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Effect modification by sex for associations of fine particulate matter ($PM_{2.5}$) with cardiovascular mortality, hospitalization, and emergency room visits: systematic review and meta-analysis

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Abstract

Particulate matter with aerodynamic diameter no larger than 2.5 μm ($PM_{2.5}$) has been linked to cardiovascular diseases (CVDs) but evidence for vulnerability by sex remains unclear. We performed systematic review and meta-analysis to synthesize the state of scientific evidence on whether cardiovascular risks from $PM_{2.5}$ differ for men compared to women. The databases Pubmed, Scopus, Embase, and GreenFILE were searched for studies published Jan. 1995 to Feb. 2020. Observational studies conducting subgroup analysis by sex for impacts of short-term or long-term exposure to $PM_{2.5}$ on target CVDs were included. Data were independently extracted in duplicate and pooled with random-effects meta-regression. Risk ratios (RRs) for long-term exposure and percent changes in outcomes for short-term exposure were calculated per 10 $\mu g/m^3$ $PM_{2.5}$ increase. Quality of evidence of risk differences by sex was rated following Grading of Recommendations Assessment, Development and Evaluation (GRADE). A total of 12,502 articles were screened, with 61 meeting inclusion criteria. An additional 32 studies were added from

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citation chaining. RRs of all CVD mortality for long-term $PM_{2.5}$ for men and women were the same (1.14; 95% CI: 1.09, 1.22) indicating no statistically different risks. Men and women did not have statistically different risks of daily CVD mortality, hospitalizations from all CVD, ischemic heart disease, cardiac arrest, acute myocardial infarction, and heart failure from short-term $PM_{2.5}$ exposure (difference in % change in risk per 10 μg/m^3 $PM_{2.5}$: 0.04 (95% CI, −0.42 to 0.51); −0.05 (−0.47 to 0.38); 0.17 (−0.90, 1.24); 1.42 (−1.06, 3.97); 1.33 (−0.05, 2.73); and −0.48 (−1.94, 1.01), respectively). Analysis using GRADE found low or very low quality of evidence for sex differences for $PM_{2.5}$-CVD risks. In conclusion, this meta-analysis and quality of evidence assessment of current observational studies found very limited evidence of the effect modification by sex for effects of $PM_{2.5}$ on CVD outcomes in adults, which can inform clinical approaches and policies.

Keywords

Cardiovascular outcomes; hospitalization; meta-analysis; mortality; particulate matter; sex; systematic review

1. Introduction

Cardiovascular diseases (CVDs) are a leading cause of death globally and CVD mortality reached 18.6 million worldwide in 2019 (Roth et al 2020). Epidemiological studies have reported adverse impacts of short-term or long-term exposure to particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) on cardiovascular outcomes including total CVDs (Karimi and Samadi 2019), ischemic heart disease (Alexeeff et al 2021b)(Lim et al 2020), cardiac arrest (CA) (Zhao et al 2017a). Some human trials have suggested the potential of reduced blood pressure and increased heart rate variability with reduced exposure to airborne particles (Faridi et al 2022). These findings imply that preventing effects of fine particulate matter is crucial to reducing disease burden from CVDs.

Previous studies showed that $PM_{2.5}$'s effects on human health differ among subpopulations (Gold and Mittleman 2013a), and estimating risks for subpopulations is an important facet of epidemiological studies. Findings are inconsistent regarding whether sex influences vulnerability to $PM_{2.5}$-CVDs risks (Gold and Mittleman 2013a). Disproportionate risks between men and women may relate to biological susceptibility and/or nonbiological factors such as different exposure level due to socioeconomic status and occupation (Sacks et al 2011) and gendered behaviors (Clougherty 2010). Proportionally smaller airways and greater airway reactivity of women than men may be a potential reason for differences by sex (Sacks et al 2011). A comprehensive systematic review of epidemiological literature examining effect modifications by sex for the associations between short-term and long-term exposure to ambient $PM_{2.5}$ on CVDs has not been previously reported, to the best of our knowledge. This means that information is needed to understand if policies to mitigate exposure to $PM_{2.5}$ can be expected to benefit men and women similarly. Identifying effect modification by sex for cardiovascular effects of $PM_{2.5}$ is important to develop clinical approaches and policy interventions for outdoor air pollution in subpopulations at risk. Such findings also can inform studies of biological mechanism.

Men and women may have different vulnerability to health effects of $PM_{2.5}$ due to different lung size and growth, gas absorption, and airway response rates. Women's higher vulnerability to cardiovascular risks from exposure to particulate matter (PM) has been suggested by some previous narrative review studies (Hamanaka and Mutlu 2018, Tibuakuu et al 2018). A meta-analysis showed higher risks in women than men for coronary heart disease mortality risks from long-term $PM_{2.5}$ exposure (Zhao et al 2017b). Another meta-analysis suggested higher out-of-hospital CA risks from $PM_{2.5}$ in men than women (Zhao et al 2017a). Although several review studies addressed the vulnerability by sex for PM-CVD associations, they have some limitations in comprehensively reviewing the study results and evaluating the quality of evidence. Narrative reviews can be prone to selective bias in searching and reviewing literature. Although systematic reviews combine research findings based on their structured inclusion criteria, there is a limitation in comparing vulnerability by sex across various CVDs. Furthermore, quality of evidence for vulnerability by sex is often omitted in existing systematic reviews. Therefore, there is a need for systematic review that can provide comprehensive summary of evidence investigating the body of studies for each CVD that have been studied in relation to vulnerability by sex to cardiovascular effects of $PM_{2.5}$, reviewing sex vulnerability across CVDs, and evaluating the quality of the evidence.

In this review research, we focused on $PM_{2.5}$ than PM in other size ranges as $PM_{2.5}$ has been the focus as a target for regulation and epidemiological study (Gold and Mittleman 2013b). For example, $PM_{2.5}$ is regulated through the National Ambient Air Quality Standards (NAAQS) in the United States because of well-established knowledge of the cardiovascular and respiratory effects of $PM_{2.5}$ from epidemiologic evidence (Bell et al 2007) and the World Health Organization (WHO) provides health-based guidelines for $PM_{2.5}$. Smaller particles are thought to be more harmful to health than larger particles as $PM_{2.5}$ is able to penetrate to the deepest parts of the lungs and gain access to other organs (Schraufnagel 2020, Yin et al 2020), although other size fractions are also harmful including larger PM (PM_{10}) and particles smaller than $PM_{2.5}$. We systematically reviewed observational studies to determine if vulnerability differs by sex (men or women) for associations between short-term and long-term $PM_{2.5}$ exposure and cardiovascular outcomes in adults. Meta-regression analysis was performed to quantitatively combine risks and compare the size of risks between men and women for each studied CVD. Findings can assist researchers, decision-makers, and health professionals by identifying quality of evidence for effect modification by sex. Systematic reviews and meta-analysis can identify, assess, and summarize a large body of literature to provide a comprehensive interpretation of the scientific evidence (Higgins and Thompson 2002, Higgins et al 2022, Van Houwelingen et al 2002, MacKenzie et al 2012, Gopalakrishnan and Ganeshkumar 2013).

2. Methods

2.1. Literature search

We conducted literature searches in the databases Medline/Pubmed, Embase, GreenFILE, and Scopus for English-language papers published between Jan. 1995 and Feb. 2020. Details of the protocol were registered on PROSPERO (Heo et al 2020). Librarians searched each

database using controlled vocabulary (eTable 4). Grey literature (i.e., non-peer reviewed) was excluded. We screened references of eligible studies that remained after full-text review and relevant systematic review studies found in the screening process. During the peer-review process, additional reference examinations (i.e., forward citation chaining) was applied using the 'citationchaser' program (Haddaway et al 2021) for the studies published during the period between Mar. 2020 and Dec. 2021.

2.2. Study selection and data extraction

This research is reported in accordance with the MOOSE Checklist for Meta-analyses of Observational Studies (eTable 5). We targeted cardiac disease, ischemic heart disease, heart failure (HF), heart attack, CA, arterial occlusive disease, myocardial ischemia, angina, emboli, arrhythmia, tachycardia, thrombosis, atrial fibrillation, and cardiac-related death. "Total cardiovascular disease" was included as an outcome. As we targeted clinical cardiovascular endpoint, pathological mechanisms (e.g., atherosclerosis, blood pressure, hypertension, cholesterol related disease) and cardiovascular abnormalities were excluded. Cerebrovascular diseases (e.g., stroke) were excluded as they are diseases affecting blood flow and blood vessels specifically in the brain.

We screened publications identified by the database searches based on our inclusion/exclusion criteria of the PICOS Worksheet (eTable 6). Two screeners in 4 teams screened an equally divided number of references. To be included, each reference required agreement from the 2-person screening team; a third screener resolved disagreements. Included studies fulfilled the following inclusion criteria of PICOS; the study: 1) addressed adults (as defined in each study); 2) examined short-term or long-term exposure to ambient $PM_{2.5}$; 3) addressed risks estimations of $PM_{2.5}$ and cardiovascular morbidity/mortality modified by sex (studies focusing on one sex group (e.g., only women) were also included); 4) included at least one of the target CVDs; and 5) was a population-based observational studies. Exclusion criteria were: 1) study population of only children; 2) $PM_{2.5}$ exposure estimated by personal sampler; 3) results not reported specifically by sex, for at least one group; 4) studies of global disease burdens or disease mapping; 5) non-research publication types of commentary, brief article without detailed texts on methodologies, or systematic review; and 6) studies of $PM_{2.5}$ exposure during wildfire, smog episodes, or Asian dust storms due to heterogeneous study characteristics.

