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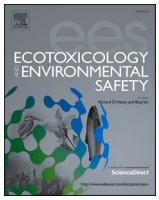

Sex/gender in the association between ambient air pollution and cardiovascular mortality: Systematic review and meta-analysis

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ABSTRACT

When assessing the association between air pollution and cardiovascular mortality, it remains unclear whether females or males are more susceptible and whether and to what extent the pre-existing studies have accounted for different sex/gender dimensions. We searched three databases to identify short-term and long-term studies on the association between air pollution and cardiovascular mortality published 2000–2023 to assess their integration of sex/gender. We further evaluated whether sex/gender was a source of heterogeneity within these through a moderator analysis using random effects models. We examined sex/gender differences through random effects pooling of the female-to-male-ratio (FMR) of each study. We identified 106 studies, all of which operationalised sex/gender in binary terms and lacked a sex/gender-theoretical concept. However, the biological and social dimensions of sex/gender were indirectly included in the discussions. Meta-analyses did not identify sex/gender as a source of heterogeneity (e.g. short-term particulate matter with a diameter <10μm (PM_{10}): *p*-value of moderator test= 0.85; long-term: 0.34). The pooled FMR showed no sex/gender differences for short-term associations (1.0[CI: 0.0;0.0] for each air pollutant) and a trend towards higher effect estimates for males than females in long-term studies with a pooled FMR ranging from 0.93 to 0.99. Binary categorisation without conceptualisation does not appear to be sufficient to identify vulnerable sex/gender groups, if any, in the association between air pollution and cardiovascular mortality. Considering the multiple biological and socio-cultural dimensions of sex/gender from the very beginning of study planning will help to move beyond speculative discussions and derive meaningful action for prevention and health care.

1. Introduction

Over many years, epidemiological studies have found clear associations between ambient air pollution and cardiovascular diseases (CVD) mortality (Rajagopalan et al., 2018; de Bont et al., 2022; Al-Kindi et al., 2020). Worldwide, ambient air pollution accounted for 28 % of all deaths from ischemic heart disease and 27 % of all deaths from stroke in 2021 (HEI, 2024). Proposed biological mechanisms include direct stimulation of pulmonary receptors activating the autonomic nervous system and triggering oxidative stress and inflammation, or translocation of air pollutants into blood circulation where they may exacerbate atherosclerosis, provoke local oxidative stress and inflammation and affect the vascular endothelium (Al-Kindi et al., 2020; Vidale and Campana, 2018). To further understand the association between air pollution and cardiovascular health, studies have aimed to identify susceptible population subgroups. Thereby, it is reasonable to distinguish between different sex/gender dimensions. Accordingly, the number of epidemiological studies on the association between air pollution and cardiovascular health which consider potential differences between the binary categories of male and female has continued to increase over the past 20 years (Heo et al., 2022; Liao et al., 2023; Orellano et al., 2020; Zhang et al., 2022a). However, findings are not always consistent from one study to another. One reason for this lack of consistency could be that the different facets of sex and gender were not adequately addressed in prior studies, or due to the difficulty or impossibility of addressing both sex and gender in epidemiological studies using a binary

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operationalisation. According to Krieger (2003). "sex is a biological construct premised upon biological characteristics enabling sexual reproduction. Among people, biological sex is variously assigned in relation to secondary sex-characteristics, gonads, or sex chromosomes". In other words, sex is usually categorised into "females" and "males" based on social conventions related to presentations of visible biological features. Gender, on the other hand, refers to a social construct formed by norms, roles, behaviors and relations of and between gendered groups which vary within and across societies, typically as a function of social categorisation based on power and authority (Krieger, 2003). Within the context of environmental epidemiology, Clougherty (2010) suggested that sex-linked biology could be understood as being related to pollutant susceptibility, biologic fate, or dose-response relationships. Aspects of gender could relate to differences in exposures due to occupation, activity patterns or social roles.

In the context of pre-existing theories, we posit and emphasise, that it is not possible to completely separate the biological from the social dimensions of an individual, which is why we use the term "sex/gender" in this article (Springer et al., 2012). This entanglement is particularly evident in the concept of embodiment, which describes how the body characteristics and processes of sex-linked biology can be altered over time by behavioural factors and the physical, chemical, biological, social and built environment (Krieger, 2005). By using the combined term "sex/gender", we avoid the mixing of the concepts "sex" and "gender". In "gender-specific medicine", these two terms are often inappropriately used interchangeably, out of alignment with current and accepted theory (Hammarström and Annandale, 2012). The term "sex/gender" does not imply that sex and gender can be used interchangeably, but points to their intertwined nature, the mechanisms of which need to be explored.

Furthermore, according to intersectional theory various social categories such as sex/gender, class, ethnicity, disability and age determine different levels of power relations, interact with each other and can influence health inequities (Hammarström and Annandale, 2012; Kapilashrami and Hankivsky, 2018). Consequently, the focus should not be only on individual identities, but also on social contexts and power relations as determinants of health inequities. However, sex/gender and societal context are still largely ignored in epidemiological analyses focusing on environmental health issues (Bolte et al., 2021). Accordingly, reviews and meta-analyses focusing on sex/gender differences in the association between air pollution and cardiovascular health have been limited so far and either did not consider the difference between sex/gender (Liao et al., 2023; Orellano et al., 2020; Zhang et al., 2022a) or included it only in the discussion section (Heo et al., 2022).

To address this gap in evidence, it is necessary to analyse the current state of the art, to describe the aspects of existing research that could benefit from the integration of a deeper understanding of sex/gender, and identify research questions that should be addressed in future studies. Our objectives were (1) to evaluate whether and to what extent sex/gender is integrated into studies of the association between air pollution and cardiovascular mortality in the general population, and (2) to use meta-analytic methods to evaluate whether the existing studies have found a difference between sex/gender groups and whether any existing heterogeneity within the studies can be explained by the use of binary sex/gender categorisations or by other study-specific characteristics.

2. Methods

2.1. Search strategy

We searched for epidemiological studies using the databases MEDLINE with the search template PubMed, Web of Science (WoS), and Scopus. We focused on studies of particulate matter with a diameter $< 2.5\mu m$ ($PM_{2.5}$) and $< 10\mu m$ (PM_{10}), nitrogen dioxide (NO_2) and ozone. Potentially relevant articles dealing with sex/gender differences were identified by using the search terms "sex", "gender", "males", "females", "men" or "women". The outcome was described with the terms "mortality" or "deaths" combined with "cardiovascular", "circulatory", "heart disease", or "CVD". We limited our search to articles published between January 1, 2000 and July, 31, 2023. Language was restricted to English and German. The full search strategy is described in supplementary material A, S1. Using a snowballing process, we complemented our systematic searches by screening other reviews and meta-analyses as well as the introduction sections and discussion sections, and reference lists of articles we identified through our systematic search and screening process.

2.2. Selection criteria

We screened the titles, abstracts and full texts of identified articles. Articles were selected for review if they met the following criteria: (1) original, peer-reviewed research, (2) observational study design (e.g. cohort, cross-sectional, case-crossover, case-control or time-series study), (3) general population, (4) CVD defined exclusively by the 9th or 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-9 or ICD-19) with ICD-9 codes 390–459 or ICD-10 codes I00-I99 covering both ischemic heart disease (ICD-9: 410–410, ICD-10: I20-I25) and cerebrovascular disease (ICD-9: 430–438, ICD-10: I60-I69), (5) ambient air pollution and (6) sex/gender-specific analysis performed (e.g. subgroup analysis, interaction analysis). We included studies analyzing individual or aggregated data. We excluded studies that (1) did not provide a linear exposure-response-function for the association between air pollutant and CVD mortality (e.g. relative risk, odds ratio, percent-change in risk), or only reported risk estimates that were stratified by exposure group, and (2) where exposure was clearly not representing background air pollution. Finally, (3) as exclusion criteria for meta-analysis, if there were more studies analyzing the same population or exposure data, we only included the study covering a longer study period or the most recent publication. Study selection was done independently by three reviewers (UK, LD, SH). In the case of conflicts, we reached consensus through discussion.

2.3. Data extraction

For each study, we extracted the full citation, the continent where the study was performed, study period, study design, study population, outcome and exposure assessment, statistical methods including adjustment, and sex/gender-specific results. The sex/gender-specific results were entered by two different persons (UK, MW). Where results were not reported as numbers in the publication, we contacted the corresponding author by email or estimated them from figures where possible. If risk estimates were provided for different exposure windows, we chose the risk estimate in the following order of preference: (1) the risk estimate the author focused on, (2) the risk estimate that was of most statistical significance (independent of direction) or(3) the largest risk estimate (independent of direction). If a study provided single as well as pooled estimates (e.g. across cities), we extracted the single estimates. We converted the estimates into standardised increments in cardiovascular mortality per $10\,\mu g/m^3$ increase in air pollutant (supplementary material A, S2). We also extracted information on the integration of sex/gender. This included mentioning underlying sex/gender concepts like intersectionality or embodiment, the rationale for the sex/gender analysis, the operationalisation and conceptualisation of sex/gender and how findings were discussed.

