Environmental Health

REVIEW

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"Low-to-moderate arsenic exposure: a global systematic review of cardiovascular disease risks"

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Abstract

High arsenic (As) exposure (≥ 100 µg/l) is associated with cardiovascular (CVD) outcomes, however, the CVD risk from low-to-moderate As exposure (< 100 µg/l) has been less explored. There is a paucity of systematic reviews that comprehensively evaluate both urine and water As exposure metrics in assessing As-related CVD outcomes within the general population. To fill this gap, this review sought to update and consolidate data regarding the correlation between low-to-moderate As exposure and specific CVD outcomes, including stroke, ischemic heart disease (IHD), acute myocardial infarction (AMI), and heart failure (HF). A search for peer-reviewed articles indexed in PubMed, Embase, CINAHL, the Global Medicos Index, and Web of Science and unpublished dissertations in Prospero until October 31, 2024, was performed. Nineteen studies were included. Relative risks were pooled by contrasting the highest v/s lowest exposure groups across studies. Positive associations were observed between urine As and stroke incidence, and water As with IHD incidence. Associations between water As and IHD and AMI mortality were suggestive and became stronger after excluding ecological studies. Sex-stratified analyses suggested an increased risk for all groups with strongest indication of an increased risk of AMI mortality in men. Increased risk was suggested for HF but only two studies assessed this outcome. These findings underscore potential risk for CVD outcomes in relation to low-to-moderate As exposure, and highlight the necessity for additional rigorous, well-structured studies to more clearly delineate the possible effects of low-to-moderate As exposure on different CVD outcomes.

Keywords Arsenic, Cardiovascular disease, Stroke, Acute Myocardial Infarction, Ischemic Heart Disease, Heart Failure

Introduction

Arsenic (As) is a metalloid that can be found in the earth's crust as inorganic arsenic (iAs) and organic compounds. It is often mobilized through drinking water wells and geothermal activities such as weathering, rock erosion, volcanic eruptions, and forest fires [1, 2]. Historically, *As* was utilized as a pesticide, in animal husbandry, for warfare, and as a medical agent to alleviate fever, intermittent headaches, and various other illnesses since medieval times [3, 4].

Humans primarily encounter *iAs* through water and dietary sources; around 200 million individuals in the world are exposed to varying concentrations of *iAs* at low (< 10 µg/l), moderate (10–100 µg/l), and high (> 100 µg/l) in drinking water [5–7]. For instance, Brazil, Chile, Australia, India, Pakistan, Bangladesh, China, Nepal,Vietnam, Burma,Thailand, Cambodia, Taiwan, and Italy are exposed to higher concentrations of *iAs* [8, 9]. Five million Americans are exposed to *iAs* levels > 10 µg/l in their drinking water via private wells or communal water systems [7]. This implies that a substantial

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proportion of the US population is ingesting *iAs* at levels that surpass the maximum contaminant limit (10 µg/l) suggested by the World Health Organization (WHO) and the Environmental Protection Agency (EPA) [9]. Diet is another substantial source of daily *iAs* exposure, particularly from food grown or prepared in water with elevated *iAs* levels [10]. Rice is a major dietary source of *iAs* exposure; it absorbs more *iAs* than other staple foods due to its high silica demand [11]. Studies from US, Bangladesh, and England confirm that frequent consumption of rice or rice based products leads to increased urinary *As* [12–14]. Seafood is also important source of organic *As* such as arsenobetaine (AsB), often considered less toxic than i*As* [15].

Despite the elevated toxicity of *iAs* compounds, they are absorbed, spread throughout the body, and excreted within 48 h post exposure [16]. In the liver, *iAs* is metabolized via methylation into monomethyl arsenate [MMA] and dimethylarsinate [DMA]; this process involves alternating reduction of *iAs* (As^{V} to As^{III}) with the subsequent addition of a methyl group [17]. Urine typically contains 10–30% iAs, 10–20% MMA, and 60–80% DMA as *iAs* metabolites, with significant inter-individual variation [18]. Urine serves as a reliable biomarker for evaluating speciated *As*, including *iAs,* DMA, and MMA [19]. Previous studies have reported strong correlation between water *iAs* and these urinary *As* species, highlighting the value of urinary *As* a biomarker for assessing short-term health impacts [20–24].