We conducted full-text review and labeled 1 primary exclusion reason for each excluded study, although multiple conditions may apply. Data from each eligible study were independently extracted in duplication using a pre-generated data extraction form. Information collected included author, publication year, study location, duration, sample size, study design, exposure methods, period of exposure (i.e., short-term vs. long-term), type of CVD, International Classification of Diseases (ICD) code(s), type of statistical models for effect modifications (e.g., stratification, interaction terms), average $PM_{2.5}$ concentration for the study, increment of pollution used for presentation of estimates of associations (e.g., 10 $\mu g/m^3$), risk estimates (e.g., relative risks (RRs), 95% confidence intervals (CIs)), lag period (if applicable), and confounders analyzed. We extracted risk estimates by sex for each study. When exact data were unavailable from an article, we

contacted the original authors twice and studies without responses from the original authors were excluded.

2.3. Data synthesis

We included both single-city and multicity studies. Risk estimates for men and women were pooled using random-effect meta-regression analysis. Meta-regression analyses were applied to CVDs with risk estimates from >5 studies. Meta-regression analysis was separately applied to long-term exposure and short-term exposure studies. A categorical variable of sex indicating risk estimates for men or women was applied as a moderator in meta-regression analysis. For example, sex-specific log-scaled risk ratios (e.g., $LogRR_{men}$, $LogRR_{women}$) for long-term $PM_{2.5}$ exposure for a standardized increment (i.e., 10 μg/m³) was referred by the moderator variable of sex in the meta-analysis. Pooled risk ratios for long-term $PM_{2.5}$ exposure were calculated separately for men and women. The difference in the risks of long-term exposure between men and women was calculated as the ratio of the RRs (O'Keeffe et al 2018) using the exponential coefficient of the moderator variable referring to sex groups for the log RRs in men and women. We combined results for hospitalization and emergency room (ER) visits together for short-term $PM_{2.5}$ exposure. Sex-specific pooled risks of mortality and hospitalization/ER visits in relation to short-term exposure were presented as percent change per 10 $\mu g/m^3$ increase in $PM_{2.5}$. The pooled risk difference between men and women was calculated by the coefficient (β) of the moderator variable referring to sex groups for the percent change in outcomes of short-term exposure studies (i.e., $100[\exp(10\beta)-1)$. Studies with a study time period <1 year for health data were excluded. Heterogeneity of included studies was examined by standard I^2 test applying the restricted maximum likelihood (REML) method. We determined the extent of between study heterogeneity with the following cut-offs based on suggestions from Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines adopted by the World Health Organization (WHO) (Schünemann et al 2013): <30% (low), 30-49% (moderate), 50-79% (substantial), and >80% (considerable).

We conducted assessment of risk of bias (RoB) for included studies using the OHAT Risk of Bias Rating Tool for Human and Animal Studies (Office of Health Assessment and Translation 2019). For each criterion of OHAT (i.e., selection bias, confounding bias, attrition/exclusion bias, detection bias, selective reporting bias), each study was rated using 4 scores: +2 (definitely low risk of selective reporting bias), +1 (probably low risk of bias), −1 (probably high risk of bias), or −2 (definitely high risk of bias). In rating selection bias, we evaluated if a given study had dissimilarity in terms of age, health status, and observation period for exposure and health outcomes. For confounding bias, we listed well-known confounders and co-exposures from previous literature and experts' opinions and evaluated if they were properly addressed in each study. For attribution/exclusion bias, we evaluated if there was direct evidence from the article that exclusion of subjects from analyses was adequately addressed or the reasons of exclusion were reported. Validity of exposure and outcome measurements used in each study was evaluated regarding detection bias. Lastly, to rate selective bias, we evaluated if each article reported their results for all health outcomes with their protocols and research methodologies outlined. The RoB assessment of each study was conducted by the same investigators who extracted data and any disagreement was

resolved by the leading author. Overall risk of bias was rated separately for each outcome across studies.

2.4. Quality of evidence

Grading evidence is a transparent and systematic process of assessing the quality of evidence for the research topic available in a body of literature. We determined quality of evidence for effect modification by sex according to the criteria of GRADE guidelines, which are established tools presenting a standardized process for grading evidence. Quality of evidence reflects the degree of confidence about findings for effect modification by sex for $PM_{2.5}$ associations with each CVD outcome. Quality of evidence (or strength of evidence) is categorized as high, moderate, low, or very low. The process initially assigns each observational study a quality of evidence as 'low'. Quality of evidence are downgraded one or two levels based on five downgrading criteria (inconsistency, publication bias, imprecision, indirectness, and risk of bias) (Schünemann et al 2013) and upgraded if 1) the estimated effect is very large (e.g., RR >2), 2) an exposure-response gradient is clear, or 3) potential residual biases would increase the effect, while no effect was observed from the current data combination. We upgraded quality of evidence by one level if it was likely that differences in exposure levels by sex were not addressed in included studies but would affect the effect modification by sex. Publication bias was examined using funnel plot of exposure-outcome combinations.

Based on the GRADE process, the extent of each criterion was categorized as 'not serious', 'serious', or 'very serious'. Inconsistency of the included studies was assessed by the direction of point estimates (i.e., RR, % change), overlap of confidence intervals, and statistical criterion of meta-regression analysis (i.e., I^2). Indirectness was rated for the following aspects: studies targeted representative samples of the population; studies measured exposure level to $PM_{2.5}$ using the same measuring systems between the exposed and comparison groups; and studies used appropriate endpoints of target CVDs rather than surrogates to identify study samples. Regarding imprecision, we judged if the confidence intervals of risk differences between men and women span the null (i.e., 1 for RR, 0 for % changes) and if so, rated down for imprecision. We considered the imprecision as more 'serious' when both of the separate risk estimates for each sex group were not significant. Asymmetry of funnel plots of meta-regression analysis were constructed for assessment of publication bias. Quality of evidence is not rated across all CVDs but rated for each CVD outcome by exposure period (i.e., long-term, short-term) and health outcome. The GRADE guideline suggests to upgrade quality of evidence when considering all potential unmeasured bias in studies is expected to result in true effect size, assuming that having unmeasured bias in a rigorous observational study would result in an underestimate/overestimate of an effect of the exposure of interest. We judged if studies have accurately measured differences in exposure levels of $PM_{2.5}$ between sex groups.

3. Results

3.1. Study characteristics of the included studies

A total of 12,502 unique articles were initially identified and screened by the search (Figure 1). After title and abstract screening, 645 studies remained for full-text review. Studies for CVD outcomes with ≤5 identified studies (n=47) and studies with methodological approaches not satisfying inclusion criteria (n=7) were excluded. During the full-text review process, we found 2 additional eligible studies for our systematic review through examining references cited in the included studies. Further, we added 30 studies to our analysis by performing forward citation chaining on the published papers from the time the paper search was completed to the peer-review period of this research (2020-2021). As a result, 93 studies were eligible for meta-analysis. Summaries of each included study are shown in eTables 1 and 2. The most applied study design was time-series analysis (n=41, 44.1%), mathematically equivalent to case-crossover design (n=25, 26.9%), which enabled quantitative synthesis of risk for short-term exposure to $PM_{2.5}$ (eTable 2). Cohort study design was applied in 24 studies (25.8%).

Two studies (2.2%) applied multiple designs including time-series and time-stratified case-crossover analyses. All CVD mortality was examined in 44 studies (41.5%) (25 studies for long-term exposure, 19 studies for short-term exposure) (Alexeeff et al 2021a, Beelen et al 2014, Berger et al 2018, Cesaroni et al 2013, Byun et al 2019, Chen et al 2018, Cheng et al 2019, Chi et al 2016, Dabass et al 2016, Dong et al 2020, Franklin et al 2007, Guiqin et al 2020, Hayes et al 2019, Hvidtfeldt et al 2019, Hystad et al 2020, Kim et al 2019, Kuźma et al 2020, Li et al 2018a, Liao et al 2021, Liang et al 2020, Lim et al 2020, Lin et al 2017, Lipsett et al 2011, Liu et al 2019, Luo et al 2016, Ma et al 2011, Miller et al 2007, Pinault et al 2016, 2018, Pope et al 2015, Qu et al 2018, Shi et al 2021, So et al 2020, Thurston et al 2016, Villeneuve et al 2015, Wang et al 2020a, Weichenthal et al 2014, Wu et al 2018, Yin et al 2017, Yu et al 2020, 2019, Zhang et al 2021b, Zhou et al 2021, 2022). All CVD hospitalization/ER visits were studied in 26 studies (28.0%) (Bell et al 2015, Chen et al 2021, 2020, Cox et al 2017, deSouza et al 2021, Gu et al 2020, Heo and Bell 2019, Hwang et al 2017, Gu et al 2020, Khan et al 2019, Lanzinger et al 2016, Liu et al 2020b, Michikawa et al 2015, Milojevic et al 2014, Motesaddi Zarandi et al 2022, Nayebare et al 2019, Ren et al 2021, Rodopoulou et al 2015, Su et al 2016, Vahedian et al 2017, Wang et al 2021, 2020b, Xu et al 2017b, Yang et al 2016, Yao et al 2019, Zhang et al 2021a, 2018, Zheng et al 2018). Hospitalization/ER visits from IHD and CA were studied in 11 (10.4%) (Bell et al 2015, Haikerwal et al 2015, Heo and Bell 2019, Liu et al 2020a, Milojevic et al 2014, Motesaddi Zarandi et al 2022, Pope et al 2006, Ren et al 2021, Xu et al 2017a, Ye et al 2016, Zheng et al 2018) and 10 (9.4%) studies (Dennekamp et al 2010, Haikerwal et al 2015, Kang et al 2016, Kojima et al 2020, Pradeau et al 2015, Silverman et al 2010, Straney et al 2014, Sullivan 2003, Wichmann et al 2013, Zhao et al 2020), respectively. AMI hospitalization/ER visits were examined in 8 studies (7.5%) (Bell et al 2015, Heo and Bell 2019, Milojevic et al 2014, Rich et al 2010, Sullivan et al 2005, Yu et al 2018, Weichenthal et al 2016, Zheng et al 2020) and HF hospitalization/ER visits were examined in 7 studies (6.6%) (Bell et al 2015, Haley et al 2009, Heo and Bell 2019, Li et al 2018b, Milojevic et al 2014, Pope III et al 2008, Zheng et al 2018). The period of 5 – 9 years was the most common