2.4. Risk of bias rating

We assessed the risk of bias (RoB) of the studies in terms of bias due to confounding, bias due to selection, and bias due to detection, which combines bias due to exposure and outcome assessment. To assess the bias due to confounding we used the WHO tool for epidemiological studies on air quality and health (WHO, 2020). For the other two

domains, we relied on the assessments of other reviews (Heo et al., 2022; Orellano et al., 2020, 2024; Zhang et al., 2022a; Chen and Hoek, 2020; Chen et al., 2024; Mahakalkar et al., 2024; Song et al., 2022; Wang et al., 2021) that either used the WHO tool or the Office of Health Assessment and Translation (OHAT) (OHAT, 2019) approach, and we assessed the domains ourselves based on the WHO tool if no other assessment was available. For each domain, a study can be assessed as having a low, moderate, or high RoB in line with the WHO tool. The OHAT tool uses the rates definitely low, probably low, probably high, and definitely high RoB. In order to align the two tools we have taken the first OHAT rating option as low, the second and third as moderate and the last as high.

2.5. Data analyses

To evaluate whether and to what extent sex/gender is integrated into studies of air pollution and cardiovascular mortality, we used the assessment matrix developed by Horstmann et al. (2023), which visualises the consideration of sex/gender through 14 items covering the entire research process and reporting of results: (1) Precise use of sex/gender-specific terminology, (2) sex/gender mentioned in the title, (3) sex/gender mentioned in the abstract, (4) rationale given for the consideration of sex/ gender, (5) sex/gender mentioned in the objective, (6) hypotheses given, (7) source of information for recruitment is reported, (8) reporting of selection of study population, (9) data collection and operationalisation reported, (10) consideration of sex/gender variety and multidimensionality, (11) sex/gender-specific analysis, (12) description of the study population, (13) sex/gender-specific results presented, and (14) discussion of sex/gender-specific results. Detailed information on these items is given elsewhere (Horstmann et al., 2023).

To quantify the sex/gender-specific associations, we first pooled all individual sex/gender-specific estimates for each air pollutant and separately for short-term and long-term studies. We used random effects meta-analysis applying the DerSimonian-Laird method to account for the within and between study heterogeneity (DerSimonian and Laird, 1986).

Second, we conducted a mixed-effects meta-analysis by additionally including sex/gender as a categorical moderator, hereafter referred to as moderator analysis. We then used an omnibus test to assess whether sex/gender contributed significantly to the heterogeneity in the association between air pollution and cardiovascular mortality. To identify other sources of heterogeneity between studies we carried out moderator analyses with the following categorical and continuous variables: continent, study type, time lag, exposure assessment method as well as number of CVD cases, exposure mean, follow-up, minimum age at baseline, population size and publication year, depending on whether it was appropriate for short-term or long-term studies. Pooled effects are reported as percent-changes in risk of CVD death per 10 $\mu g/m^3$ increase in air pollutant.

Third, in order to make the direction of a possible effect modification by sex/gender visible and to take into account that two estimators always come from the same study, we pooled the female-to-male ratio (FMR) of Odds Ratios (supplementary material A, S2) (O'Keeffe et al., 2018; Wang et al., 2019) by random effects meta-analysis, using the DerSimonian-Laird method.

We assessed heterogeneity across studies using a Chi-squared test (Cochran's Q) and calculating inconsistency (I^2), which represents the proportion of total variation in effect estimates due to heterogeneity across the studies (Higgins et al., 2003). Publication bias was evaluated in moderator analyses by visual examination of funnel and trim and fill plots of the effect sizes plotted against its standard error.

To test the robustness of the results we excluded effect estimates that were extreme in both males and females. These estimates were identified using influence analyses based on the leave-one-out-method and Cook's distance, with the threshold set at the 50th percentile of a Chi-squared distribution with 1 degree of freedom (i.e. $X^2(1;\ 0.5) \approx 0.45$)). Additionally, we repeated the pooling of the FMR with the rating for each risk of bias due to selection and confounding included as categorical moderator.

Analyses were done in R software, version 4.3.2, using the metafor package (Viechtbauer, 2010). Our study was conducted in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines (supplementary material A, S3).

3. Results

3.1. Selection process

In total, the systematic literature search yielded 5864 studies. After removal of duplicates and reviews and after exclusions based on title, abstract and full-text screening, 103 articles were identified for in-depth review. The snowballing procedure led to the inclusion of three additional articles (Alexeeff et al., 2023; Byun et al., 2019; Goldberg et al., 2001) meaning that 106 studies were eligible for qualitative synthesis (67 short-term and 39 long-term studies). For the meta-analysis, 12 studies had to be excluded because more recent analyses or analyses with a longer study period were available in other articles (Chen et al., 2018a; Cheng et al., 2019; Duan et al., 2019; He et al., 2020; Liu et al., 2015; Luo et al., 2016; Raaschou-Nielsen et al., 2012; Thurston et al., 2016; Wong et al., 2015; Yi et al., 2010; Yin et al., 2017; Zhang et al., 2017). In eight other studies, we had to exclude the estimates for single air pollutants due to overlaps with other studies (supplementary material A, S4) (Guo et al., 2017; Hvidtfeldt et al., 2019; Qian et al., 2010; Shin et al., 2022; Son et al., 2012; Su et al., 2015; Xu et al., 2020a; Zhang et al., 2011). For 22 of the remaining studies the estimates for the exposure-response-function were not available in numeric form, but we received numeric estimates for nine of these studies through direct communication with study authors (Cesaroni et al., 2013; Chen et al., 2013; Dehbi et al., 2017; Fischer et al., 2015; Gariazzo et al., 2023; Maciejewska, 2020; Ostro et al., 2008; Pope et al., 2015; Yang et al., 2018). For three studies the estimates could be assessed based on the corresponding figure (Chen et al., 2017; Lim et al., 2021; Sui et al., 2021). Two other studies and single estimates of one study had to be excluded due to ambiguity (Zhang et al., 2011; Ren et al., 2010; Rudolph et al., 2022). After this process, 82 studies (52 short-term and 30 long-term) were eligible for meta-analysis. The detailed selection process is shown in Fig. 1.

3.2. Study characteristics

The basic characteristics of the included studies are described in supplementary material B. The short-term studies eligible for qualitative synthesis mostly used a time series design (51 versus 16 case-cross-over studies) and were mainly conducted in China (48 versus ten in Europe, seven in North America, and one each in South America and Africa). Air pollutant exposure was assessed using data from monitoring stations except for in three studies which used modelling techniques. Short-term exposure was in generally expressed as a 24-hour mean. In addition to the 24-hour mean, ozone was analysed as an 8-hour mean and an 8-hour maximum. Outcome information was based on death certificates.

All 39 long-term studies were cohort studies, 13 of which were conducted in Asia, one in Australia, nine in Europe, 15 in North America and one study included countries from all over the world. In most studies, air pollution exposure was assessed using modeling techniques, but six studies solely used monitoring station data. The duration of long-term exposure to air pollutants varied from study to study, but summarised exposure for at least one year through the calculation of a 1-year mean value. Outcome information was mainly acquired through death certificates. Data collection for all studies took place before the start of the COVID-19 pandemic in 2019. Only 24 of 106 studies reported differences between females and males in the association between air pollutants and cardiovascular mortality (p-value <0.1).

