as well as mediation analysis in the subset of never-smokers (current and former smokers eliminated) due to smoking being a major confounder. Statistical analyses were carried out in R (version 4.0.2. R Core Team, 2019) using the "survival" and "mma" packages (Therneau, 1999; Yu and Li, 2020).

3. Results

3.1. *Descriptive statistics*

A descriptive analysis of the exposure concentrations and lung function parameters as well as the population characteristics and co-variate distributions are provided in Table 1. The cohort was exposed to a wide range of air pollution concentrations. The exposures to PM_{10} and $PM_{2.5}$ were strongly correlated ($r_s = 0.896$), as well as the exposures to NO_x and NO_2 ($r_s = 0.961$). Furthermore, the exposures to PM_{10} and NO_x were highly correlated ($r = 0.745$) as well as the exposures to $PM_{2.5}$ and NO_x ($r_s = 0.805$). At baseline, the women were on average 54 years old and had a mean BMI in the overweight range (27.6 $kg*m^{-2}$) and relatively low tobacco consumption (14% current smokers, 8% former smokers). Nevertheless, almost 50% of them had been exposed to second-hand smoke at home or at work. Of the whole sample, 8.4% had reduced FVC, 14.7% reduced FEV_1 and 10% reduced FEV_1/FVC.

3.2. *Survival probabilities in participants with reduced vs. normal lung function*

Among the 2527 women included in the present analyses, 130 cardiopulmonary deaths were observed. Most of the participants died of unspecified cardiovascular causes (44.7%) or ischaemic heart disease (21.1%). The survival time (time between recruitment and death/censoring) ranged from minimum of 4.7 months to maximum of 23.8 years. Survival probabilities from cardiopulmonary mortality in participants with reduced (z-score below LLN) vs. normal lung function are presented as Kaplan Meier curves in Fig. S1. The survival analysis showed that reduced lung function (in terms of FVC, FEV_1 and $FEV_1/$

Table 1

Characteristics of lung function measurements, long-term ambient air pollution exposure and socio-demographic variables of the German SALIA Cohort (n = 2527).

Characteristics	Mean ± SD	Min – Max
FVC z-score	−0.26 ± 1.01	−4.67 – 3.25
FEV_1 z-score	−0.51 ± 1.10	−4.54 – 3.85
FEV_1/FVC z-score	−0.49 ± 0.91	−4.32 – 4.04
Age [years]	54.5 ± 0.7	51.9–56.3
BMI [$kg*m^{-2}$]	27.6 ± 4.6	15.4–61.7
Air pollutants	**Mean (IQR)**	**Quantiles (25%, 50%, 75%)**
PM_{10} [$\mu g*m^{-3}$]	49.4 (5.5)	(47.8, 50.9, 53.3)
$PM_{2.5}$ [$\mu g*m^{-3}$]	32.6 (3.9)	(31.6, 33.4, 35.6)
$PM_{2.5}$ absorbance [$10^{-5}*m^{-1}$]	2.7 (0.9)	(2.2, 2.6, 3.1)
NO_x [$\mu g*m^{-3}$]	71.0 (46.0)	(46.0, 57.3, 92.0)
NO_2 [$\mu g*m^{-3}$]	38.9 (16.7)	(29.8, 35.4, 46.5)
Socioeconomic status [years]	**n (%)**	
<10 school years	665 (26.3)	
= 10 school years	1232 (48.8)	
>10 school years	627 (24.8)	
Missing values	3 (0.1)	
Smoking status	**n (%)**	
Current smokers	360 (14.2)	
Former smokers	201 (8.0)	
Never smokers	1966 (77.8)	
Second hand smoke	1232 (48.8)	

Abbreviation: SD, Standard deviation; IQR, Interquartile range; FVC, Forced vital capacity (transformed to z-scores); FEV_1, Forced expiratory volume in 1 s (transformed to z-score); NO_x, Nitrogen oxides; NO_2, Nitrogen dioxide; $PM_{2.5}$, Particulate matter with aerodynamic diameter ≤ 2.5 μm; PM_{10}, Particulate matter with aerodynamic diameter ≤ 10 μm; $PM_{2.5}$ absorbance, Absorbance of particulate matter with an aerodynamic diameter ≤ 2.5 μm or less.