This systematic review focuses on water *As* and urine *As* because they are widely used to estimate exposure in *As* epidemiology. We considered including additional *As* biomarkers such as toenail, blood, and hair but only a few studies included these biomarkers. Additionally, prior reviews did not directly use the *As* values in these biomarkers, but instead converted them into estimated drinking water concentrations [7, 23]; we worried this could introduce additional heterogeneity in the pooled analyses. Accordingly, this review exclusively incorporates water and urinary *As.*

The association between chronic exposure to *iAs* and CVD has been widely reported at high concentrations (> 100 µg/l) [25]. Consistent exposure of *iAs* increases oxidative stress, endothelial dysfunction, epigenetic aberrations, and changes in the activity of enzymes responsible for CVD development [26]. Populations in *As*-endemic regions like Taiwan and Bangladesh exposed to water *iAs* > 100 µg/l are more likely to experience cardiac arrhythmia, hypertension, carotid atherosclerosis, ischemic heart disease (IHD), and vascular disease mortality [27–30]. However, uncertainty persists regarding the CVD-related effects of low-to-moderate *iAs* (< 100 µg/l). The importance of this review lies in updating our understanding of the association between low-to-moderate *As* exposure and CVD with pooled analyses now possible on additional CVD outcomes that were not possible in prior systematic reviews and meta-analyses (AMI, IHD and HF).

CVD remains the leading cause of morbidity and mortality worldwide; stroke, IHD, AMI, and HF collectively account for approximately 80% of the global CVD burden [31]. Previous meta-analyses have often examined all CVD outcomes combined, rather than focusing on specific outcomes. This broad approach makes it difficult to clarify the distinct associations between *As* exposure and individual CVD outcomes. Furthermore, current regulatory guidelines often consider water *iAs* concentrations < 10 µg/l to be safe. However, emerging evidence suggests that even these low-to-moderate exposure levels may contribute to adverse CVD outcomes, raising questions about the adequacy of existing standards. By focusing on both water *As* and urinary biomarkers, this review aims to update, synthesize and provide a more comprehensive assessment of low-to-moderate *As* exposure and its relationship with the specific CVD outcomes stroke, IHD, AMI, and HF.

Methods

Protocol registration

The protocol of this review was pre-registered on Prospero (ID CRD42023467794) to reduce the possibility of duplication. This review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) (Figure S1) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [32, 33]. An experienced librarian was consulted to evaluate the plan for the literature search across the relevant databases (Table S1). Author MG conducted an independent literature search, applied eligibility criteria, and compiled the studies. Subsequently, author JM provided significant guidance in data synthesis and interpretation of studies. Together, JM and MG resolved discrepancies in coding for study quality and relevance through detailed discussions.

Search Strategy

A comprehensive literature search was conducted using bibliographic databases (Web of Science, PubMed, Embase, CINAHL, Global Medicus Index) for published papers, and ProQuest (Dissertation & Thesis) for unpublished dissertations on October 31, 2024, for studies investigating the association between low-to-moderate *As* exposure and the CVD outcomes stroke (ischemic/hemorrhagic), IHD, AMI, and HF. To ensure a more comprehensive synthesis and reduce publication bias, we incorporated grey literature as unpublished dissertations,

which were not included in prior reviews. The complete set of search terms and keywords used across all databases is provided in Table S1.

Inclusion and exclusion

Studies were included if they: (1) assessed As exposure through drinking water and/or urine biomarker; (2) provided information on CVD risk associated with low-to-moderate levels of drinking water *As* < 100 µg/l; and (3) used an observational design with the general population (i.e., not a population exposed occupationally or due to industrial contamination). Our definition of CVD outcomes included incidence or mortality from stroke (ischemic/hemorrhagic), IHD, AMI, and HF. We excluded studies if they: (1) had no human data; (2) included outcomes other than stroke, IHD, AMI, HF: 3) were case reports/case series; 4) had no measure of association specified such as odds ratio, hazard ratio, risk ratio, or risk difference; (6) reported only on *As* exposure > 100 µg/l; (7) reported exclusively neonatal or childhood *As* exposure [34]; (8) measured occupational exposure; (9) reported on *As* trioxide (the least prevalent form of *As*); or (10) were conference papers, editorials, and commentaries. This systematic review focused on studies assessing *As* exposure via water and urine as biomarker; alternative biomarkers such as blood, hair and toenail *As* were excluded due to differences in measurement methods, temporal exposure representation, and limited availability of studies using these biomarkers, which could have hindered pooling for risk estimates.