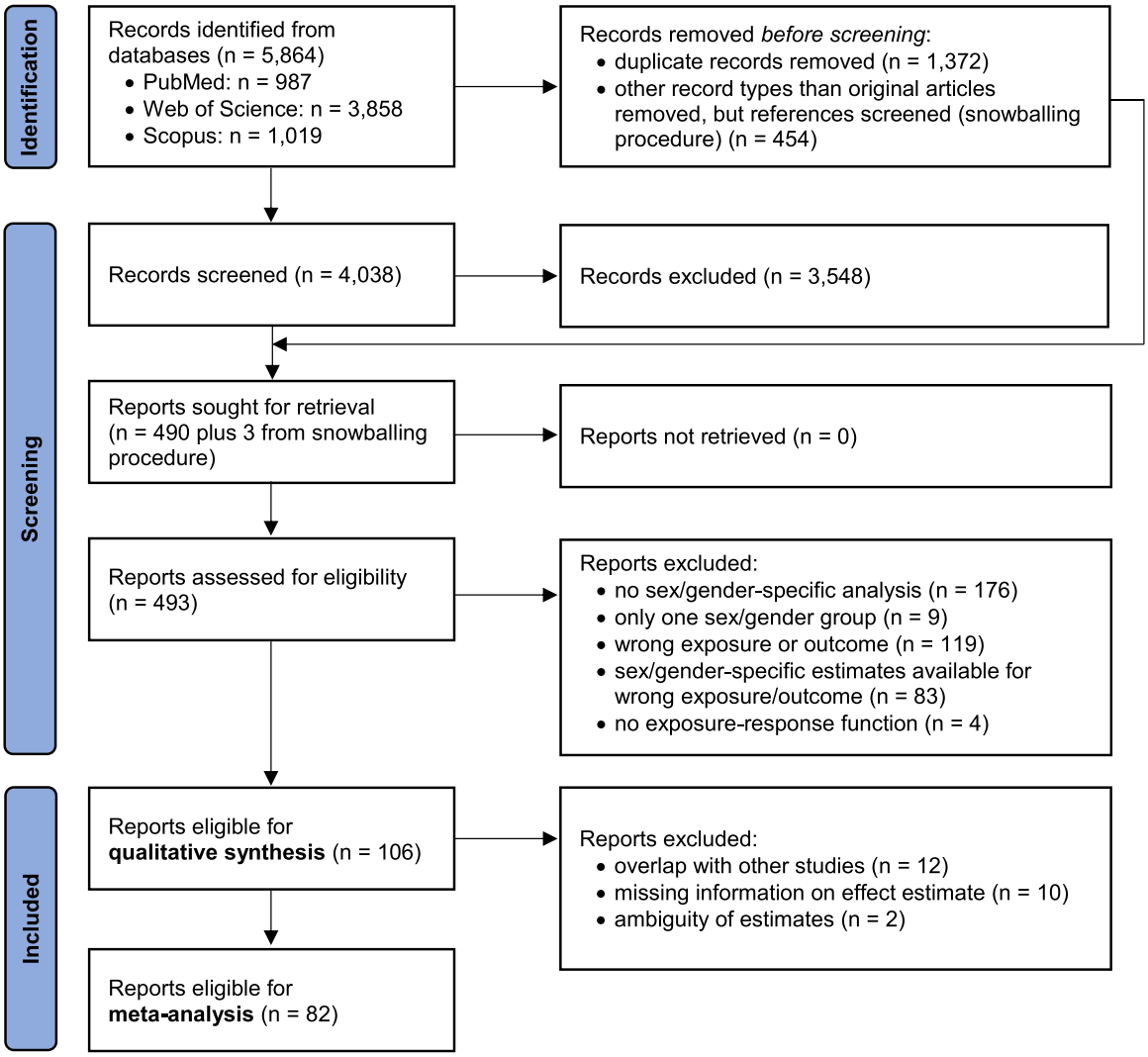

Fig. 1. Flow chart, identification process for eligible studies.

3.3. *Integration of sex/gender*

The evaluation of the integration of sex/gender using the assessment matrix proposed by Horstmann et al. (2023) showed that sex/gender was either barely or only partially integrated in the studies (Figs. 2 and 3; supplementary material A, S5). All studies used either the term 'sex' or 'gender' without explaining it and sometimes both terms were used interchangeably. Nevertheless, two different groups of authors were

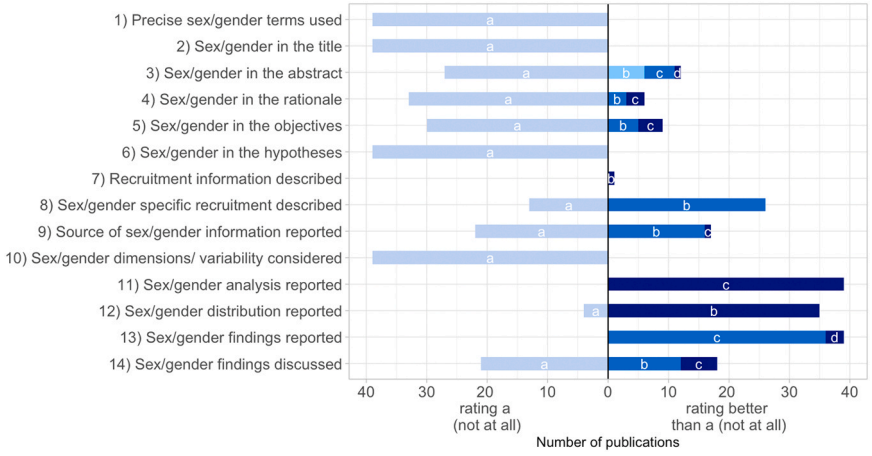

Fig. 2. Number of short-term studies of the association between air pollution and cardiovascular mortality with a specific rating of the 14 criteria to assess sex/gender consideration. Fulfilment of the evaluation criterion: a - not at all; b, c or d - to a certain extent depending on the specific criterion (for a detailed explanation see Horstmann et al (Horstmann et al., 2023)).

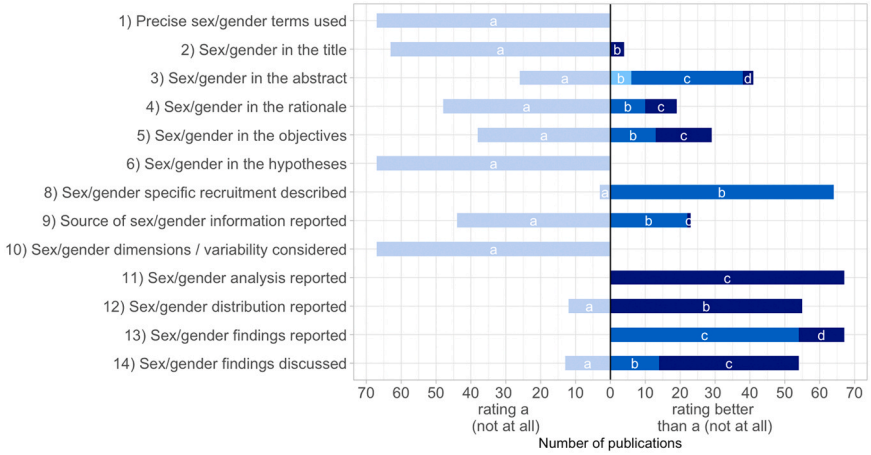

Fig. 3. Number of long-term studies of the association between air pollution and cardiovascular mortality with a specific rating of the 14 criteria to assess sex/gender consideration. Fulfilment of the evaluation criterion: a - not at all; b, c or d - to a certain extent depending on the specific criterion (for a detailed explanation see Horstmann et al. (2023)).

aware of the difference between sex and gender, as the authors mentioned both in the introduction and/or discussion section when referring to biological and social factors (Shin et al., 2022, 2020; Hůnová et al., 2013). Sex/gender specific analysis was not indicated within the titles of the studies except in the case of four studies (Shin et al., 2022; Son et al., 2012; Kuźma et al., 2020; Psistaki et al., 2023). In long-term studies sex/gender was not included as part of the rationale for the sex/gender-specific analyses or in the study's stated objectives. In short-term studies, sex/gender was more frequently referenced in relation to identifying susceptible groups or modifying factors in the association between air pollution. However, no study included sex/gender in the hypotheses if stated at all. The source of information on the sex/-gender of the participants like death certificates or death registries was stated in less than half of the studies. Reported sources of sex/gender data in short-term studies were death certificates and in long-term studies sources were registries, existing cohort databases or basic questionnaires or interviews that included a question on sex/gender. Furthermore, we could not identify any study that considered different sex/gender dimensions or their variability. All studies operationalised sex/gender in a binary way, dividing the study population into males and females, but only two studies described this in the text (Rudolph et al., 2022; Shi et al., 2020). As we exclusively searched for studies that conducted a sex/gender-specific analysis the item No. 11 "sex/gender analysis reported" was fulfilled for every study. While most studies gave information on the sex/gender distribution, only 16 studies reported sex/gender-specific outcome data or further baseline characteristics.

In general, the discussion of results in the identified studies did not necessarily depend on whether the authors found significant differences between males and females. Thirty-four studies, of which five studies observed sex/gender specific differences, did not discuss these results at all. Another 23 studies without and three with sex/gender-specific differences merely summarised their results and/or reported results of other studies without further discussion. The authors of the remaining studies (N = 46) speculate on possible explanations, with 18 of these studies showing significant differences between males and females. In general, most studies that provided explanations described them as enumerations, without referring to their own results and without putting forward a hypothesis as to whether the effect estimate is larger in females or males. These explanations referred on the one hand to biological aspects (Table 1), which mainly included the physiology of the lung. The articles broadly agreed that women have smaller lungs, smaller airways, and higher respiratory reactivity, which leads to a greater deposition of particles. Eleven of these studies found higher risk estimates for females than males and concluded, based on lung physiology, that women were more susceptible to the effects of air pollution

Table 1
Overview of explanations given for possible sex/gender-specific differences in air pollution associations.