study time period (n=25, 38.7%). One cohort study had a study period under 5 years (Shi et al 2021). Time-series analysis or case-crossover designs had study time periods under 20 years. The most studied countries were China (n=35, 37.6%) and the United States (n=26, 28.0%). Nine studies (9.7%) were conducted in Europe. Averages of $PM_{2.5}$ concentrations from multiple monitoring stations were used in 48 studies (51.6%). Monitoring data from a single monitoring site was used in 11 studies (11.8%). Most studies were based on all ages but some targeted a narrower age range (e.g., ≥65, 50-64, 50-71 years) (eTable 1).

3.2. Meta-regression analysis and RoB assessment

For long-term exposure, pooled risk estimates by sex were assessed for all CVD mortality (Figure 2). For short-term exposure, sex-specific risk estimates were pooled for all CVD mortality, all CVD hospitalization/ER visits, IHD hospitalization/ER visits, CA hospitalization/ER visits, AMI hospitalization/ER visits, and HF hospitalization/ER visits (Figures 3 to 8). Numeric results of pooled risks are shown in eTable 3.

Long-term exposure—Results of meta-analysis for the risk ratio of all CVD mortality per 10 μg/m^3 $PM_{2.5}$ was 1.15 (95% CI, 1.09 to 1.22) for men and 1.15 (95% CI, 1.09 to 1.22) for women. The risk difference by sex (men vs. women) in risk ratio was 1.00 (95% CI, 0.93 to 1.08), indicating that the difference was null. Some studies reported risk estimates only for one sex group. We also applied a meta-regression analysis to compare the risks in men and women by only including the studies that reported risk estimates for both male and female groups. The results were robust to the main analysis. The risk difference between men and women increased to 1.03 (95% CI: 0.94 to 1.12) but the difference was not statistically significant (RR in men = 1.16, 95% CI: 1.09 to 1.23; RR in women = 1.13, 95% CI: 1.06 to 1.20; I^2 = 85.8%). The results of RoB assessment are shown in eTable 7. Almost half of the included 25 studies showed ‘definitely low risk of bias’ for all the 5 domains of RoB assessment. Two studies showed ‘definitely high risk of bias’ for selection bias. Studies that were rated as ‘probably high risk of bias’ for any of the 5 domains were 11 out of 25 studies. Overall, RoB was rated as ‘probably high’ for selection bias and as ‘probably low’ for the other 4 domains of RoB assessment.

Short-term exposure—The percent change in mortality per 10 μg/m^3 $PM_{2.5}$ increase was 0.71 (95% CI, 0.38 to 1.04) for men and 0.66 (95% CI, 0.33 to 0.99) for women (Figure 3). The risk difference (men vs. women) was 0.04 (95% CI, −0.42 to 0.51), indicating no statistically significant difference (eTable 3). The percent change in all CVD hospitalization/ER visits per 10 μg/m^3 $PM_{2.5}$ was 0.53 (95% CI, 0.23 to 0.83) for men and 0.58 (95% CI, 0.28 to 0.88) for women (Figure 4); the risk difference between men and women was −0.05 (95% CI, −0.47 to 0.38). The percent change of IHD hospitalization/ER visits for men (0.66; 95% CI, −0.08 to 1.40) was higher than for women (0.49; 95% CI, −0.29 to 1.27) (Figure 5). For CA hospitalization/ER visits, the percent change for men (2.95; 95% CI, 1.22 to 4.71) was higher than for women (1.51, 95% CI: −0.32 to 3.37) (Figure 6). The percent change of AMI hospitalization/ER visits for men (1.02, 95% CI: 0.08 to 1.97) was higher than for women (−0.30, 95% CI: −1.30 to 0.70) (Figure 7). The percent change of HF hospitalization/ER visits was higher for women (1.45, 95% CI: 0.38

to 2.54) than for men (0.97, 95% CI: −0.07 to 2.02) (Figure 8). None of these differences in $PM_{2.5}$-CVD risk by sex was statistically significant.

The meta-regression model including the subset of studies that reported risks for both men and women for CA showed higher risk in men (% increase in men = 2.42, 95% CI: 1.12 to 3.74; % increase in women = 1.46, 95% CI: 0.08 to 2.87), but the difference was not statistically significant (0.94, 95% CI: −0.93 to 2.86).

Most studies were rated as ‘probably low risk’ or ‘definitely low risk’ of bias in the 5 domains of RoB assessment (eFigure 1). RoB assessment for each study is shown in eTables 7–13. Detailed assessment for each RoB domain is described below.

Selection bias: We found that few studies had selection bias for study population (e.g., recruiting study participants from some select hospitals within a study region, restricted to a narrow age range for adults) (Ribeiro et al 2019, Rodopoulou et al 2015, Xu et al 2017b, Vahedian et al 2017) and were rated as ‘probably high risk of bias’. Studies where only one sex group was studied were rated as ‘definitely high risk of bias’ (Chi et al 2016, Miller et al 2007, So et al 2020, Villeneuve et al 2015, Pradeau et al 2015, Lipsett et al 2011, Yin et al 2017).

Confounding bias: Cohort studies considered community-level socioeconomic status as well as several individual-level confounders (e.g., smoking, age, sex, BMI, etc.). Most time-series analysis and case-crossover studies adjusted for seasonality and temporal trend of mortality or morbidity for CVDs, weather, day of the week, and holidays resulting in a categorization of ‘probably low risk of bias’. Studies considering influenza epidemics were rated as ‘very low risk of bias’. A few studies did not control for the potential effects of weather (e.g., humidity, temperature) or holidays (Franklin et al 2007, Khan et al 2019, Haikerwal et al 2015, Milojevic et al 2014, Pradeau et al 2015) and were rated as ‘probably high risk of bias’.

Attrition/exclusion bias: Many studies did not report the criteria for exclusion of study participants, which led to grading as ‘probably high’ risk of bias of attrition/exclusion bias for all CVD hospitalization/ER visits associated with short-term $PM_{2.5}$ exposure and ‘probably low’ risk of bias for the other CVD outcomes associated with short-term $PM_{2.5}$ exposure.

Detection bias: CVDs were identified from population-representative medical or administrative records such as death certificate or hospitalization data, which reduces risk of poor detection of outcome. Exposure to air pollution was mostly based on community-level air pollution concentration rather than air pollution assessed with individual-level monitors. Studies using $PM_{2.5}$ data from single monitoring site or multiple monitoring sites was rated as ‘probably low risk of bias’, whereas studies using modeling data were rated as ‘definitely low risk of bias’.

Selective reporting bias: Due to the large volume of analysis considering complex lag structure as well as types of CVDs, we found some potential for selective reporting bias in the included studies. However, most studies provided results with sensitivity analysis.

3.3. Quality of evidence

The evidence profiles for quality of evidence are shown in eTable 3. Heterogeneity of effect estimates across studies was considered substantial or considerable in all cases. The quality of evidence for effect modification by sex was assessed as low for all CVD mortality associated with long-term $PM_{2.5}$ exposure and all CVD mortality and hospitalization/ER visits associated with short-term $PM_{2.5}$ exposure. Quality of evidence of effect modification by sex was very low for hospitalization/ER visits from IHD, CA, AMI, and HF associated with short-term $PM_{2.5}$ exposure. Thus, our confidence in the effect modification by sex is limited. Detailed assessment for each upgrading/downgrading criterion is shown below.

Publication bias: The funnel plot of all CVD mortality from long-term $PM_{2.5}$ exposure showed asymmetry with an outlier on the lower left side (eFigure 2). This outlier was a cohort study (Weichenthal et al 2014) and no potential source of standard error of the risk estimates was identified. Also, this outlier would lead to a conservative bias towards the null for the mortality risk. Thus, the extent of publication bias was rated as ‘unlikely’.