Figure S1 shows studies excluded based on pre-specified criteria such as lack of specific CVD outcomes, occupational *As* exposure, and *As* levels > 100 µg/l. Additionally, grey literature such as dissertations were excluded if they did not meet inclusion criterion or if they had been subsequently published in peer-reviewed journals. A list of the seven studies (3) stroke [35–37], (3) IHD [28, 29, 38], and (1) HF [39] excluded from final synthesis along with their citations, is provided in Table S5. Finally, we manually reviewed references, cross-references, and bibliographies of four highly cited reviews to ensure no relevant studies were disregarded [7, 23, 27, 40]. After cross-reference, five more studies were included [41–45] resulting in a total of 19 studies, with several studies reporting on multiple CVD outcomes (Figure S1).

Data abstraction & synthesis

We extracted descriptive information for each study, which included geographic location, sample size, study design, exposure categories, outcome ascertainment, demographic factors such as age and gender, and potential confounding variables (Table S2). To define low-to-moderate *As* exposure, we applied < 100 µg/l cutoff for water As, and studies of urinary *As* came from communities exposed to < 100 µg/l water *As.* For each exposure category, we abstracted the low-to-moderate *As* metric (water and urine biomarker), number of cases/non-cases (in case control studies) or person-years (in incidence rate studies) or persons (in cumulative incidence/mortality studies), the measure of association (rate ratio, hazard ratio, odds ratio), and a measure of statistical uncertainty (standard error and confidence interval). For studies that used wider categories for *As* we only considered categories within our inclusion range (≤ 100 µg/l) and disregarded categories (> 100 µg/l) (Table S3) [41, 42, 46, 47].

Statistical analysis

For pooling risk estimates, we retrieved measures of association (odds ratios, prevalence ratios, hazard ratios, rate ratios) with 95% confidence intervals (CI) from nineteen studies. For studies with multiple exposure categories, we pooled relative risks for highest versus lowest *As* exposure categories across CVD outcomes, including stroke, IHD, AMI and HF. Among the final set of studies, only one reported both urine biomarker and water *As* [48]. For the pooled analysis, we used water *As* if urine *As* concentration exceeded the inclusion criteria. Of the three studies on urine *As* and stroke incidence, only two were included in the forest plot; the third study was excluded as it reported *As* species in proportions rather than absolute values [49]. Finally, relative risks were calculated through inverse variance weighting under a random effect model. This approach assigns greater weight to studies with smaller variances, ensuring more precise estimates contribute more to the pooled results. Consistency of findings across individual studies was assessed using standard $\chi 2$ tests and the I2 statistic. Forest plots were generated using the statistical packages metafor, meta, and forest plot in R (Version 4.4.1) [50, 51].We also performed a gender-stratified analysis to clarify risks separately for men and women. In addition, a sensitivity analysis was conducted by excluding ecological studies to better understand the influence of study design on the relationship between low-to-moderate *As* exposure and CVD. Following prior review [7] standards, we assessed study quality using the Newcastle Ottawa Scale (NOS) [52, 53]. The NOS uses eight questions to assess cohort or case–control study robustness by addressing participant selection, comparability between groups, and outcome determination. (Table S4).

Results

This review identified 19 studies examining the relationship between low-to-moderate *As* exposure and CVD outcomes, including stroke, IHD, AMI and HF. This included studies on the following CVD outcomes: stroke incidence (k = 8) and mortality (k = 9), AMI incidence (k = 3) and mortality (k = 4), IHD incidence (k = 2) and mortality (k = 5), and HF incidence (k = 2) and mortality (k = 1). These studies were conducted across diverse geographical locations, primarily in the United States (k = 6), followed by Bangladesh (k = 3), Taiwan (k = 1), Chile (k = 2), Italy (k = 2), Denmark (k = 2), China (k = 2), and Spain (k = 1). The study designs included prospective cohort, retrospective cohort, case-cohort, case–control, ecological, and cross-sectional approaches (Table S2). Among the 19 studies, As exposure was assessed using urinary biomarkers in four studies, while the remaining 15 relied on water *As* levels to evaluate the association with CVD outcomes.