BIOLOGICAL ASPECTS	
Physiology of the airway system	Airway reactivity
	Airway resistance
	Airway size
	Breathing patterns
	Deposition of particles
	Gas absorption
	Gas blood barrier permeability
	Inflammatory responses
	Lung function
	Lung size, capacity
	Mucociliary clearance
	Size of pharyngeal area
Physiology other	Age
	Cardiac structure and function
	Comorbidities
	Hereditary factors
	Hormone status/menopause
	Mechanisms controlling fat distribution
	Metabolic rate
	Mortality baseline hazards
	Oxidative stress
	Red blood cell count
	Stress axis dysregulation
	Vascular transport
NON-BIOLOGICAL ASPECTS	
Lifestyle factors	Alcohol consumption
	Nutrition habits
	Physical activity
	Smoking rate
	Willingness to seek health care
Socioeconomic factors	Education
	Occupation
	Index for socioeconomic position
Exposure distributions	Activity patterns/time spent outdoors
	Exposures to indoor allergens and cleaning agents
	Indoor pollution caused by solid fuels, kitchen fumes, household painting
	Occupational exposure
CHANCE RESULTS	

(Shin et al., 2022; Son et al., 2012; Zhang et al., 2011, 2022b; Sui et al., 2021; Chen et al., 2018b; Lu et al., 2023; Ma et al., 2011; Qu et al., 2018; Zhong et al., 2018; Zhu et al., 2017). In contrast, five studies consistently observed a higher risk estimate in males than in females. Two of them mentioned lung physiology as a reason without further explanation (Wu

et al., 2018; Xu et al., 2020b). One study concluded in contrast to its result that females were more susceptible to air pollution due to lung physiology (Li et al., 2021). Stojić et al. (2016) argued that particle deposition occurs in females mainly in the upper respiratory tract, where it can be removed more efficiently, which is why females are at a lower risk than males. On the other hand, a large part of the explanations concerned non-biological topics (Table 1), namely lifestyle, especially smoking, socioeconomic position, and exposure distribution or even that the results were due to chance.

Seventeen studies named different smoking habits as the reason for possible sex/gender differences and most studies unanimously reported a lower smoking rate in females. However, one half of these studies observed higher risk estimates in females, the other half higher risk estimates in males. Three studies providing more detailed explanations hypothesised that the response to air pollution exposure is attenuated in males is because smoking already triggers oxidative and inflammatory processes, and therefore women were more susceptible and at higher risk than men (Chen et al., 2018b; Zhong et al., 2018; Zhu et al., 2017). Contrary, Yi et al. (2010) argued that smoking increases the oxidative and inflammatory effects, which would explain their results of higher estimates observed in men.

In addition, several studies cited the distribution of exposure as a possible reason for sex/gender-specific differences, namely in relation to occupation, activity patterns and time spent outdoors. In two studies, the latter would be higher for men (Duan et al., 2019; Zhang et al., 2022b; Wu et al., 2018; Li et al., 2021; Zhou et al., 2022), which is why men were exposed to more air pollutants and therefore had a higher risk. Two other studies speculated that women inhale more smoke because they spent more time indoors where they may be exposed to air pollution from domestic sources like the combustion of solid fuels (Gong et al., 2019; Mokoena et al., 2019), kitchen fumes, household painting and other indoor sources (Gong et al., 2019).

Nearly all these possible explanations of sex/gender-specific differences in the association between air pollution and CVD mortality were speculative. Although in some studies individual data were available to test these hypotheses in the study population, this was mostly not done.

3.4. Results of meta-analyses

As all studies used a binary variable, we extracted two estimators per study, one for males and one for females. Among short-term studies, this resulted in 66 estimates for $PM_{2.5}$, 52 for PM_{10} and 42 for NO_2. Regarding ozone most eligible studies analysed its 8-hour maximum (9 estimates versus 6 each for 8-hour means and 24-hour means), which we therefore focused on in reporting the results of our meta-analysis. Among long-term studies, we pooled 42 estimates for $PM_{2.5}$, 12 for PM_{10}, and 24 for NO_2. We did not perform a meta-analysis regarding the long-term associations of ozone because we could identify only two studies. Results of the meta-analyses where we pooled all sex/gender estimates showed significant associations of all air pollutants with death from CVD (Table 2 & 3).

Heterogeneity between studies was high with $I^2 > 75$ % for most air pollutants. The mixed effects meta-analyses revealed that sex/gender did not explain this heterogeneity at all (R^2=0). Hence, we did not find any significant differences between females and males in pooled results. However, in long-term studies, the effect estimates were higher for males than for females (Table 3). When we further examined heterogeneity by including other moderators, we identified few that significantly explained some of the heterogeneity between short-term studies (e.g. lag), but without reducing it meaningfully. Regarding long-term studies, in contrast, we found that inclusion of most study characteristics as moderators reduced heterogeneity. For example, after including the population size as moderator in the meta-analysis of PM_{10}, the I^2 reduced from 89.1 to 73.1. For detailed information see supplementary material A, S6.

The FMR analysis showed no significant differences in the pooled effect estimate between females and males, with an FMR of one for short-term studies and an FMR less than one for long-term studies indicating a trend towards a stronger association of long-term air pollution with CVD mortality in males than in females (Figs. 4 to 10).

3.5. Results of sensitivity analyses

Visual examination of funnel and trim and fill plots indicated a publication bias for short- and long-term association between CVD mortality and NO_2 as well as for long-term associations with $PM_{2.5}$ caused by the absence of studies showing negative associations (supplementary material A, S7). Through influence analyses, for short-term studies we identified two studies of being influential regarding $PM_{2.5}$ and PM_{10} (Li et al., 2022; Zhang et al., 2018) and one study regarding Ozone (Zhang et al., 2019). After its exclusion, the pooled sex/gender specific estimates expressed as percent-changes decreased for $PM_{2.5}$ from 1.15 % (0.81 %; 1.49 %) to 0.63 % (0.49 %; 0.77 %) for females and from 0.99 % (0.65 %; 1.33 %) to 0.50 % (0.36 %; 0.64 %) for males. The other exclusions for short-term associations did not meaningfully change the pooled results (supplementary material A, S8). For long-term studies we identified two influential studies for $PM_{2.5}$ (Kazemiparkouhi et al., 2022; Raaschou-Nielsen et al., 2020). After their exclusion the difference in estimates for males and females slightly decreased. When we pooled five remaining studies regarding PM_{10} after exclusion of one influential study (Fischer et al., 2015), sex/gender explained 54.4 % of heterogeneity between the remaining studies and I^2 was substantially reduced from 89.1 to 40. The effect estimate for males increased from 19.65 (7.56;33.10) to 26.43 (15.85;37.97), while the

Table 2
Results of meta-analyses: random effects and mixed effects model (random intercept and sex/gender as moderator) for short-term associations.

Short-term	Model	Categories	N	I^2	QEp	QMp	R^2	%-change (CI)[a]
$PM_{2.5}$	Random	–	66	97.0	< 0.001	–	–	1.06 (0.83;1.30)
	Mixed	Males	33	96.9	< 0.001	0.52	0.0	0.99 (0.65;1.33)
		Females	33					1.15 (0.81;1.49)
PM_{10}	Random	–	52	98.0	< 0.001	–	–	0.66 (0.48;0.84)
	Mixed	Males	26	97.3	< 0.001	0.85	0.0	0.65 (0.38;0.91)
		Females	26					0.68 (0.42;0.95)
NO_2	Random	–	42	74.4	< 0.001	–	–	1.07 (0.79;1.35)[b]
	Mixed	Males	21	75.0	< 0.001	0.95	0.0	1.01 (0.66;1.49)
		Females	21					1.02 (0.67;1.52)
Ozone (8-h max)	Random	–	18	71.3	< 0.001	–	–	0.34 (0.19;0.48)
	Mixed	Males	9	72.2	< 0.001	0.59	0.0	0.31 (0.05;0.57)
		Females	9					0.41 (0.15;0.67)

CI, confidence interval, QEp, *p*-value of test for heterogeneity (in case of mixed model: test for residual heterogeneity); QMp, p-value of test of differences between categories of moderator (test if at least part of the moderators explains some heterogeneity); R^2, amount of heterogeneity accounted for

[a] %-change in CVD death risk for an increase of 10 µg/mˆ3 in exposure

[b] publication bias evident, results may be overestimated

Table 3
Results of meta-analyses: random effects and mixed effects model (random intercept and sex/gender as moderator) for long-term associations.

Long-term	Model	Categories	N	I^2	QEp	QMp	R^2	%-change (CI)[a]
$PM_{2.5}$	Random	–	42	87.9	< 0.001	–	–	9.65 (7.94;11.40)[b]
	Mixed	Males	21	88.1	< 0.001	0.08	0.0	11.32 (8.76;13.95)
		Females	21					8.08 (5.51;10.66)
PM_{10}	Random	–	12	89.1	< 0.001	–	–	15.15 (7.70;21.11)
	Mixed	Males	6	89.1	< 0.001	0.34	0.0	19.65 (7.56;33.10)
		Females	6					11.13 (−0.35;23.95)
NO_2	Random	–	24	98.4	< 0.001	–	–	6.04 (3.14;9.02)[b]
	Mixed	Males	13	98.5	< 0.001	0.75	0.0	6.92 (2.09;11.99)
		Females	13					5.74. (0.72;11.01)
Ozone (8-h max)	Random	–	2	NA	NA	–	–	NA
	Mixed	Females	1	NA	NA	NA	NA	NA
		Males	1					NA

CI, confidence interval; NA, not applicable; QEp, *p*-value of test for heterogeneity (in case of mixed model: test for residual heterogeneity); QMp, p-value of test of differences between categories of moderator (test if at least part of the moderators explains some heterogeneity); R^2, amount of heterogeneity accounted for

[a] %-change in CVD death risk for an increase of 10 μg/m^3 in exposure

[b] publication bias evident, results may be overestimated

effect estimate for females exhibited only minor change. The exclusion of one study (Eum et al., 2022) for the pooling of estimates for long-term associations with NO_2 resulted in a decrease of the effect estimates while the observed association for females became non-significant (supplementary material A, S8).