For short-term exposure to $PM_{2.5}$, we rated publication bias as ‘unlikely’ for all CVD mortality, all CVD hospitalization, CA hospitalization, and IHD hospitalization based on the funnel plots from meta-regression analysis (eFigure 2). The funnel plot for AMI hospitalization for short-term $PM_{2.5}$ exposure showed outliers on the lower right side, which were from one study (Rich et al 2010). Methodological issues for exposure assessment and patient ascertainment were not found among the included studies. The asymmetry of the funnel plot due to one study showing heterogeneity was not sufficient to conclude publication bias, which led to ‘not serious’ for grading publication bias for AMI. Asymmetry was found in the funnel plot of HF due to one study (Pope III *et al* 2008) showing high standard deviation for the risk estimates in men and women, but this was not likely associated with publication bias (‘not serious’ publication bias).

Inconsistency: Sources of inconsistency of the included studies were different population, exposure (e.g., exposure range, co-exposure, composition of particulate matter), age range (e.g., variation in underlying health conditions), studied lag days, different exposure period (e.g., whole year, summer, or wildfire season), and difference definitions of CVDs (e.g., different ICD code range) in addition to differences in short-term and long-term exposure periods. Even though study designs differ across the observational studies, men and women were analyzed under the same analytical approach within each study. Although I^2 from the meta-regression analysis indicated substantial or considerable heterogeneity of the studies, estimated risks from the included studies showed consistent directions (i.e., positive associations). The CIs were overlapping for all included studies. Overall, the substantial inconsistency among the studies was not sufficient to downgrade the strength of evidence except for IHD hospitalization/ER visits. The risk estimates of IHD hospitalization/ER visits showed inconsistent directions of risk (i.e., negative and positive impacts of $PM_{2.5}$) with

confidence intervals that did not overlap (see Figure 5). Heterogeneity of the included studies was extremely high (I^2 = 99.5%).

Indirectness: As this review targeted specific end points of cardiovascular diseases excluding surrogate conditions (e.g., blood pressure, serum lipids, coronary calcification), there are no or minimum indirectness of outcome measurements. Exposure to air pollution has been measured based on the community- or region-level air pollution level that would not lead to systematic misclassification among study regions or between sex groups. Thus, we determined that the indirectness would be very low in the included studies and would not be sufficient to downgrade the strength of evidence.

Imprecision: The estimated risk difference between men and women was not objectively high and the confidence intervals were wide. The risk differences do not lead us to a conclusion that a certain sex group is more vulnerable to the risks of CVDs from $PM_{2.5}$ exposure. We downgraded quality of evidence by one level for imprecision for all CVD outcomes. IHD, CA, AMI, and HF did not find statistically significant sex-specific risk estimates either for men or women, which lead to an additional downgrade of quality of evidence by one level.

Risk of bias: Although there were some studies rated as ‘definitely high risk of bias’ for some RoB domains, most studies showed probably low risk of bias (eTables 7–13, eFigure 2). Overall, there were no serious limitations among the included studies and the evidence of risks and effect modification by sex mostly came from studies at low RoB.

Upgrading quality of evidence: The included studies did not incorporate in the analysis fact that men and women may have different time-activity patterns (e.g., indoor vs. outdoor) or occupational exposures to $PM_{2.5}$. Given the likelihood that residence-based pollutant exposure models (e.g., monitored $PM_{2.5}$ exposure) may not represent exposure levels across subpopulations by sex and could lead to estimates that do not identify risk difference by sex, we upgraded the quality of evidence by one level (e.g., supporting the theory that there could be still a possibility that sex may modify the risks of CVDs from $PM_{2.5}$ exposure).

4. Discussion

Our meta-analysis found that effect modification by sex differed by type of CVD outcome and exposure period. Women tended to show higher risks of hospitalization/ER visits from all CVD and HF associated with short-term $PM_{2.5}$ exposure, whereas men showed higher hospitalization risks for all CVDs and specific sub-types of CVDs including IHD, CA, and AMI associated with short-term $PM_{2.5}$ exposure and all CVD mortality associated with long-term $PM_{2.5}$ exposure, although risks were not statistically different by sex.

We focused on $PM_{2.5}$ as it is widely used as the key form in air pollution regulation, however datasets for particulate matter in non-industrialized countries may be more reliant on PM_{10} or total suspended particles rather than $PM_{2.5}$. Review studies focusing on particulate matter with various size distributions may be helpful to represent the impact of particulate matter on CVDs globally. Due to the large volume of searched studies with a

variety of CVDs of interest, we did not consider sizes of particulate matter other than $PM_{2.5}$. We note that the results of insignificant effect modification by sex in our review may not apply to risks from PM_{10}.

$PM_{2.5}$ entering the lung through respiratory system can flow to the terminal bronchi and alveoli and access to the tissues or organs through blood circulation causing acute and chronic damages (Zhao et al 2021). Substantial studies have suggested mechanisms of cardiovascular effects of $PM_{2.5}$. Oxidative stress from $PM_{2.5}$ exposure could release pro-inflammatory cytokines, which can lead to inflammatory response, apoptosis, and activation of pathways for vascular damage repair (Zhang et al 2007, p 2, Lederer et al 2021). Reduced vascular permeability caused by inflammatory response and apoptosis from $PM_{2.5}$ exposure can accumulate fat and cholesterol molecules in the vascular walls, which can reduce blood flow and oxygen supply (Zhao et al 2021). $PM_{2.5}$ can reduce the vascular reparative capacity by affecting viability, migration, and formation of pro-inflammatory cytokines (e.g., Interleukin 8) and Tumor necrosis factor Alpha (Zhao et al 2021, Chen et al 2017). $PM_{2.5}$ can break the balance of macrophages, which are important for immune system, and this can lead to the deterioration of CVD (Zhao et al 2021). A growing body of evidence suggests that $PM_{2.5}$ can induce hypermethylation of several key gene promoters that affects the progression of heart diseases (Huang 2013).

Differences between gender (i.e., self-representation, socially derived roles and behaviors) and sex (biologic differences) are important to explore potential mechanisms of vulnerability to cardiovascular effects of $PM_{2.5}$ (Clougherty 2010). Vulnerability by different lung size and growth, gas absorption, and airway response rates would be based on sex. Certain comorbid diseases affect women differently than men as well (Norris et al 2020). Gender-related factors would include education, socioeconomic status, social disparities, psychologic factors, and lifestyle (Pucci et al 2017). Differences in exposure by occupation may relate to both sex and gender. Many epidemiological studies have not distinguished between sex and gender because many datasets, especially databases for death or medical records, have information for sex only, and occupational and cultural gender roles may be interwound with persistent job classifications by sex (Clougherty 2010). We recognize that sex and gender are different and that multiple genders exist, but none of the included studies addressed differences between sex and gender. Most studies were based on sex although some studies used the wording “sex” and “gender” interchangeably, as is currently common in some countries. Several studies (Franklin et al 2007, Xu et al 2017b) used the wording “gender” comparing the results between men and women but discussed biological differences by sex for their comparisons between men and women. In this review, we use the term “sex” as many epidemiological studies of $PM_{2.5}$ and CVDs depend on health databases providing information of biological sex while we investigate differences between men and women. A few recent studies suggested that the risk of CVDs may differ between sex and gender. For example, a cross-sectional study conducted in Canada and Australia found that female gender based on psychosocial and cultural gender had higher associations with risk factors for CVDs than did female sex (Azizi et al 2021). We recognize that sex and gender refer to different concepts, and that more genders than “male” and “female” exist, but cannot investigate this issue due to the available information in existing studies. Uncertainties remain for how $PM_{2.5}$-CVD associations differ by sex and gender, which

warrants future research. Also, future systematic reviews are needed on these topics when such epidemiological evidence becomes available.

Measurement errors from the use of monitor measurements have been noted among studies, and some topical reviews focusing on a specific country have recommended utilization of modeling data (e.g., satellite-derived) for $PM_{2.5}$ exposure assessment (Miller and Xu 2018). However, using data from monitoring stations has the strength of use of measurements rather than estimates and might be “best practice”, particularly, in low-income or middle-income countries with limited data input for more complex exposure models. Exclusion of studies using certain exposure measurements approaches may lead to including research only from particular countries. About 71.0% of the studies included in our review used fixed monitoring station data. We suggest that research findings based on monitoring data should not be dismissed when the research question relates to vulnerability of subgroups and some regions of the world necessarily rely on such methods.