Among the four studies on urinary *As* for exposure assessment, two major adjustments were witnessed: (1) for AsB and (2) for creatinine. Two studies corrected for creatinine and AsB in their analysis: The first Strong Heart Study (SHS), which reported urinary *As* levels (< 5.8—> 15.7 µg/g); and the second is a recent conference abstract, non–peer-reviewed study combining data from three distinct cohorts: SHS (8.57 µg/g), Multi-Ethnic Study of Atherosclerosis (MESA) (2.81 µg/g), and Hortega Study (6.52 µg/g) [54, 55]. The remaining two studies adjusted for creatinine but not AsB. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study assessed total toxic *As* levels, ranging from < 4.22 to 66.82 µg/g, while the Health Effects of Arsenic Longitudinal Study (HEALS) analyzed the proportions of *iAs* (0.3%–69.3%) and methylated species (%MMA, %DMA) [49, 56]. Measurement techniques also varied: SHS and HEALS measured total *As* using Graphite Furnace Atomic Absorption Spectrometry (GFAAS) and Inductively Coupled Plasma Mass Spectrometry (ICP-MS), with speciation (iAs, MMA, DMA) via High-Performance Liquid Chromatography coupled with ICP-MS (HPLC-ICP-MS). REGARDS, MESA, and Hortega primarily used ICP-MS. These differences affect the comparability of urine *As* measurements and could contribute to heterogeneity in pooled relative risk (RR) estimates across studies.

Exposure assessment methods for water *As* varied substantially across studies, contributing to heterogeneity in risk estimates. Some studies assigned exposure based on individual well water measurements [41–43, 47, 48] directly quantifying *As* levels in drinking water sources used by participants. Some used geographic groundwater models [57, 58], a few relied on municipal water supply zones where *As* exposure was determined by measurements from public water systems [59–64], while others reconstructed historical population-weighted exposure estimates over time [44, 45, 61, 63, 64] such as Time-Weighted Average (TWA) exposure [59, 61, 62]. For example, D'ippoliti et al [60] applied Cumulative As Index (CAI), Chiou [43] employed Cumulative *As* Exposure (CAE), and Medgyesi et al [64] used a 10-year moving average to assess time-varying exposure. Temporal variability in *As* exposure was inconsistently addressed; some studies assumed stable long-term exposure [44, 45, 59, 60] and others incorporated historical fluctuations and changes in water sources [61–64]. Handling of non-detect values also differed with some studies applying MDL/2 substitution [41, 42, 47]and others using regression-based imputation [63, 64]. Furthermore, studies in this review displayed a wide range of reference groups in their comparison to highest-exposure categories, introducing an additional layer of heterogeneity.

In addition, studies also differed in laboratory methods used for quantifying *As* in water. Some studies employed high-precision techniques such as Inductively Coupled Plasma Mass Spectrometry (ICP-MS) [41, 42, 48, 59–62] others relied on Atomic Absorption Spectrometry (AAS) [43–45, 57, 58, 63, 64], or Hydride-Generation AAS (HG-AAS) enhancing sensitivity for detecting low-level *As*. [43, 47] These methodological differences introduce potential exposure misclassification and variability in dose–response estimates.

For CVD outcome ascertainment, considerable variability was witnessed across studies (Table S2). Most studies relied on the International Classification of Diseases (ICD) criteria, supplemented by self-reports, death registries or hospital data and verbal autopsies. However, a smaller subset of studies combined ICD criteria with diagnoses made by panels of medical experts, including cardiologists, neurologists, and nosologists. Only one case–control study used standard clinical criteria for diagnosing AMI, supplemented by physician diagnoses [41].

Pooled association between low-to-moderate arsenic exposure and CVD outcomes

We independently pooled the relative risks for water and urinary *As* exposure for each CVD outcome, including stroke, IHD, AMI and HF. For urinary *As,* an association was observed with stroke incidence, with a pooled relative risk (RR) of 1.62 (95% CI: 1.14–2.31) (Fig. 1). There was a suggestive association between water *As* and stroke incidence, with or without excluding ecological studies (RR = 1.42; 95% CI: 0.94–2.16) (Fig. 2). For stroke mortality, only one study on urinary *As* reported a positive association, but the relative risk was not pooled as this