Including the RoB domains as moderator did in general not change the results of FMR analyses (supplementary material A, S8). However, the RoB due to confounding explained 100 % of heterogeneity of short-term studies on NO_2. Compared with the analysis without moderator (FMR: 1.000 [0.997;1.004]) the pooled FMR of four studies rated with low RoB due to confounding got significant indicating higher risks for males than females (0.985 [0.975;0.994]). Instead, four studies with high RoB rating led to a significant result in the opposite direction (1.005 [1.002;1.008]).

4. Discussion

4.1. Conceptualisation and operationalisation of sex/gender in identified studies

To increase the validity and generalizability of research findings, much of the literature has advised including sex/gender in the design, implementation, analysis and reporting of health research (Day et al., 2016; Heidari et al., 2016; Johnson et al., 2009; Gahagan et al., 2015; Rich-Edwards et al., 2018). Accordingly, Clougherty (2010) noted in 2010 that sex/gender should also be integrated into air pollution epidemiology research. However, the current systematic review showed, that sex/gender is still not given adequate consideration in studies on the association between air pollution and cardiovascular mortality. We could not find any reference to a sex/gender-theoretical concept in any identified study, and "sex" and "gender" were not defined or even used interchangeably. Additionally, the identified studies provided only a general reason, if at all, for the sex/gender-specific analysis, namely that susceptible groups should be identified or that previous studies have not shown a clear picture. In addition, no study hypothesised a differential effect between males and females nor its direction. Furthermore, all studies used a binary operationalisation dividing the study population into males and females, without providing a coherent conceptualisation of sex/gender. The division of participants solely into male or female prevents the incorporation of intersectionality and embodiment which contribute important facets to a sex/gender theoretical concept (Bolte et al., 2021) by allowing a diversity of sex/gender configurations that are the result of the interplay between physiological, physical and social structures. Possible operationalisations of sex/gender can refer to genetics, physiology, anatomy, sex/gender identity, sex/gender roles, sex/gender expressions, and societal power relations (Krieger, 2003, 2005; Johnson and Repta, 2012; Hammarström et al., 2014; Lindqvist et al., 2020). Additionally, most of the identified studies also lacked information on the source of their sex/gender data. Long-term studies reported that it was obtained from basic questionnaires or interviews, but it remains unclear whether participants indicated their sex/gender through, for example, self-report on predefined categories, in a free-text format, or simply by the examiner judging and characterizing the study participants' sex/gender from their outward experience. The studies also did not report whether the sex/gender data collected at baseline were also used in the analysis or whether the data were taken from death certificates instead, or even whether a comparison was made between sources. In addition, the failure to adequately address sex/gender is also reflected in the lack of reporting of sex/gender-specific baseline characteristics and exposure levels, or even simple CVD mortality counts. One reason for missing case numbers, however, may be that CVD mortality is often only a secondary outcome and case numbers are often only reported for total mortality. Overall, this deficiency of conceptualisation shows that the authors do not consider sex/gender as very important for their research question or are not aware that great value can be added to their research by going beyond a mere binary categorisation of sex/gender, incorporating a conceptualisation based on gender-theoretical concepts, operationalising this conceptionalisation, and conducting theory-based interpretation.

4.2. Results of meta-analyses

The results of the meta-analyses consistently showed adverse associations between air pollution and cardiovascular mortality, overall and separately for males and females, which is in line with the current state of research (Al-Kindi et al., 2020; Orellano et al., 2020; Chen and Hoek, 2020; Atkinson et al., 2018; Mannucci et al., 2019). With regard to different air pollutants and timeframes for their associations the results of our meta-analysis showed that the identified studies were very heterogeneous. However, moderator analysis indicated that the categorisation of the study population into sex/gender did not explain the observed heterogeneity between studies. Rather, it arose from differences in other characteristics, such as study type, lag time or exposure mean in short-term studies and continent, exposure assessment methods, population size or minimum age at baseline in long-term studies. In addition, the analysis of the FMR also showed no differences in the associations, but estimates tended be higher in males for long-term studies. These results indicate that the associations for long-term air pollution may somehow differ between males and females. But due to a lack of conceptualisation and definition of sex/gender, the results can hardly be interpreted in terms of the underlying facets of sex/gender. Associations were not significantly different in a statistical sense and results partly changed in opposite directions after the

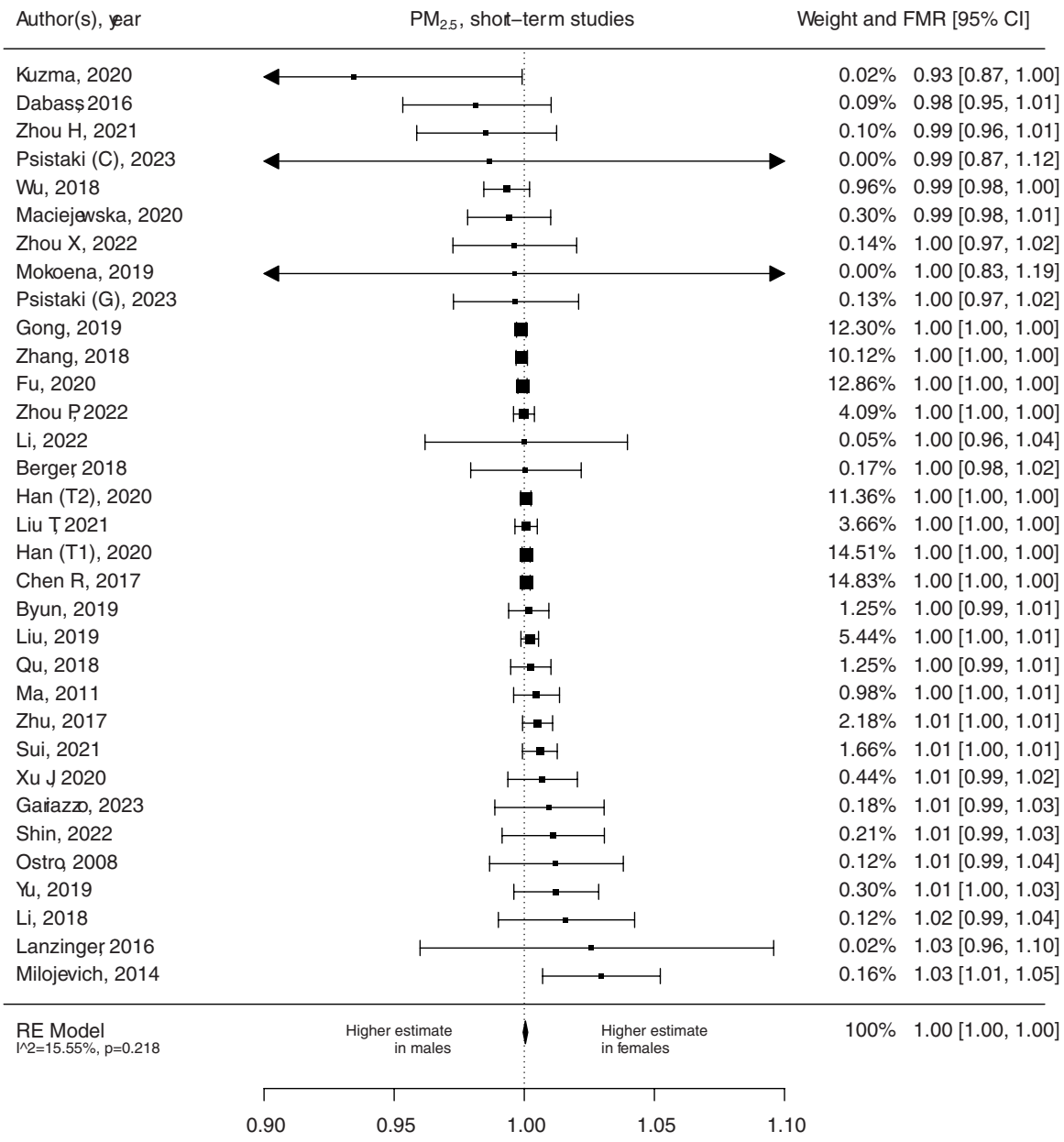

Fig. 4. Pooled female-to-male ratio of Odds Ratios for CVD deaths risk associated with short-term $PM_{2.5}$. OR, odds ratio; Han (T1), study period: 2009–2013; Han (T2), study period: 2013–2016; Psistaki (C), study region: Cyprys; Psistaki (G), study region: Greece.