Some CVDs (e.g., thrombosis, atrial fibrillation) were excluded due to the small number of studies or absence of studies on our research question. We note that exclusion from our review does not indicate absence of relationships with $PM_{2.5}$ or risk difference by sex. These CVDs warrant future investigation for effect modification by sex. Also, we did not apply GRADE to rate quality of evidence for effects from $PM_{2.5}$ for those outcomes for which we did not conduct meta-analysis as our research was systematic review along with meta-analysis. GRADE provides transparent processes for explicit judgments for each factor that determines the quality of evidence for each outcome (Dijkers 2013). It is important to note that tools for rating risk of bias of each study are often used to select studies to pool the risk of an outcome based on the quality of studies, but GRADE offers process to present summary of findings across studies in systematic reviews. While a measure of the risk for each outcome is an important element of a summary of findings table in GRADE, they may not be available in the summary of findings for outcomes for which meta-analysis is not available (Guyatt et al 2013). Thus, we note that assessments of the quality of evidence based on the GRADE approaches are warranted for the omitted CVD outcomes in our review to understand the quality of evidence and develop evidence-based recommendations in guidelines as such studies become available. There has been disagreement on GRADE’s applications to observational studies. GRADE prioritizes randomized trials over observational studies for rating quality of evidence and lacks the ability to distinguish quality among reasonably well-supported evidence from various study designs of observational studies (Rehfuess and Akl 2013). Due to insufficient possibilities for upgrading quality of evidence for observational studies, some previous research started with a baseline of “moderate” rather than “low” quality (Orellano et al 2020). We consider that observational studies are critical components to understanding health effects of air pollution, given ethical limits to personal exposure studies and inherent limitations of toxicological studies, although all study designs contribute key evidence; thus, starting at “low quality” for quality of evidence based on GRADE may underestimate findings. Therefore, we considered that study characteristics related to generalizability but not quality in observational studies (e.g., studying specific age ranges or exposure period relying on existing environmental and health datasets, differences in population characteristics and pollution level) as criteria to downgrade quality of evidence.

A strength of this meta-analysis is that we assessed both long-term and short-term $PM_{2.5}$ exposure on mortality and morbidity of various CVDs to identify effect modification by sex. Most previous systematic reviews focused solely on either short-term or long-term exposure. We also summarized quality of evidence, which is often omitted in existing systematic reviews. Further, our study provides the most up-to-date synthesis of evidence, which includes many studies not available when the previous reviews were conducted.

Our study also has several limitations. Focusing on English-written literature may have affected publication bias or focused findings on global north countries. Most studies identified were from China and the United States, indicating the need for additional research in additional locations. While the focus on English-language articles may have missed some articles in other locations, further studies are likely needed in other regions. In particular, summarizing evidence for developing countries that have been less studied is needed in future studies to understand the risk differences by sex for the associations between $PM_{2.5}$ and CVDs. Clinical trials are very rare for our research question. The needs and challenges for randomized clinical trials have been discussed elsewhere (Brook et al 2018). A recent systematic review study evaluating the efficacy of wearing respirators for reducing the impacts of air pollution on blood pressure and heart rate variability identified only a small number of trials (Faridi et al 2022). Nonetheless, evidence from observational studies based on adequate and plausible study designs can reasonably support evidence-based decision making and inform individuals at risk. We focused on the closest lag from events of CVDs (i.e., lag0) when combining risk estimates across studies to avoid publication bias, and did not conduct risk synthesis for all analyzed lag periods. The potential resulting bias might be small as a previous meta-analysis combining risk at multiple lags for CA risk from $PM_{2.5}$ suggested small differences between polled risks from different lags (Zhao et al 2017a). We could not examine whether observed risk difference by sex was attributable to biological susceptibility or to exposure or other differences as the included studies were only based on observational studies. Future research is needed to explore these suggestive findings and investigate causal mechanisms. Additional work is also needed on a wider range of variables related to potential differences in populations that may explain differences in health response to air pollution by sex, such as differences in smoking patterns and healthcare systems. There are factors for heterogeneity across the included studies such as study population, particle size, and exposure methods as we applied meta-analysis to provide an overarching risk estimation addressing the heterogeneity across populations, regions, and study designs. Further, research is needed on additional health endpoints and how health impacts from particulate matter may differ across various health responses. Also, review of studies on other size fractions of $PM_{2.5}$, especially smaller particles (e.g., PM_1) may be warranted as such studies become available. Exposure assessment based on monitoring stations was used in more than 70% the included studies in our review. The effect of applying different exposure methods on the pooled risk of the outcomes should be further investigated.

In summary, we did not find evidence that the impacts of $PM_{2.5}$ on mortality, hospitalization, and ER visits from CVDs differ between men and women. The findings imply that the current scientific evidence does not provide support for different policies for preventing cardiovascular risks from $PM_{2.5}$ exposure for men and women. However, several factors as discussed above (e.g., sex vs. gender, PM chemical composition) limit a full understanding

of this issue. For instance, individual-level exposure has not been considered in the included studies in this review. Addressing individual-level exposure between men and women and other relevant factors in comparing $PM_{2.5}$-CVD associations remains a challenge in future epidemiologic studies and policy recommendations.

5. Conclusions

This meta-analysis summarized the current state of scientific evidence on whether $PM_{2.5}$'s impact on CVDs differs for men and women. We pooled sex-specific $PM_{2.5}$-CVDs risk estimates and assessed evidence of risk differences by sex. Overall, across the identified studies, differences in $PM_{2.5}$-CVD risk were not statistically different by sex. There was low and very low quality of evidence that men or women were more vulnerable to effects of $PM_{2.5}$ on CVD mortality or hospitalization/ER visits, which can inform policies and future work.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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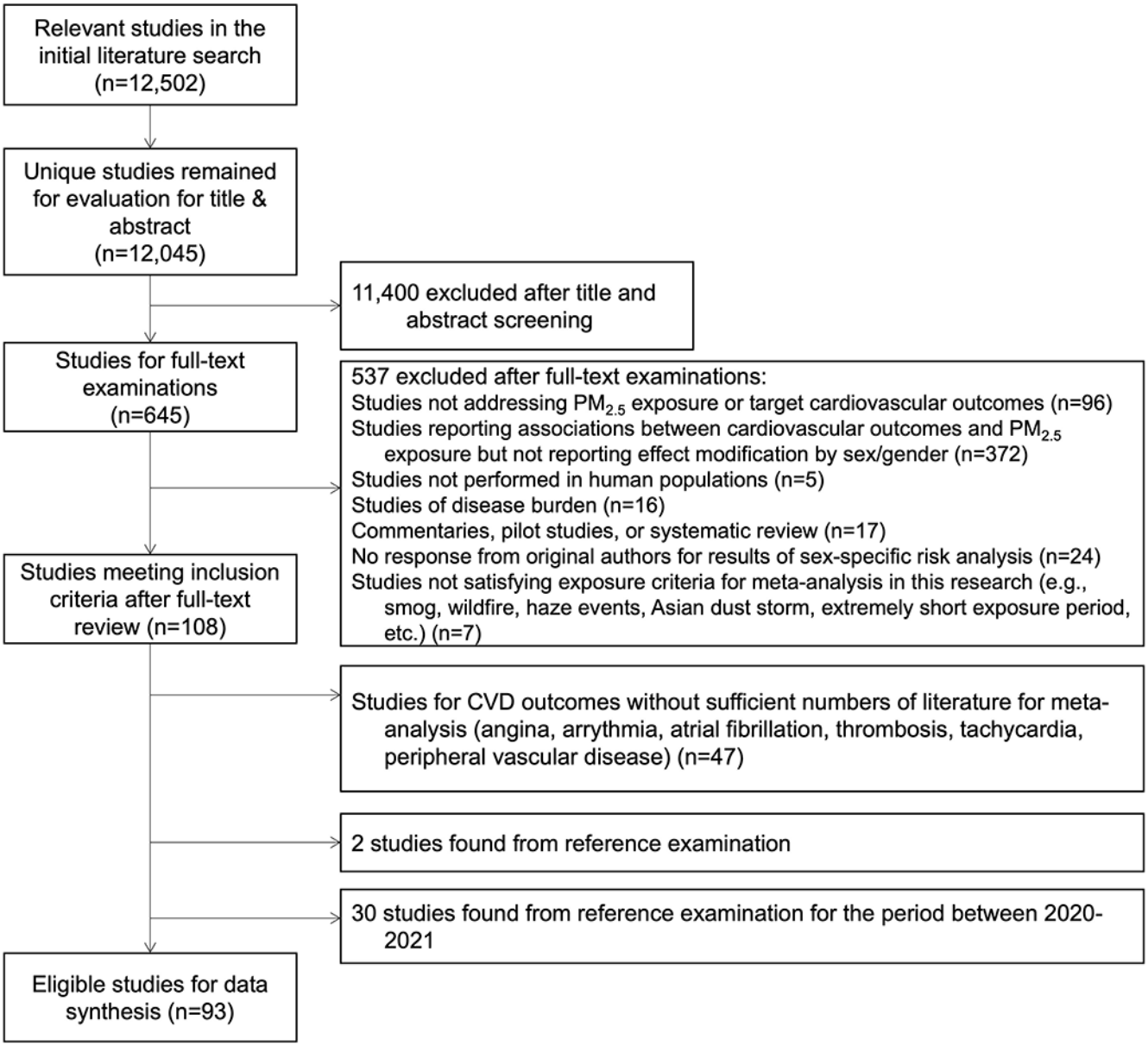

Figure 1.
Flow chart of identified studies for systematic review and meta-analysis.