FVC) was associated with lower probability of survival. The differences between normal and reduced FVC or FEV_1 were significant according to the log-rank test ($p < 0.001$), but borderline for FEV_1/FVC ($p = 0.06$).

3.3. *Associations of air pollution with cardiopulmonary mortality*

Hazard ratios and corresponding 95% confidence intervals for the crude and adjusted (for potential confounders) Cox PH models are presented in Fig. S2 and Fig. 1, respectively. In the crude models, significant impacts of long-term exposures to all pollutants (increase of one interquartile range in concentrations) on cardiopulmonary mortality were observed when adjusting only for reduced lung function (FVC, FEV_1 and FEV_1/FVC z-score below LLN). The covariate adjusted models confirmed significant associations of an IQR increase in concentrations of NO_x and NO_2 with survival, after adjusting for reduced lung function and potential confounders (for example FEV_1: HR = 1.215; 95%CI: 1.017–1.452 for NO_x; HR = 1.209; 95%CI: 1.011–1.445 for NO_2). The impacts of long-term exposure to PM_{10} and $PM_{2.5}$ were no longer significant after adjusting for the covariates, apart from associations with $PM_{2.5}$ absorbance in the case of crude model adjusting for reduced FEV_1/FVC. (Fig. 1).

A sensitivity interaction analysis was performed to examine the combined effect of lung function reduction and exposures to NO_2 or NO_x on mortality. Significant interactions were not observed (irrespective of the combination of lung function indicator and air pollutant). Some of the covariates were strongly associated in this interaction model. In general, more than 10 school years (an indicator of higher socioeconomic status) appeared as a protective factor for cardiopulmonary mortality (for example: HR = 0.418; 95%CI: 0.223–0.783). Increased HRs were observed for current smoking (for example: HR = 3.057; 95% CI: 2.033–4.596) and increased BMI (for example: HR = 1.294; 95%CI: 1.106–1.515) (Table S1). As an additional sensitivity analysis, a model was fitted with two strata, namely smokers and never-smokers. In never-smokers, the association between cardiopulmonary mortality and $PM_{2.5}$ absorbance was (still) significant (HR: 1.233; 95%CI: 1.004–1.514 for FVC and HR: 1.252; 95%CI: 1.020–1.537 for FEV_1/FVC), but only borderline for the other pollutants.

3.4. *Mediation of the associations by reduced lung function*

The results of mediation analysis confirmed the association between long-term exposures to NO_x and NO_2 and likelihood of cardiopulmonary mortality. Significant indirect effects of an IQR increase in concentrations of NO_x and of NO_2 on cardiopulmonary mortality mediated by reduced FEV_1, and significant indirect effects of an IQR increase in concentrations of $PM_{2.5}$ absorbance, NO_x and NO_2 mediated by reduced FVC were observed (Table 2). The largest indirect effect was found for exposures to NO_2 (HR = 1.037; 95%CI: 1.005–1.070) (Fig. 2a) and NO_x (HR = 1.028; 95%CI: 1.004–1.052) (Fig. 2b) mediated through reduced FVC. The proportion mediated ranges from 13.9% to 19.6% in covariate-adjusted models. The mediation effect of reduced FVC was also shown in the effect of exposure to $PM_{2.5}$ absorbance on cardiopulmonary mortality. The results of the joint effect of all mediators (reduced FVC, FEV_1 and FEV_1/FVC) were consistent with mediator-separated models (Table 2).

As a sensitivity analysis, a mediation analysis was fitted in never-smokers. Mediation proportion of FEV_1 was the highest for NO_x exposure 16.6% (−3.6 – 30.6). However, none of the mediation effects were statistically significant (Table S2).

4. Discussion

In the present analysis, we found significant impacts of long-term exposures to air pollution on cardiopulmonary mortality in models that adjusted for reduced lung function (FVC, FEV_1 and FEV_1/FVC z-scores below LLN). The effect was substantial for exposure to nitrogen oxides (NO_x and NO_2), but less pronounced for PM_{10} and $PM_{2.5}$. Traffic (vehicles fueled by diesel in particular) is a major source of nitrogen oxides, and especially in some urban areas the concentration might still exceed the EU limit values, even though the air quality has significantly improved since more stringent legislation and regulations were implemented. To our knowledge, this is one of the first epidemiological studies showing a partially mediated effect of reduced lung function in the association of air pollution exposure on cardiopulmonary mortality. The strongest mediator was reduced FVC, especially in the case of NO_2 and NO_x long-term exposures. These results contribute to explaining the pathway of adverse effects of air pollution on cardiopulmonary mortality through lung function impairment.