inclusion of RoB due to confounding. This further suggests that a crude dichotomous categorisation by sex/gender and, moreover, the lack of a definition of terminology is not sufficient to adequately represent the variety of related biological and sociocultural dimensions. It was pointed out many times that risk and outcomes of CVD differ on the one hand by the biological sex due to differences in gene expression by sex chromosomes and differences in the effects of sex hormones on, for example, vascular function (Regitz-Zagrosek and Kararigas, 2017). On the other hand, it was also recognised that sociocultural factors lead to different CVD profiles for males and females as these groups vary in several ways regarding, for example, CVD-significant life-style factors, health-related behaviours, mental stress and in the way their disease is treated (Vitale et al., 2010; EUGenMed et al., 2015; O'Neil et al., 2018). Furthermore, according to the embodiment approach, physical and social environmental factors and living conditions in turn influence gene expression and the production of sex hormones. In the identified studies many variables would have been available, either on the individual or area-level that could have helped in explaining structural inequalities between different sex/gender groups and could therefore have been used to apply intersectional theory. However, they were generally only considered as confounders or as single effect modifier in the statistical models. Incorporating sex/gender-theoretical concepts into quantitative research analyses is, of course, not easy to implement and there is a need for innovative methods (Mena and Bolte, 2019; Bauer et al., 2021). There is also a lack of methods to adequately measure sex and gender (Horstmann et al., 2022). However, we have recently shown how the multidimensionality of sex/gender can be operationalized for use in quantitative research by creating questionnaire modules that address sex/gender's multidimensionality and variety as well as intersectionality and embodiment (Kraus et al., 2023). Despite this advance in methods for quantitative collection of sex/gender data, there is still a need for methods that can be used to analyse such complex data. Nevertheless, some commonly used approaches to consider at least a variety of intersections do exist, for example, through interaction

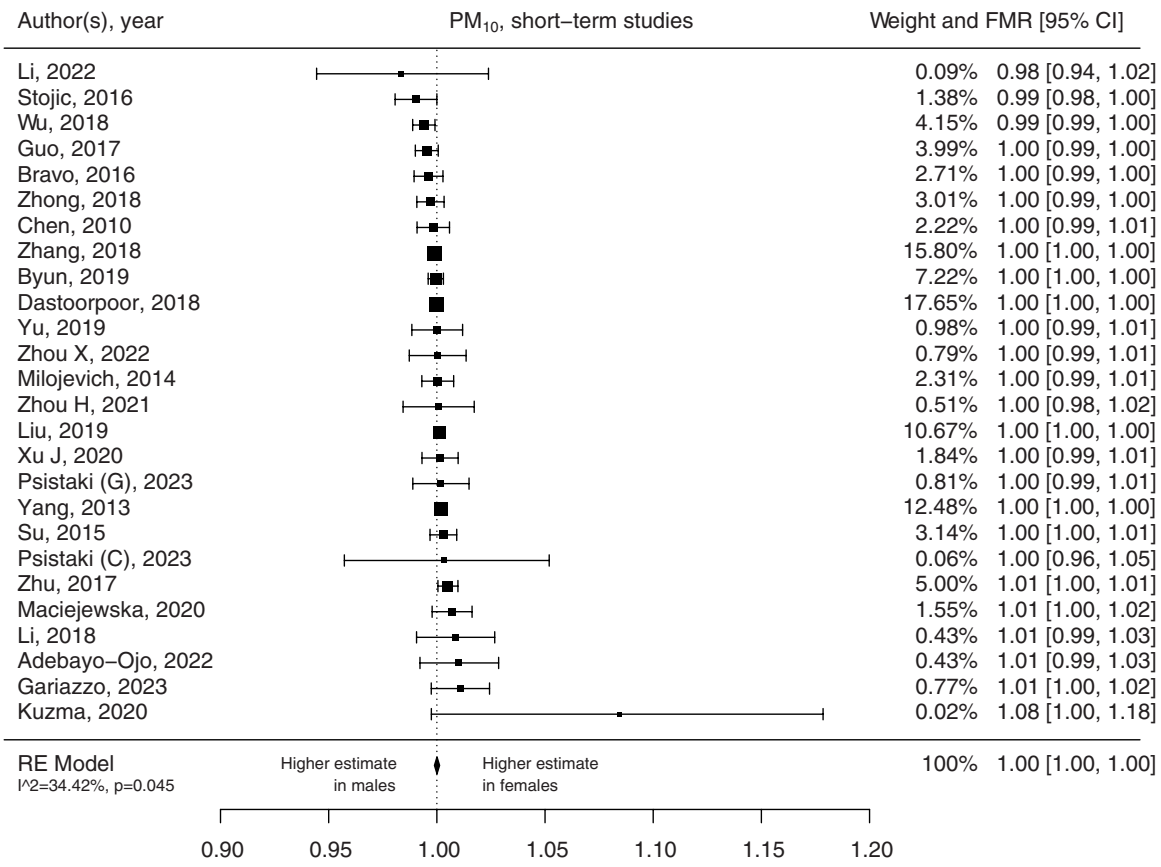

Fig. 5. Pooled female-to-male ratio of effect estimates for CVD deaths risk associated with short- term PM_{10}. OR, odds ratio; Psistaki (C), study region: Cyprys; Psistaki (G), study region: Greece.

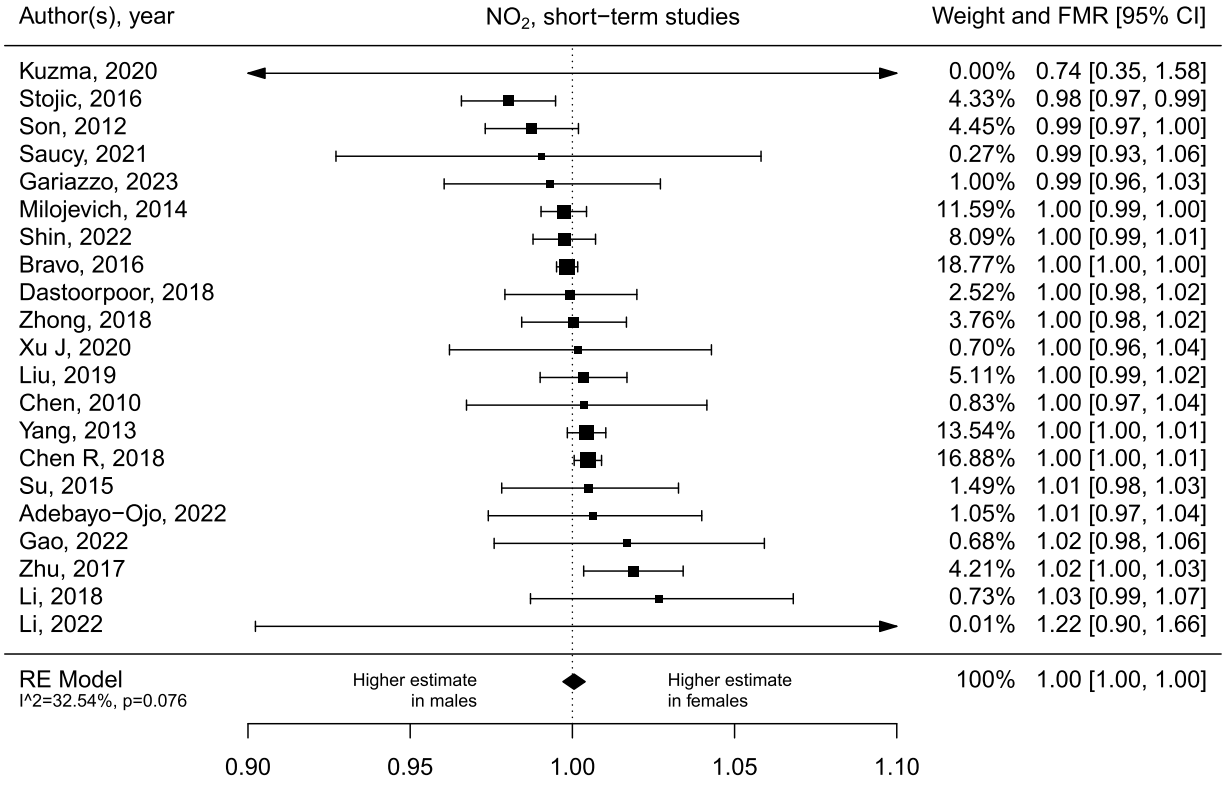

Fig. 6. Pooled female-to-male ratio of effect estimates for CVD deaths risk associated with short- term NO_2. OR, odds ratio.