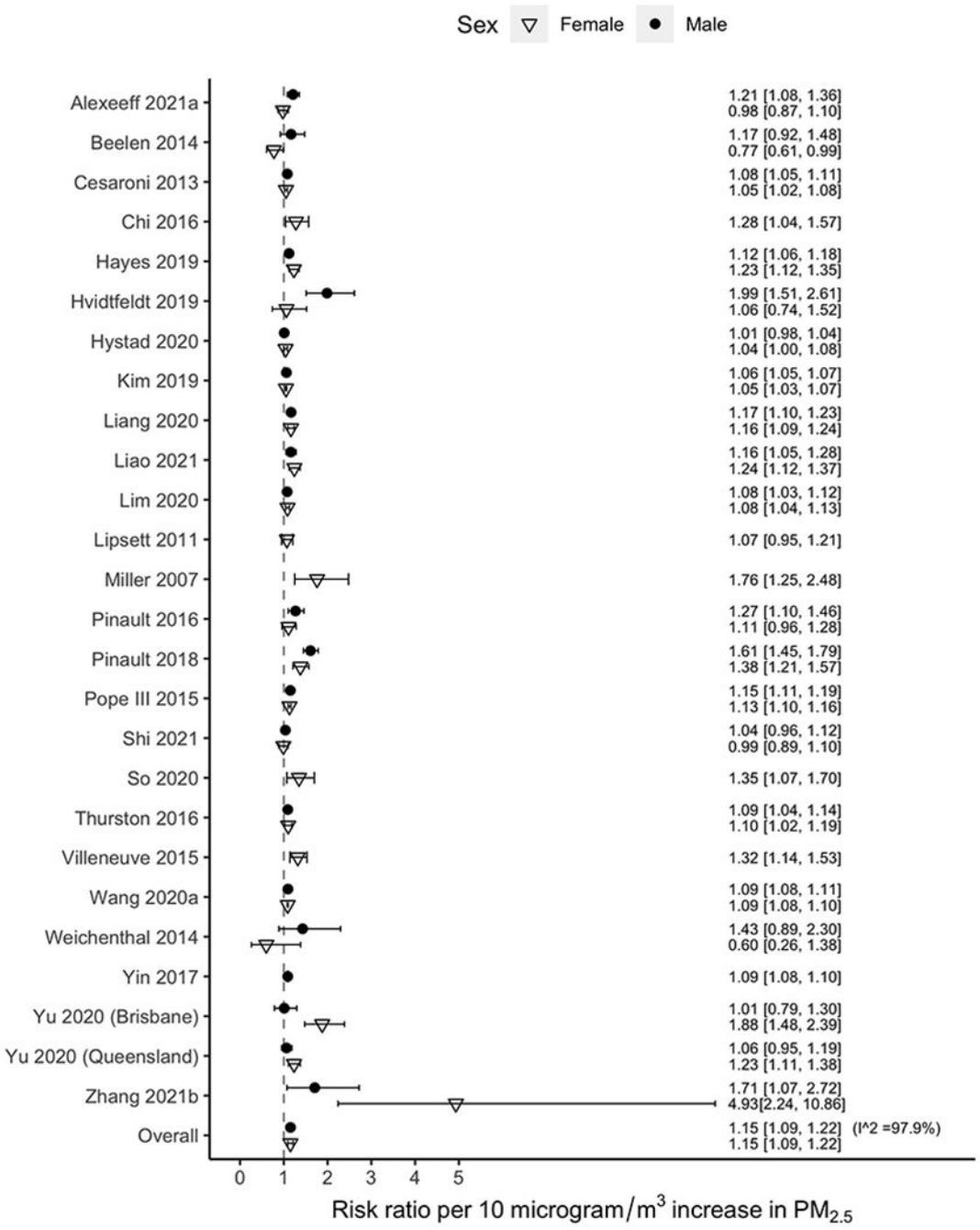

Figure 2.

Risk ratio of all cardiovascular disease mortality for a 10 μg/m^3 increase in $PM_{2.5}$ concentration for the included studies in a meta-analysis, by sex. Horizontal lines represent 95% confidence intervals.

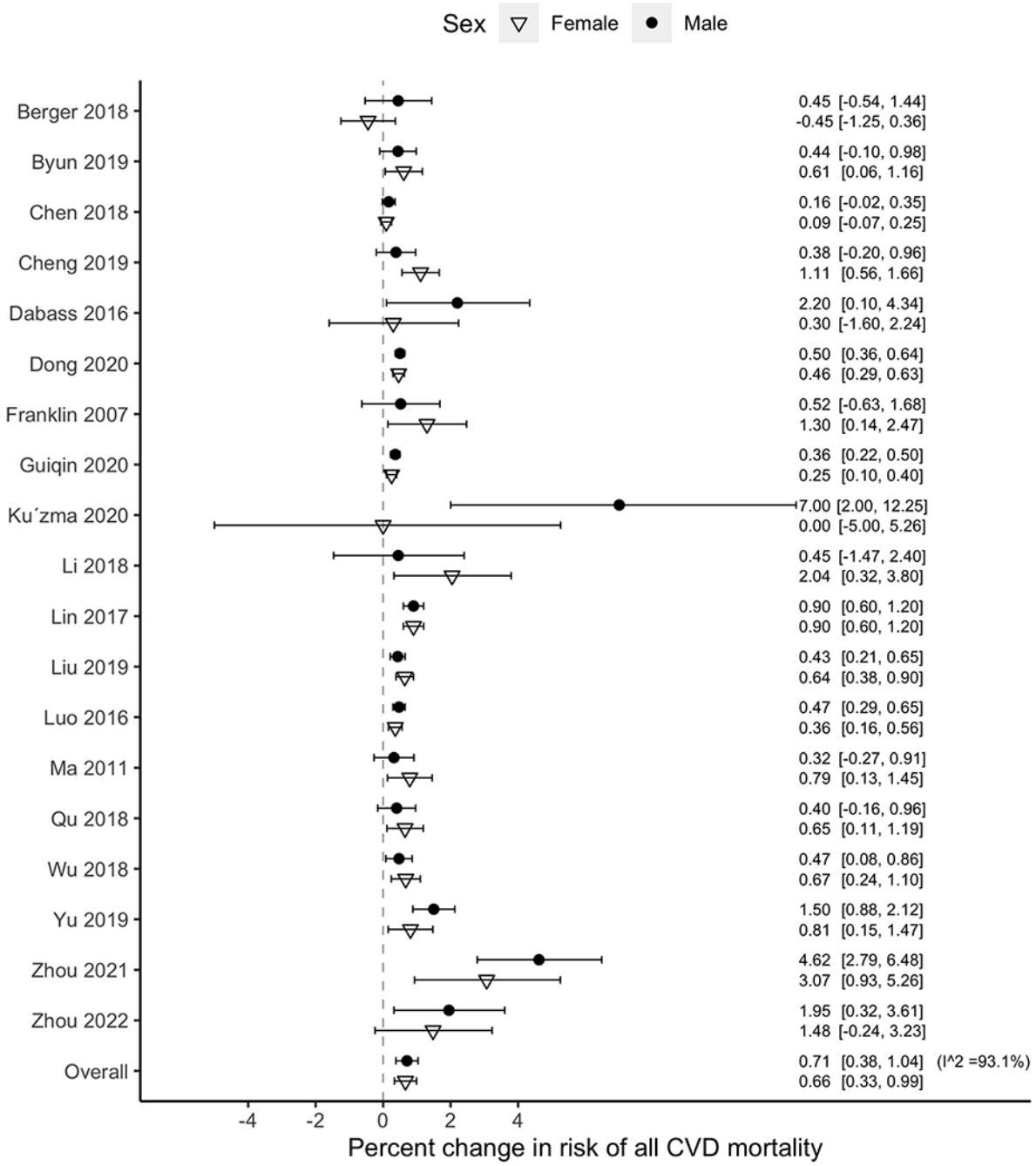

Figure 3.

Percent changes in all CVD mortality for a 10 μg/m^3 increase in $PM_{2.5}$ (short-term) for the included studies in a meta-analysis, by sex. Horizontal lines represent 95% confidence intervals.