Our findings of significant effects of NO_2 and NO_x exposure on cardiopulmonary mortality confirm previous results in the same cohort (HR = 1.39, 95%CI: 1.17 to 1.64 per 16 $\mu g/m^3$ increase in concentration of NO_2) (Heinrich et al., 2013). Our findings are also comparable with previous results of SALIA cohort study showing higher cardiovascular mortality risk in women with impaired lung function (chronic bronchitis diagnosed) (RR = 1.53; 95%CI: 0.83–2.79). However, this analysis could not indicate that women with impaired respiratory health would have an increased risk of cardiovascular death associated with increased long-term air pollution exposure (Schikowski et al., 2007). The current

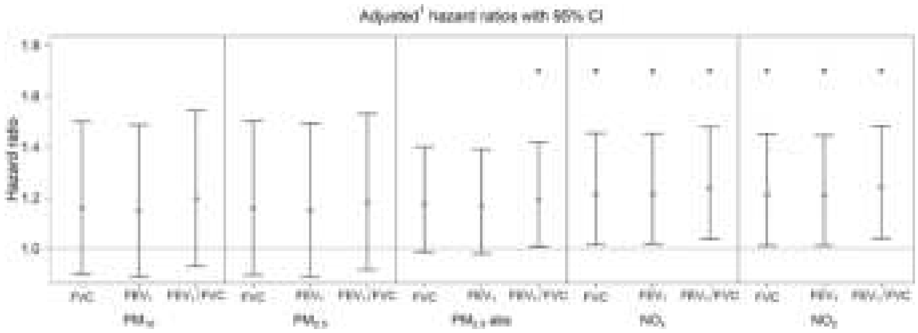

Fig. 1. Adjusted hazard ratios and 95% confidence interval of cardiopulmonary mortality for long-term exposures (per interquartile range (IQR) increase in the concentration of each pollutant) and additionally adjusting for reduced lung function, the German SALIA Cohort (n = 2527).

[1] Model adjusted for age, socioeconomic status, BMI, current smoking, former smoking and passive smoking. The hazard ratios are expressed per one IQR increase in concentrations of PM_{10} (IQR = 5.5 $\mu g*m^{-3}$), $PM_{2.5}$ (IQR = 3.9 $\mu g*m^{-3}$), $PM_{2.5}$ abs (IQR = 0.9 $10^{-5}*m^{-1}$), NO_x (IQR = 46.0 $\mu g*m^{-3}$) and NO_2 (IQR = 16.7 $\mu g*m^{-3}$); $*p < 0.05$. Abbreviation: CI, Confidence interval; FVC, Forced vital capacity (transformed to z-scores); FEV_1, Forced expiratory volume in 1 s (transformed to z-scores); FEV_1/FVC, Tiffeneau index (transformed to z-scores); NO_x, Nitrogen oxides; NO_2, Nitrogen dioxide; $PM_{2.5}$, Particulate matter with aerodynamic diameter of ≤ 2.5 µm; $PM_{10,}$ Particulate matter with aerodynamic diameter of ≤10 µm; $PM_{2,5}$ abs, Absorbance of particulate matter with an aerodynamic diameter of 2.5 µm or less.

Table 2
Mediation analysis (exposure: air pollution; mediator: reduced lung function; outcome: survival time from cardiopulmonary mortality) of the German SALIA Cohort (n = 2404). Direct, indirect and total effects (Hazard ratios and 95% confidence intervals per IQR increase in concentration), proportion of mediated effects (%, 95% confidence intervals).