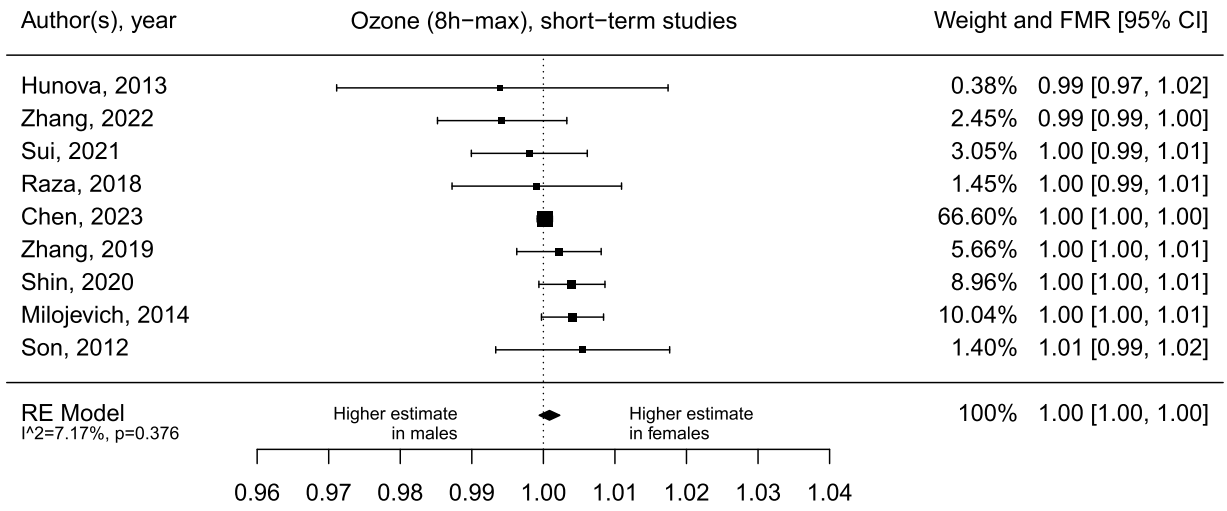

Fig. 7. Pooled female-to-male ratio of effect estimates for CVD deaths risk associated with short- term Ozone (8-hour maximum). OR, odds ratio.

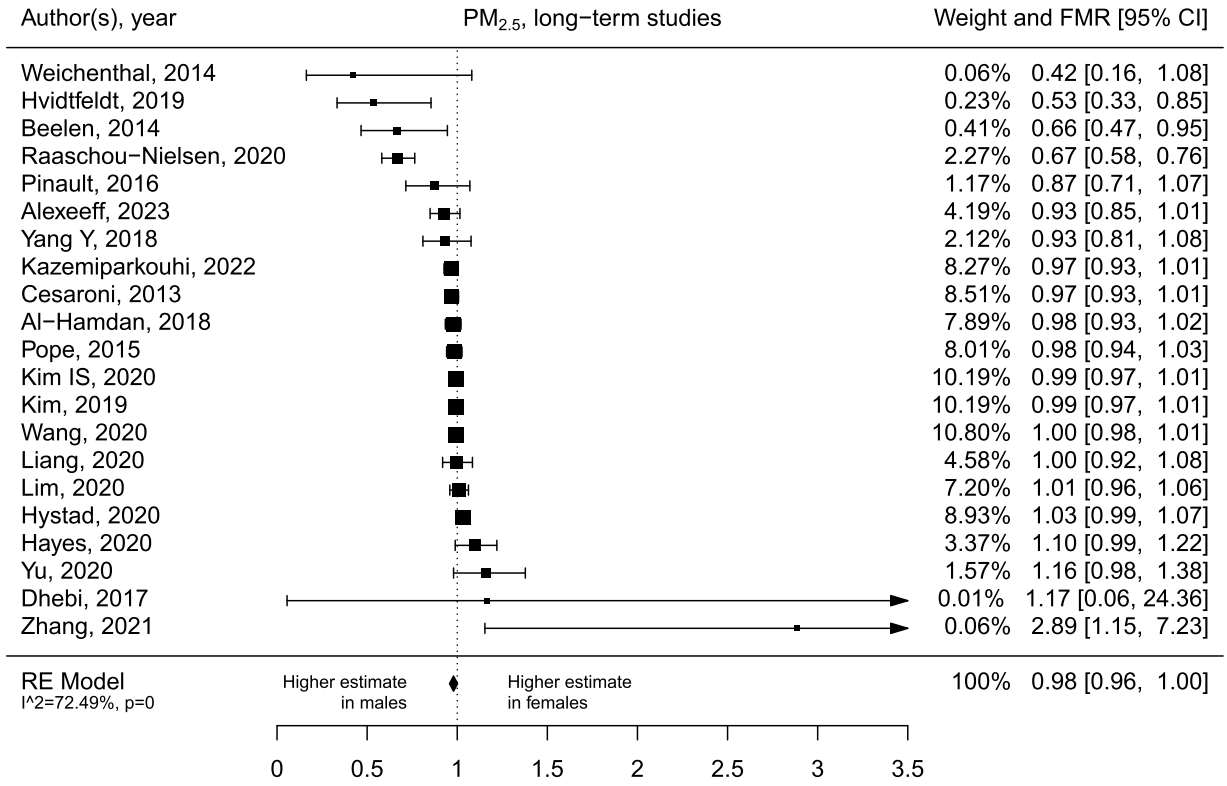

Fig. 8. a. Pooled female-to-male ratio of effect estimates for CVD deaths risk associated with long-term $PM_{2.5}$. OR, odds ratio.

analysis or Classification and Regression Trees (CART) analysis or simply through the joint use of subgrouping variables (Oiamo and Luginaah, 2013; Scott and Siltanen, 2017; Dandolo et al., 2022; Bauer, 2014). This is also how intersectionality got its start more than 30 years ago, when Kimberlé Crenshaw first pointed out that Black women face an experience of discrimination that is different than the sum of racism and sexism (Crenshaw, 1989). With regard to a mathematical process, this means that it is not sufficient to consider single variables for example through the analysis of individual effect modifications. There is indeed a need here for the development of innovative analysis strategies. For example, model-based recursive partitioning, a decision tree method that can handle complex data, was recently used in a related study (Dandolo et al., 2023). Nevertheless, it would be better to at least look at different variables in combination, even if the otherness or quality of experience can hardly be adequately addressed in this way. However, this also requires a large study population, which is often not available. Still, six studies identified in our review analysed the differences between males and females in the association between air pollution and CVD mortality at least within a further subgroup based on age, race, education, smoking, time spent outdoors or BMI (Thurston et al., 2016; Son et al., 2012; Pope et al., 2015; Shin et al., 2020; Næss et al., 2007; Weichenthal et al., 2014). These are promising approaches, but they are not yet sufficiently addressing intersectional theory because the social context including power relations is not taken into account.

Admittedly, data that are of interest for the integration of gender-theoretical concepts are often not available, either because the evaluation of a research question is done with previously collected data, as it is often the case in cohort studies, or, as in ecological short-term studies,

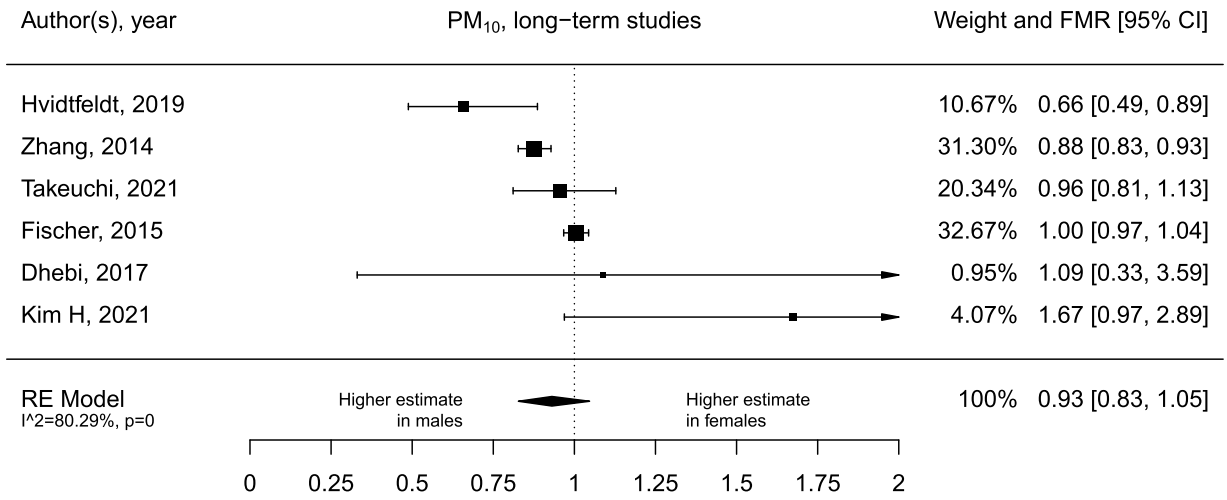

Fig. 9. Pooled female-to-male ratio of effect estimates for CVD deaths risk associated with long-term PM_{10}. OR, odds ratio.