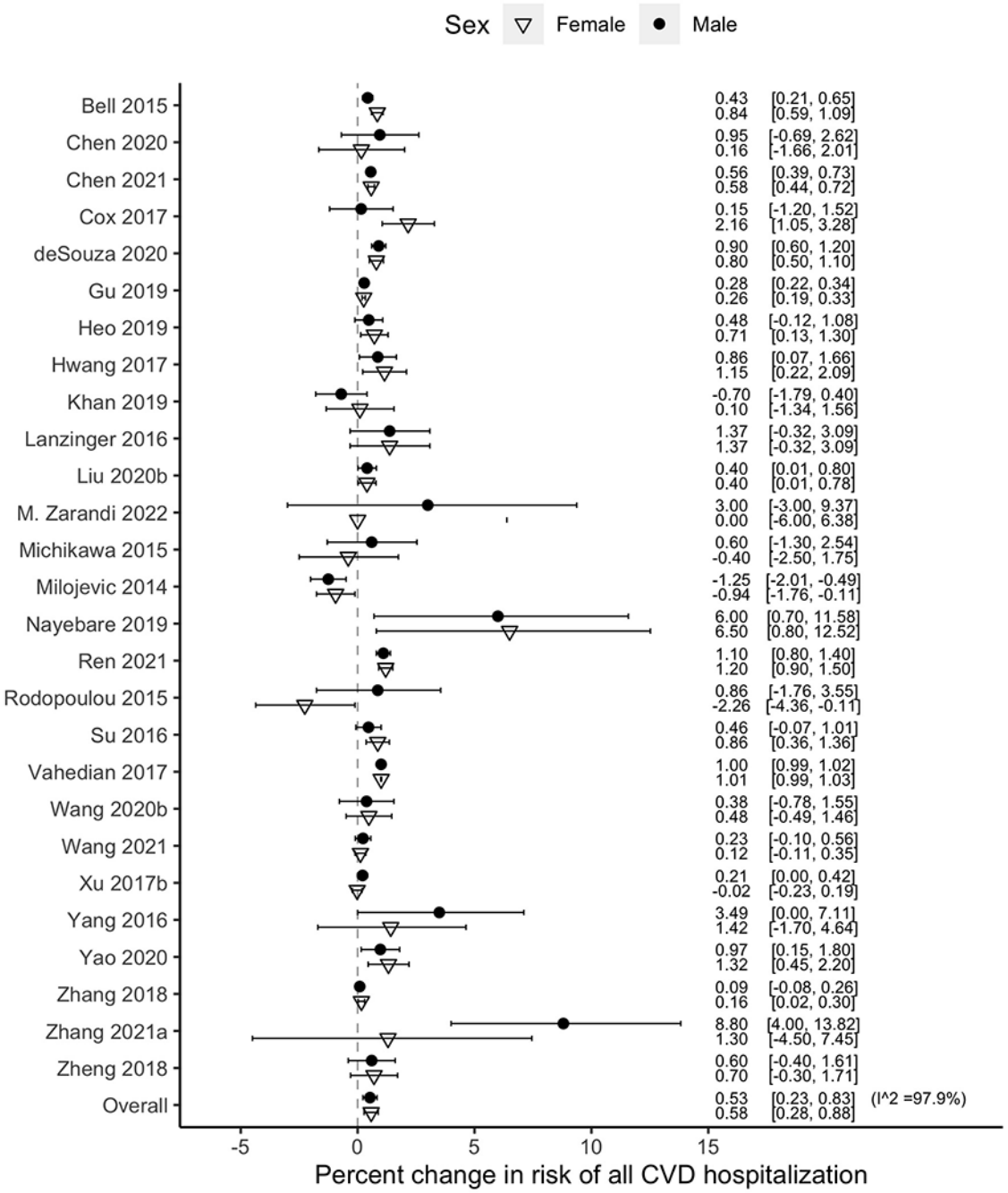

Figure 4.

Percent changes in all cardiovascular hospitalization for a 10 μg/m^3 increase in $PM_{2.5}$ (short-term) for the included studies in a meta-analysis, by sex. Horizontal lines represent 95% confidence intervals.

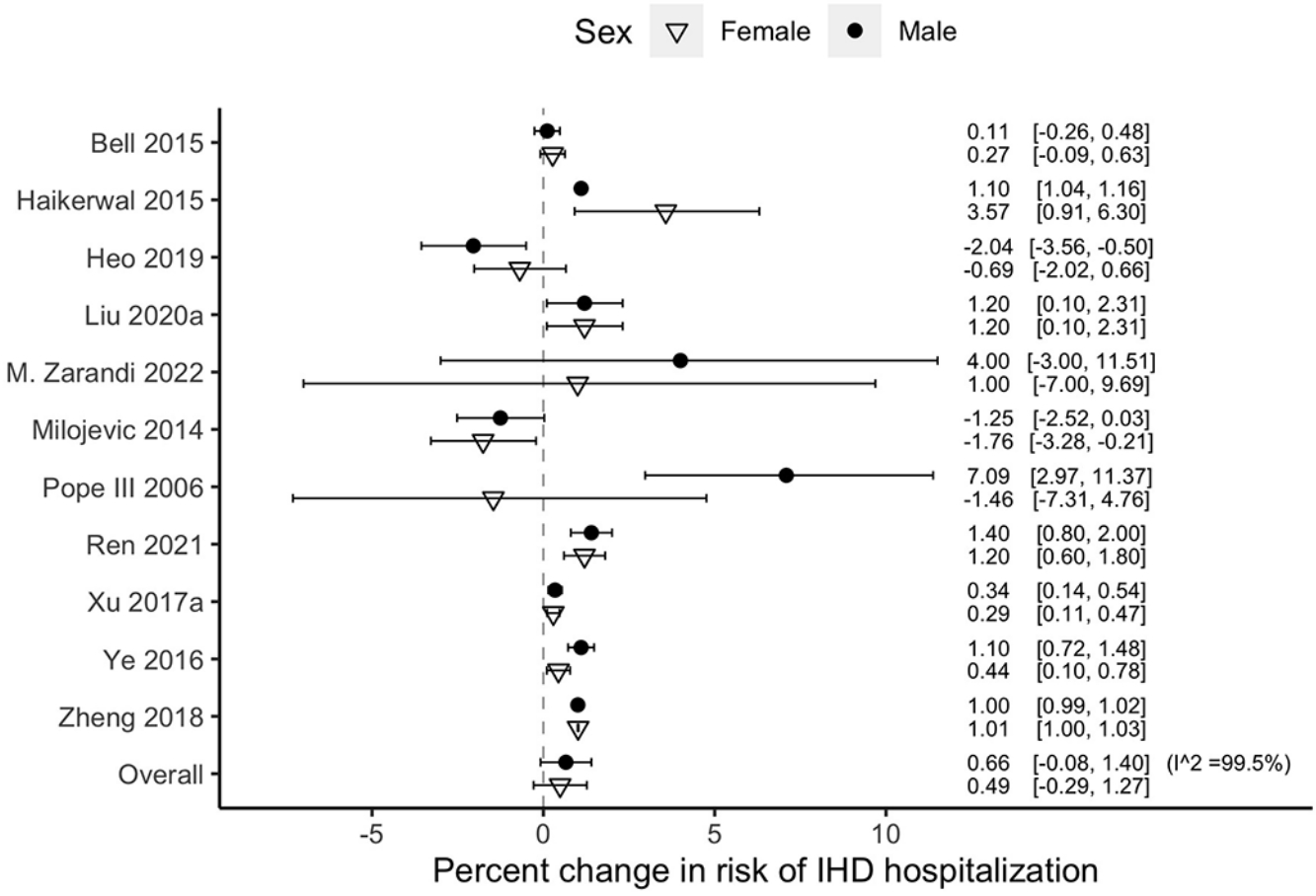

Figure 5.

Percent changes in ischemic heart disease hospitalization for a 10 μg/m^3 increase in $PM_{2.5}$ (short-term) for the included studies in a meta-analysis, by sex. Horizontal lines represent 95% confidence intervals.

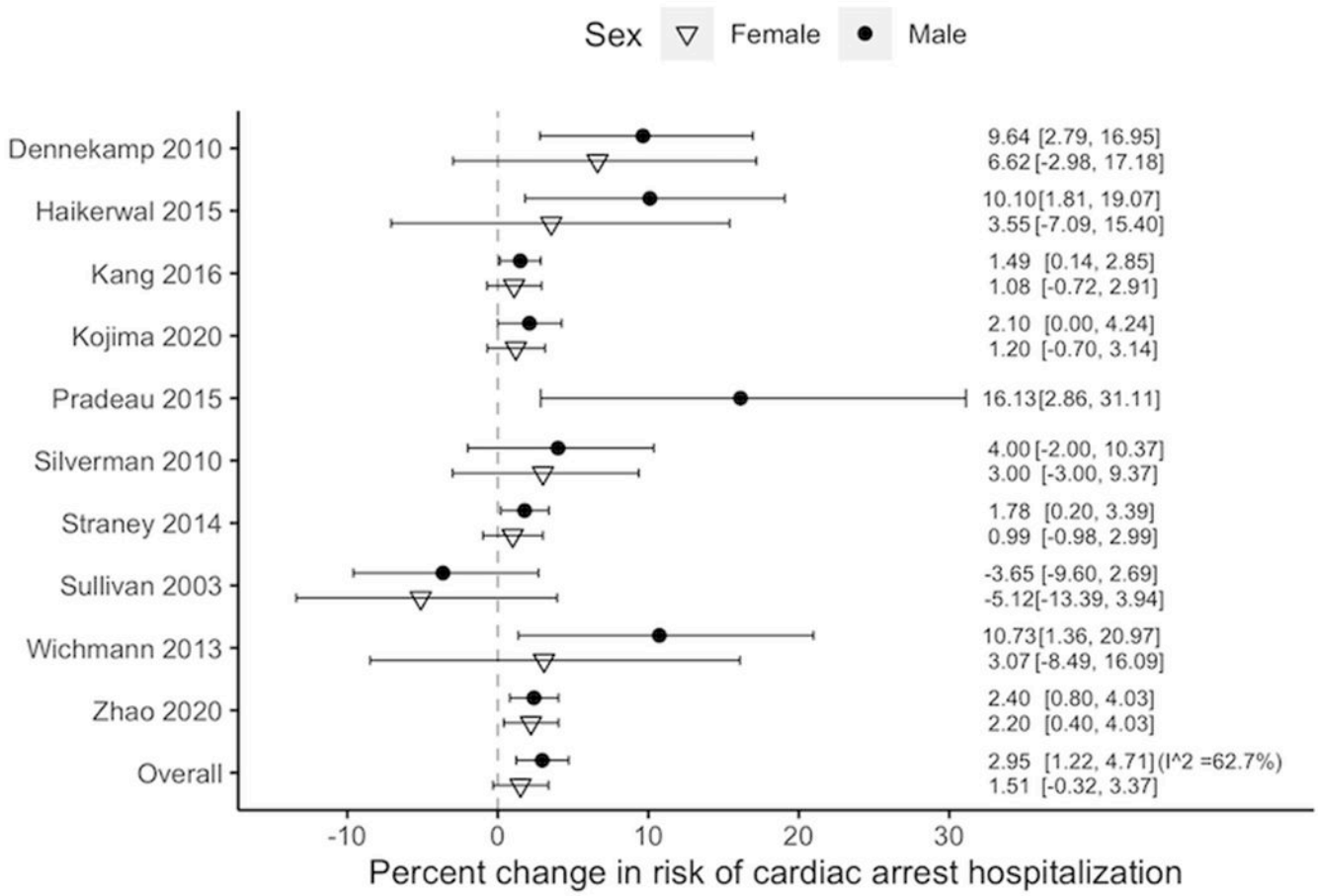

Figure 6.