Pollutant	Direct effect	Indirect effect	Total effect	Proportion mediated
	HR (95% CI)	HR (95% CI)	HR (95% CI)	% (95% CI)
Mediator: reduced FEV_1				
PM_{10}	1.123 (0.926, 1.409)	1.027 (1.005, 1.060)	1.154 (0.942, 1.423)	38.7 (−251, 676)
$PM_{2.5}$	1.136 (0.862, 1.366)	1.023 (1.006, 1.046)	1.162 (0.875, 1.392)	49.8 (−36, 979)
$PM_{2.5}$ abs	1.177 (0.922, 1.417)	1.028 (1.004, 1.053)	1.209 (0.942, 1.442)	22.8 (−35.6, 137)
NO_x	1.306 (0.977, 1.589)	1.027 (1.006, 1.055)	1.340 (1.017, 1.636)	14.9 (1.6, 241.6)*
NO_2	1.291 (0.980, 1.603)	1.035 (1.006, 1.074)	1.336 (1.025, 1.676)	16.5 (2.0, 180.9)*
Mediator: reduced FVC				
PM_{10}	1.143 (0.958, 1.414)	1.021 (1.004, 1.038)	1.167 (0.983, 1.434)	64.1 (−215, 2556)
$PM_{2.5}$	1.144 (0.933, 1.510)	1.017 (1.004, 1.030)	1.163 (0.952, 1.527)	14.6 (−230, 272)
$PM_{2.5}$ abs	1.188 (1.009, 1.478)	1.023 (1.002, 1.043)	1.215 (1.035, 1.494)	14.3 (0.8, 78.8) *
NO_x	1.298 (1.041, 1.538)	1.028 (1.004, 1.052)	1.334 (1.076, 1.569)	13.9 (1.1, 51.7) *
NO_2	1.291 (0.963, 1.613)	1.037 (1.005, 1.070)	1.339 (1.020, 1.621)	19.6 (1.0, 285)*
Mediator: reduced FEV_1/FVC				
PM_{10}	1.176 (0.976, 1.439)	1.006 (0.997, 1.014)	1.183 (0.987, 1.452)	−2.0 (−166, 25.8)
$PM_{2.5}$	1.180 (0.946, 1.448)	1.006 (0.997, 1.014)	1.187 (0.950, 1.465)	5.0 (−9.0, 34.3)
$PM_{2.5}$ abs	1.225 (1.002, 1.536)	1.007 (0.994, 1.019)	1.233 (1.008, 1.551)	4.8 (−11.8, 73.4)
NO_x	1.359 (0.973, 1.631)	1.007 (0.995, 1.020)	1.369 (0.979, 1.656)	1.7 (−31.7, 12.3)
NO_2	1.358 (1.019, 1.605)	1.009 (0.994, 1.024)	1.370 (1.027, 1.617)	3.3 (−1.4, 27.6)
Joint mediation effects of FEV_1, FVC, FEV_1/FVC				
PM_{10}	1.128 (1.013, 1.381)	1.029 (0.995, 1.072)	1.160 (1.032, 1.420)	24.7 (−2.6, 68.4)
$PM_{2.5}$	1.146 (0.990, 1.433)	1.024 (0.994, 1.062)	1.174 (1.001, 1.461)	48.9 (−2.4, 1345)
$PM_{2.5}$ abs	1.157 (0.886, 1.520)	1.031 (0.990, 1.064)	1.193 (0.923, 1.538)	16.7 (−78.5, 72.9)
NO_x	1.287 (1.035, 1.681)	1.033 (1.006, 1.072)	1.329 (1.071, 1.711)	14.5 (1.4, 58.3) *
NO_2	1.274 (1.024, 1.748)	1.043 (1.005, 1.093)	1.329 (1.093, 1.784)	18.4 (1.2, 74.4) *

All models are adjusted for age, socioeconomic status, BMI, current smoking, former smoking and second-hand smoking. The hazard ratios are expressed per one IQR increase in concentrations of PM_{10} (IQR = 5.5 $\mu g*m^{-3}$), $PM_{2.5}$ (IQR = 3.9 $\mu g*m^{-3}$), $PM_{2.5}$ abs (IQR = 0.9 $10^{-5}*m^{-1}$), NO_x (IQR = 46.0 $\mu g*m^{-3}$) and NO_2 (IQR = 16.7 $\mu g*m^{-3}$); * Statistically significant ($p < 0.05$) mediation effect of reduced lung function in air pollution-induced cardiopulmonary mortality (significant indirect and total effect). Abbreviation: HR, hazard ratios; CI, confidence interval; Proportion mediated, proportion in percent of indirect effect in the total effect; FVC, Forced vital capacity (transformed to z-scores below LLN); FEV_1, Forced expiratory volume in 1 s (transformed to z-scores below LLN); FEV_1/FVC, Tiffeneau index (transformed to z-scores below LLN); NO_x, Nitrogen oxides; NO_2, Nitrogen dioxide; $PM_{2.5}$, Particulate matter with aerodynamic diameter ≤ 2.5 μm; PM_{10}, Particulate matter with aerodynamic diameter ≤ 10 μm; $PM_{2.5}$ abs, Absorbance of particulate matter with an aerodynamic diameter ≤ 2.5 μm or less.