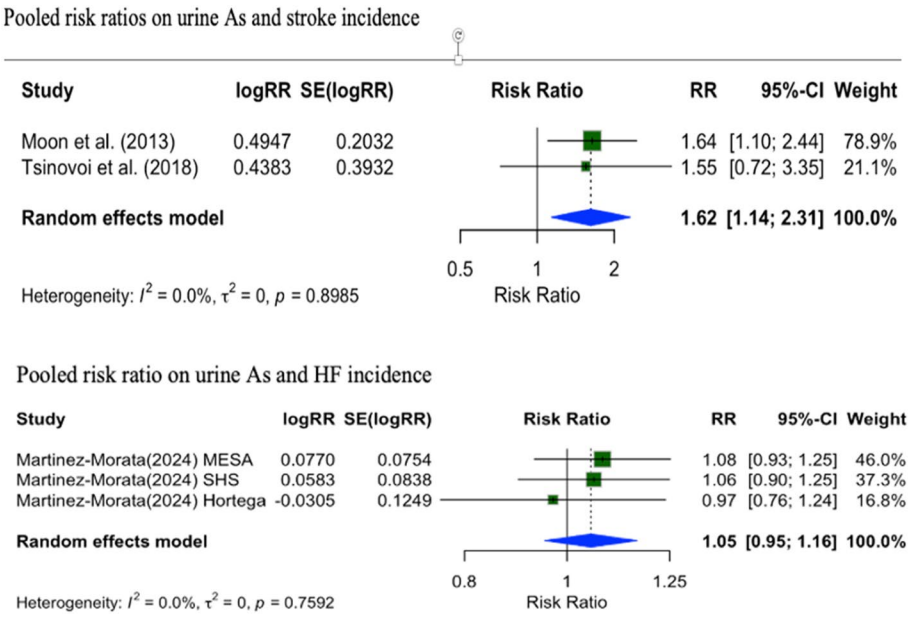

Fig. 1 Pooled risk ratios for urine As and CVD outcomes

was the sole study included in the review. For IHD incidence, a positive association was found with pooled RR of 1.37 (95% CI: 1.16–1.63) (Fig. 3). For IHD mortality, the association with water As was stronger after excluding ecological studies, with a pooled RR of 1.31 (95% CI: 1.02–1.68) and suggestive when ecologic studies were included (RR =1.16; 95% CI: 0.98–1.36) (Fig. 3). In the case of AMI, a positive association was observed between water As and AMI mortality after the exclusion of ecological studies, with a pooled RR of 1.46 (95% CI: 1.09–1.94) suggestive when ecologic studies were included (RR =1.18; 95% CI: 0.96–1.44) (Fig. 4). No association was observed for AMI incidence or HF incidence, regardless of the inclusion of ecological studies. The sex-stratified pooled analyses showed suggestion of associations for both men and women across all outcomes, and those associations became stronger when ecologic studies were removed (Figures S2-S13).

Discussion

This systematic review provides a comprehensive and up-to-date synthesis of literature on the association between low-to-moderate *As* exposure and specific CVD outcomes stroke, IHD, AMI and HF in the general population. This review synthesized a total of 19 studies, as summarized in Tables S2 and S3. The findings revealed a positive association between urinary *As* and stroke incidence. An association was also observed between water As and IHD incidence. Notably, positive associations were identified between water *As* and both IHD and AMI mortality, which became stronger after excluding ecological studies. Furthermore, sex-stratified analyses using pooled risk ratios indicated an increased risk for all groups which became stronger when ecologic studies were removed.

Unlike previous reviews, our review offers a novel contribution by examining the association of low-to-moderate *As* exposure (urine and water) with several specific CVD outcomes—stroke, IHD, AMI, and HF. Prior systematic reviews have examined risk from multiple environmental exposures, including but not limited to *As* [40, 65–67], or relied on narrative summaries of studies [2, 25, 26, 68]. Additionally, very few systematic reviews have focused exclusively on *As* exposure and its association with CVD outcomes, offering a more targeted perspective [27, 69]. Among two published meta-analyses on As and CVD, one includes a wider range of *As* exposures; the other study specifically focuses on low *As* levels in water (< 10 µg/l) [7, 23] but does not include specific CVD outcomes we address such as IHD, AMI, and HF. Stroke is one of the CVD outcomes that is frequently included in meta-analyses and reviews; we included stroke in our review to provide an updated synthesis by incorporating newer studies.