Percent changes in cardiac arrest hospitalization for a 10 μg/m^3 increase in $PM_{2.5}$ (short-term) for the included studies in a meta-analysis, by sex. Horizontal lines represent 95% confidence intervals.

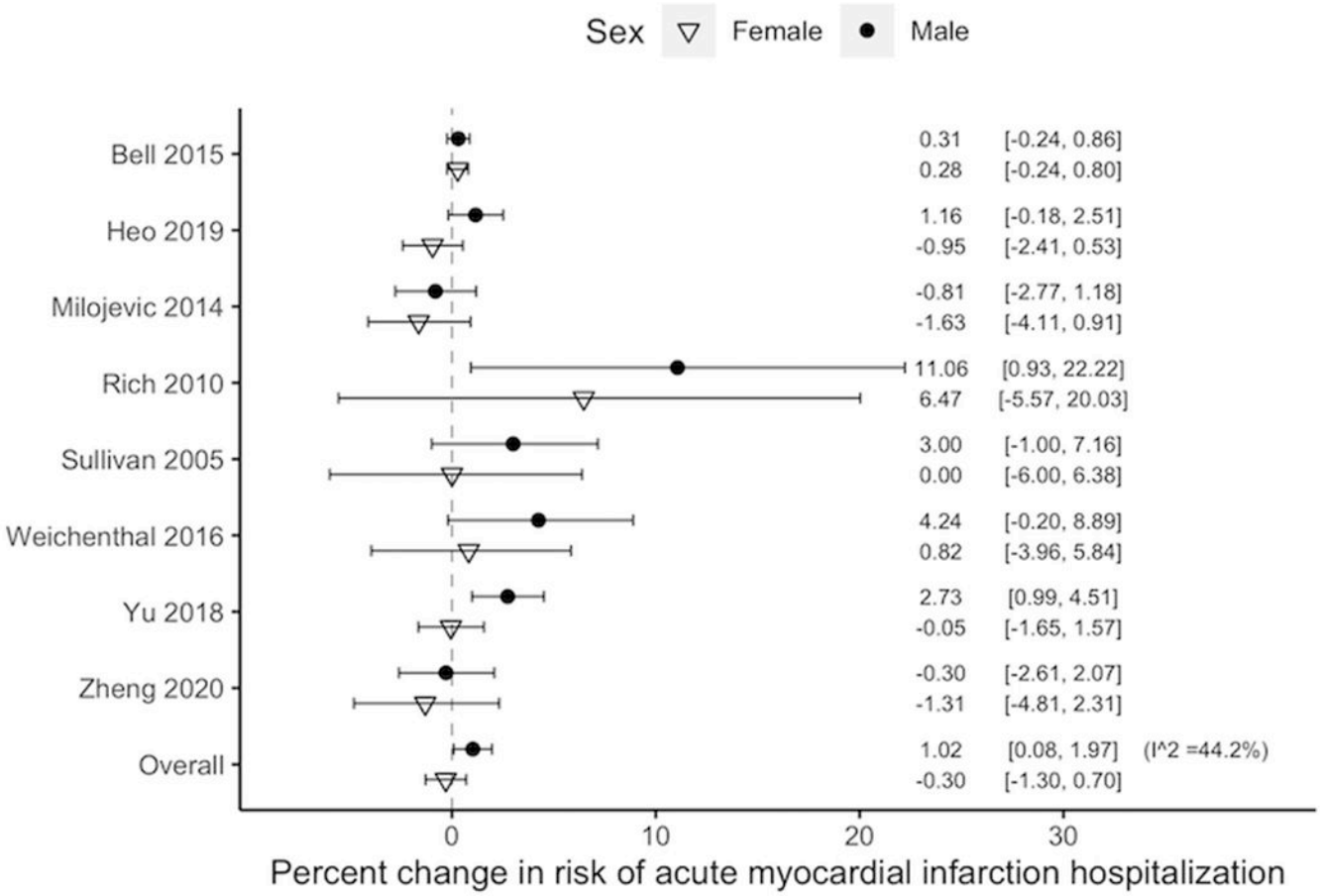

Figure 7.

Percent changes in acute myocardial infarction hospitalization for a 10 μg/m^3 increase in $PM_{2.5}$ (short-term) for the included studies in a meta-analysis, by sex. Horizontal lines represent 95% confidence intervals.

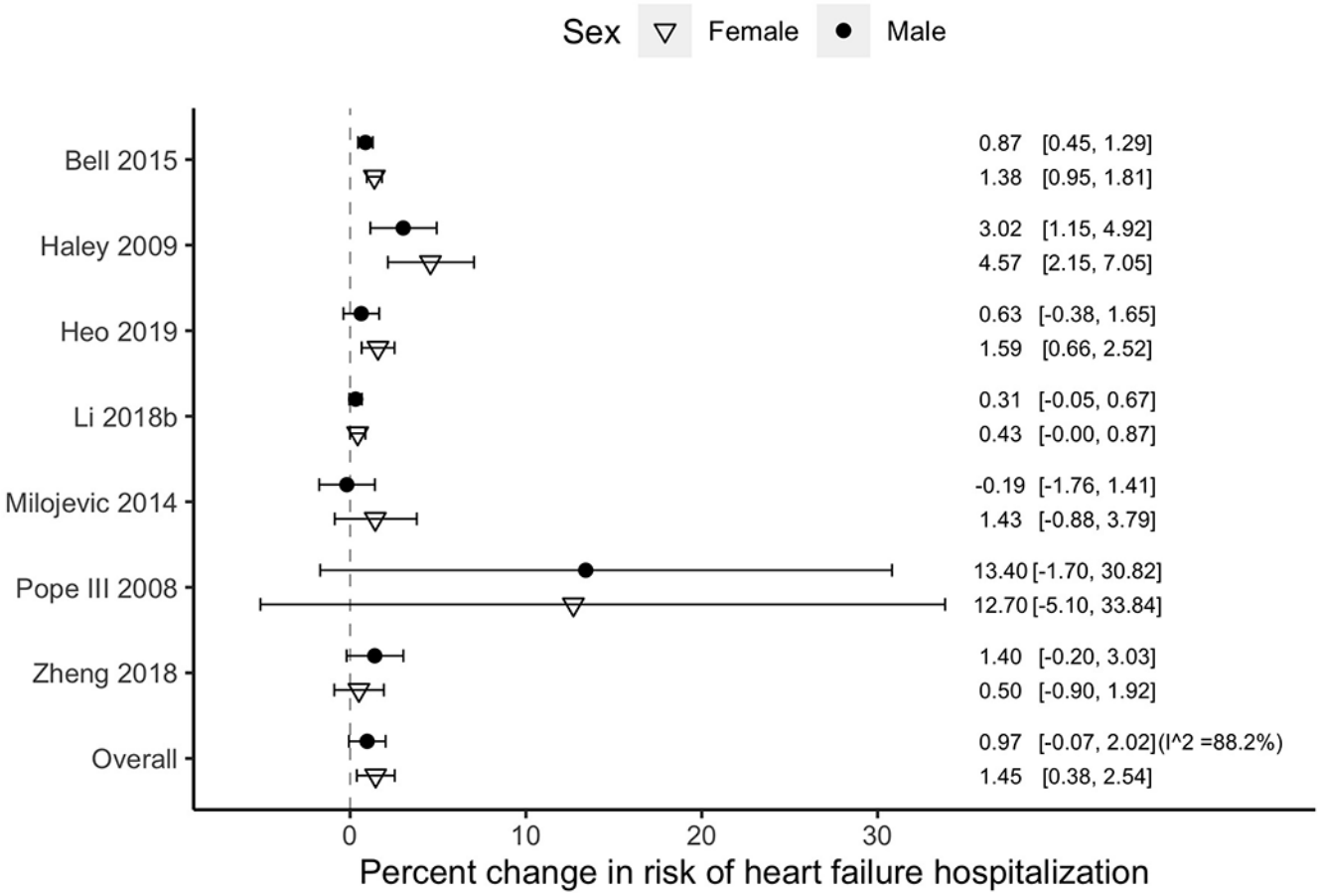

Figure 8.

Percent changes in heart failure hospitalization for a 10 μg/m^3 increase in $PM_{2.5}$ (short-term) for the included studies in a meta-analysis, by sex. Horizontal lines represent 95% confidence intervals.