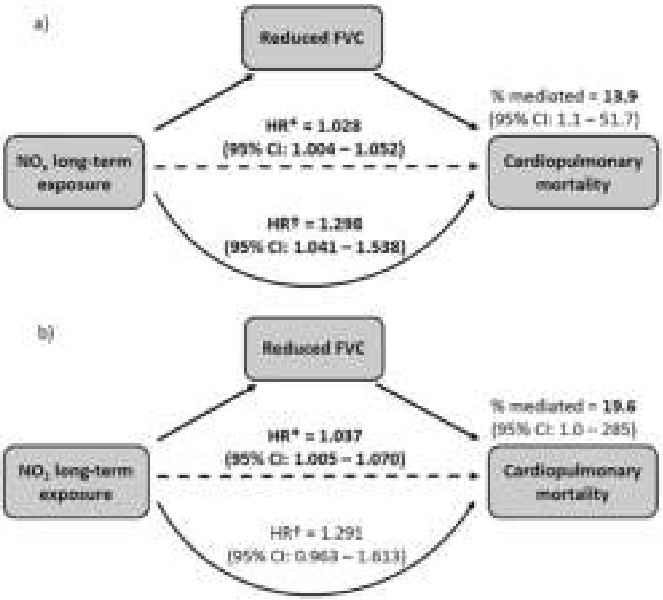

Fig. 2. Pathway of the mediation process; indirect and direct effects (Hazard ratios and 95% confidence intervals) of long-term exposures on cardiopulmonary mortality through FVC, German SALIA Cohort (n = 2404).
a) Pathway of the mediation process of long-term exposures to NO_x on cardiopulmonary mortality; b) Pathway of the mediation process of long-term exposures to NO_2 on cardiopulmonary mortality. Abbreviation: HR, Hazard ratio; CI, Confidence interval; β*, Mediated indirect effect; $β^{†}$, Direct effect; FVC, Forced vital capacity (transformed to z-scores); NO_x, Nitrogen oxides; NO_2, Nitrogen dioxide. Model adjusted for age, socioeconomic status, BMI, current smoking, former smoking and passive smoking.

analysis is based on more advanced exposure modelling and more recent mortality follow-up. Furthermore, our study provides evidence about impact of both long-term air pollution exposure and reduced lung function on cardiopulmonary mortality by mediation analysis.

These findings might be explained by lifestyle differences between women who were living in industrial and nonindustrial areas. For instance, women from the Ruhr area could differ from women living in nonindustrial area not only in terms of air pollution concentrations, but also in terms of physical (in-)activity and other potential risk factors which were highly associated both with lung function, and cardiopulmonary mortality. Additionally, the Netherlands cohort study (Hoek et al., 2002) found that the air pollution effect estimates were substantially smaller than those associated with active smoking. However, in our analysis of never smokers, we still saw an effect of air pollution, albeit the effect estimates were a bit weaker. Besides, the heterogeneity of lung function among elderly should be also considered. There are several recent studies investigating the underlying biological aging processes and related epigenetic based biomarkers, explaining these differences among never-smoking individuals with the same height and chronological age (Lowsky et al., 2014; Wang et al., 2020).