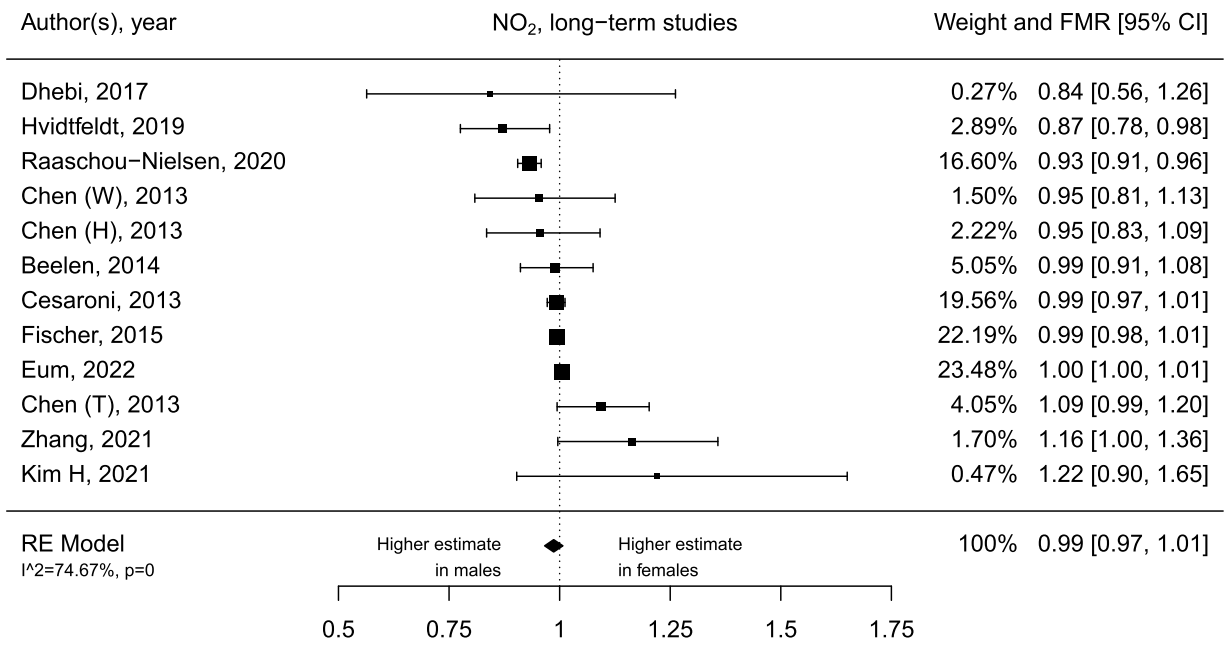

Fig. 10. Pooled female-to-male ratio of effect estimates for CVD deaths risk associated with long- term NO_2. OR, odds ratio. Chen (W), study region: Windsor; Chen (H), study region: Hamilton; Chen (T), study region: Toronto.

such data simply do not exist or do not exist at the individual level. Therefore, it is necessary to consider the comprehensive inclusion of sex/gender dimensions during the study planning phase, so that the right study design is chosen, the necessary data, describing individual and structural factors, can be collected and appropriate power and sample size calculations are performed. Accordingly, we have recently compiled a detailed guide as part of a checklist to promote sex/gender-specific research (Hartig et al., 2024).

4.3. Discussion sections of identified articles

Although identified studies in the current review did not define the terms sex and gender and did not specifically consider any sex/gender concept, explanations for possible differences between males and females referred to both sex-linked biology and the social dimensions of gender. At least on an individual level, but not yet on a structural level, this distinction has even been made quite clear in some studies by dividing the discussion points into biological and non-biological aspects. Upon closer examination of the discussion sections, three aspects stood out. First, to a large extent, possible differences in associations between males and females were discussed without reference to the results and without reference to a priori hypotheses due to the fact that differences mainly were tested as post hoc exploratory analyses. Second, reasons for differences were given to fit the results. Therefore, explanations between studies sometimes contradicted each other. We observed this particularly with respect to smoking. In general, there was a consensus that females have lower smoking rates than males. However, this difference was cited in one set of studies as a rationale for stronger associations among females and in the other set as a rationale for stronger associations among males. Although 20 out of 39 long-term studies provided effect estimates by smoking status, only Pope et al. (2015) examined the combined influence of sex/gender and smoking status, and additionally in combination with age, on the association between long-term air pollution and CVD mortality. Even though not significant, at age > 60 years *never*-smoking females showed higher effect estimates than never-smoking males whereas there was no difference between

ever-smoking females and males in this age group. In contrast, < 60 years old males showed higher effect estimates than < 60 years old females, regardless of smoking status. This shows once again that considering multiple variables simultaneously adds value to understanding sex/gender differences in the association between air pollution and CVD mortality, even if intersectionality is not yet included at this point due to the lack of structural aspects. The third striking aspect is that different patterns of exposure distribution have only been briefly and superficially discussed. However, according to the approach by Clougherty (2010) it would help to disentangle sex-linked biological susceptibility from gendered behavioral and occupational exposure differences. The known exposure assessment methods represent a major limitation of many epidemiological studies on air pollution and health. In short-term studies, air pollution is usually measured at fixed monitoring stations, which only reflect exposure at the population level and do not consider individual differences due to commuting patterns, time spent indoors or occupational exposure. In long-term studies, modelling techniques are generally used to estimate individual exposure at the residential address of the study participants. However, the limitation remains that individual locations outside the home address (such as workplaces or places where leisure activities occur) are not included. For groups that spend less time at home and are characterised by high mobility, assessment of exposure will be less valid. If women and men systematically differ in the amount of time they spend at home, differential misclassification will occur. To advance research in this field, future studies should consider incorporating more precise exposure assessments, such as time-activity diaries, GPS-based movement tracking, or occupation-specific exposure models. Finally, they could also provide a basis for a more in-depth discussion of sex/gender specific association.

Overall, the discussions were largely speculative and lacked depth, allowing explanations to be chosen to best fit the results. However, making hypotheses without testing them gives rise to stereotypical explanations and promotes gender bias (Desai et al., 2021; Hamberg, 2008). This does not help in identifying the reasons for the observed differences between males and females, if any are found at all based on this insufficient classification by binary sex/gender.

4.4. Strengths and limitations

To our knowledge, this is the first review on the integration of sex/gender in studies on the association between air pollution and cardiovascular mortality. We used a comprehensive search strategy applied to three databases and ensured the identification of each relevant study by searching for the sex/gender keywords not only in titles and abstracts but also within the full-text articles and by screening reviews. Furthermore, we calculated and pooled the FMR, which makes the difference in mortality risk between males and females more visible than just pooling the single sex/gender-specific estimates in subgroups. However, our meta-analysis also has some limitations. The pooled studies on the association between air pollution and CVD mortality were very heterogeneous, and this heterogeneity was not explained by sex/gender but rather by other study characteristic like continent, study design, exposure mean and population size. It would have been ideal to perform another analysis on the interaction between sex/gender and these variables. However, since we do not have data for all studies across all considered study characteristic, and because there were too few studies for the many categories of some variables (such as different time lags) such analyses would have had only limited informative value. Another limitation is that the results of the meta-analysis for short- and long-term NO_2 as well as long-term $PM_{2.5}$ should be treated with caution because there seemed to be publication bias leading to an overestimation of the pooled percent-change in CVD mortality risk. Furthermore, we could not include every identified study in meta-analyses as data on estimates were not available. In general, data are not shown in the case of insignificance, so these data would have weakened our results towards zero. In addition, we had to exclude many studies from the meta-analyses because they either analysed data from the same cohort or, in the case of time-series studies, data from the same city over a similar time period. Nevertheless, these studies were included in the review.

5. Conclusions

This systematic review showed that sex/gender is not given adequate consideration in studies on the association between air pollution and cardiovascular mortality. We did not find any definition of sex/gender terms or descriptions of underlying concepts in the reviewed studies. Nevertheless, the distinction between sex and gender was indirectly taken up in the discussion of the results by mentioning biological and social aspects. Results of our meta-analysis did not show that sex/gender modified the association between air pollution and CVD mortality. However, there was a tendency towards stronger associations for males in long-term studies than for females. Future studies should consider sex/gender-theoretical concepts during the study planning, set up hypotheses regarding possible differences between a variety of sex/gender groups and evaluate the speculative explanations often included in discussion sections. The results of these future studies would finally allow for the valid identification of susceptible sex/gender population subgroups defined beyond binary categorisation and consequently allow the possibility of deriving strategies for health protection.

CRediT authorship contribution statement

Annette Peters: Writing – review & editing. **Alexandra Schneider:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Lisa Dandolo:** Writing – review & editing, Data curation, Conceptualization. **Gabriele Bolte:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Sophie Horstmann:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Ute Kraus:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

Registration and protocol

The review was not registered and a protocol was not prepared.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used the translator and the better writing tool of DEEPL to improve written English as the authors are not native speakers. After using this tool/service, the author (s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. INGER Study Group

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German Environment Agency, Section II 1.2 Toxicology, Health-related Environmental Monitoring, Berlin, Germany (Malgorzata Dębiak, Ph.D.; Sophie Fichter; Katrin Groth; Marike Kolossa-Gehring, Ph.D.)

Humboldt-University of Berlin, Institute of History, Gender and Science research unit, Berlin, Germany (Katharina Jacke, Ph.D.; PD Kerstin Palm, Ph.D.)

Appendix B. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.118443.

Data availability

Data will be made available on request.

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