Even though, the impact of long-term exposure of $PM_{2.5}$ was no longer significant after adjusting for lung function and potential covariates, we reported the association with cardiopulmonary mortality per 10 $\mu g/m^3$ increase in concentration of pollutant after adjusting for FEV_1, for example, HR = 1.424; 95%CI: 0.741–2.74. This result was directly comparable to other key studies. For example, the most recent results of a large, nationwide cohort of U.S. adults provided evidence, that each 10 $\mu g/m^3$ increase in long-term $PM_{2.5}$ exposure contributed to cardiopulmonary mortality risk (HR = 1.23; 95%CI: 1.17–1.29) (Pope et al., 2019). In earlier studies, Pope et al. found approximately 6% increased risk of cardiopulmonary mortality for each 10 $\mu g/m^3$ elevation in fine particulate air pollution (RR = 1.09; 95%CI: 1.03–1.16 for $PM_{2.5}$) (Pope et al., 2002). Moreover, a recent Canadian study also showed statistically significant effects of long-term $PM_{2.5}$ exposure on cardiovascular disease (HR = 1.25; 95%CI: 1.19–1.31), ischaemic heart disease (HR = 1.36; 95%CI: 1.28–1.44) and chronic obstructive pulmonary disease (COPD) mortality (HR = 1.24; 95%CI: 1.11–1.39) per 10 $\mu g/m^3$ increase in concentration (Pinault et al., 2017).

4.1. Strengths and limitations

Due to over 20 years follow up, we were able to estimate the survival probability as well as mortality risks for diseases with long latencies, such as lung cancer. The SALIA cohort has been well characterized. The restriction of the study population to elderly women with German nationality has ensured better control of several covariates (the limitation of occupational exposures, lower prevalence of active smoking and similar dietary habits between women). Detailed questionnaires provided sufficient information about known confounders during two decades. Exposure estimation has been conducted on individual level by LUR modelling, which is used in an increasing number of epidemiological studies of air pollution (Eeftens et al., 2012). The exposure estimation was conducted based on a relatively low number of measurements during a relatively short measurement campaign (Basagaña et al., 2012). However, the back-extrapolated concentrations estimated by the LUR models were validated in previous studies and therefore, represent an adequate exposure assessment (Hüls et al., 2019).

Since the lung function measurements were collected only for a subgroup of the SALIA cohort, the sample size was limited. Moreover, the women received only one lung function measurement. Due to the young age of women at baseline, the number of deaths was small during the follow-up investigation. Furthermore, data from death certificates might be potentially biased for specific cause of death. That the study population included women living in non-industrial as well as the Ruhr area might also be a limitation, because of potential differences in lifestyle with respect to socioeconomic factors and physical activity, which were associated with cardiopulmonary mortality. We controlled socioeconomic factors by adjusting for the highest education of the women or their spouses, but not for occupational exposures which could differ between areas. Moreover, there was no detailed information about other lifestyle factors.

The enrollment of the cohort extended over a period of 1985–1994, therefore, there were some differences in the follow-up duration. This could also cause inaccuracy in the back extrapolated individual air pollution estimates, because air pollution declined during the enrolment period. Another limitation of our study is that the air pollution exposure was estimated based on the baseline exposure only, despite the exposure substantially decreasing between the baseline investigation and time of the death certificate collection. According to a recent analysis by Hüls and colleagues, improvement of air quality has a beneficial effect on lung function in the SALIA cohort (Hüls et al., 2019). Since, a mortality follow-up from recent years is not yet available, we could not compare the effects of an improvement of air quality, potential positive lifestyle changes and lung function on cardiopulmonary mortality during the current analysis. However, our study primarily aimed to examine the long-term effects of the air pollution exposure, and revealed that reduced lung function in mid-life (age 55 years at baseline) has a significant impact on mortality in elderly. Nevertheless, further follow-ups are worthwhile to investigate the effects of improvements of air quality and mitigation in lung function reduction on future mortality to even enhance our findings.

5. Conclusion

This study provides insights into the mechanism of reduced lung function in association between long-term air pollution exposure and cardiopulmonary mortality. We found that reduced lung function indirectly mediated the air pollution-induced mortality of elderly women and partially explained this pathway. However, there is evidence that a decline in air pollution exposure has a positive impact on lung function in elderly, thus more studies examining the association with cardiopulmonary mortality are needed. Moreover, the underlying mechanism between long-term air pollution and lung function impairment in elderly should be studied further and clarified on a molecular level, since there is growing body of evidence suggesting interaction of long-term air pollution and genetic susceptibility which might play an important role in age-related diseases and mortality.

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Declaration of competing interest

The co-author Prof. Michael Abramson declares financial interests related to investigator initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. He has taken an unrelated consultancy for and received assistance with conferences travel from Sanofi. He has also received a speaker's fee from GSK. The other authors declare they have no actual or potential competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2021.113705.

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