The individual association of both high and low *As* levels with CVD has been demonstrated in previous studies [38, 55]. However, two meta-analyses warrant further discussion. Moon et al [7] examined low-to-high *As* levels and reported a positive association with coronary heart disease, and a suggestive association with stroke. These

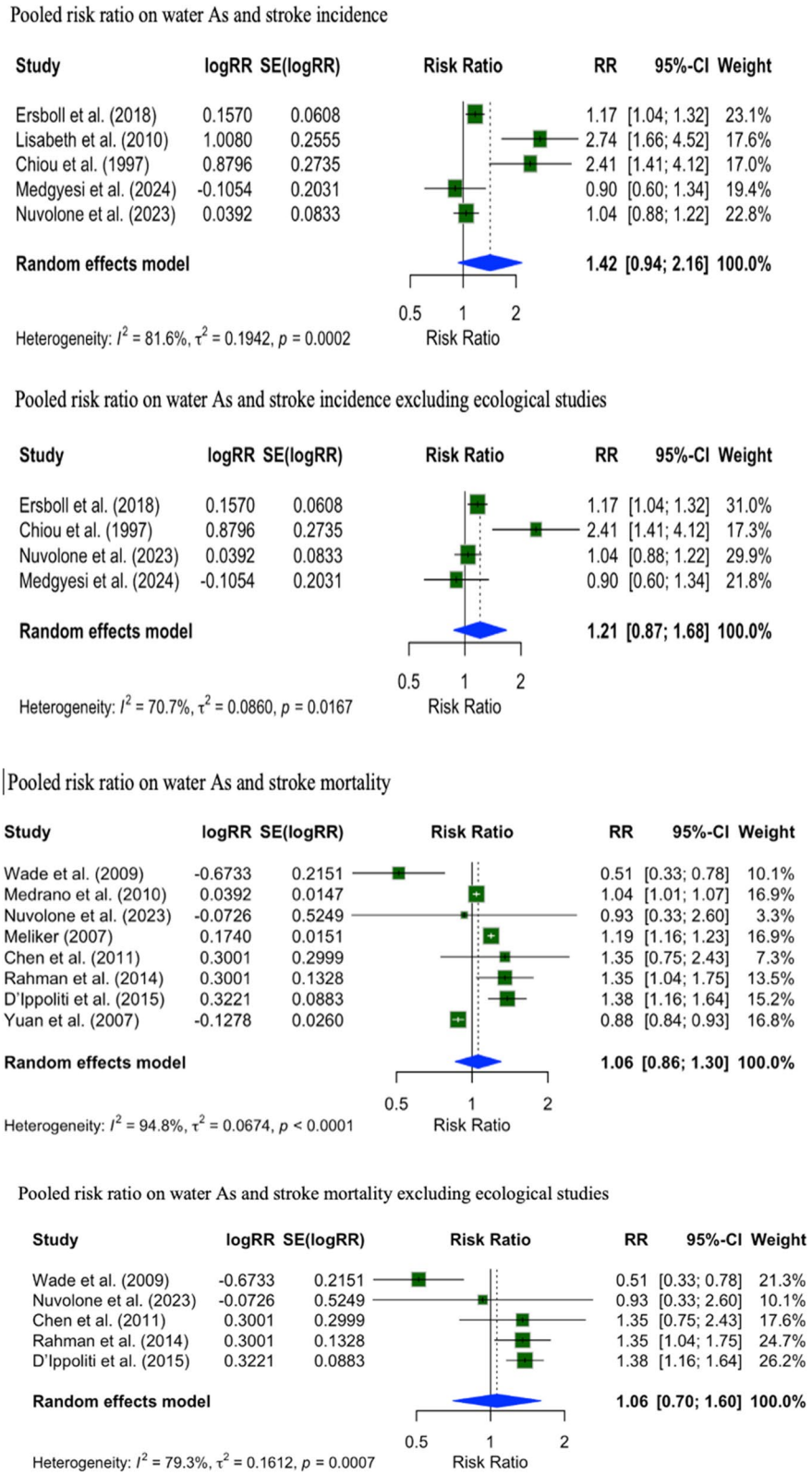

Fig. 2 Pooled risk ratios for water As and stroke incidence/mortality

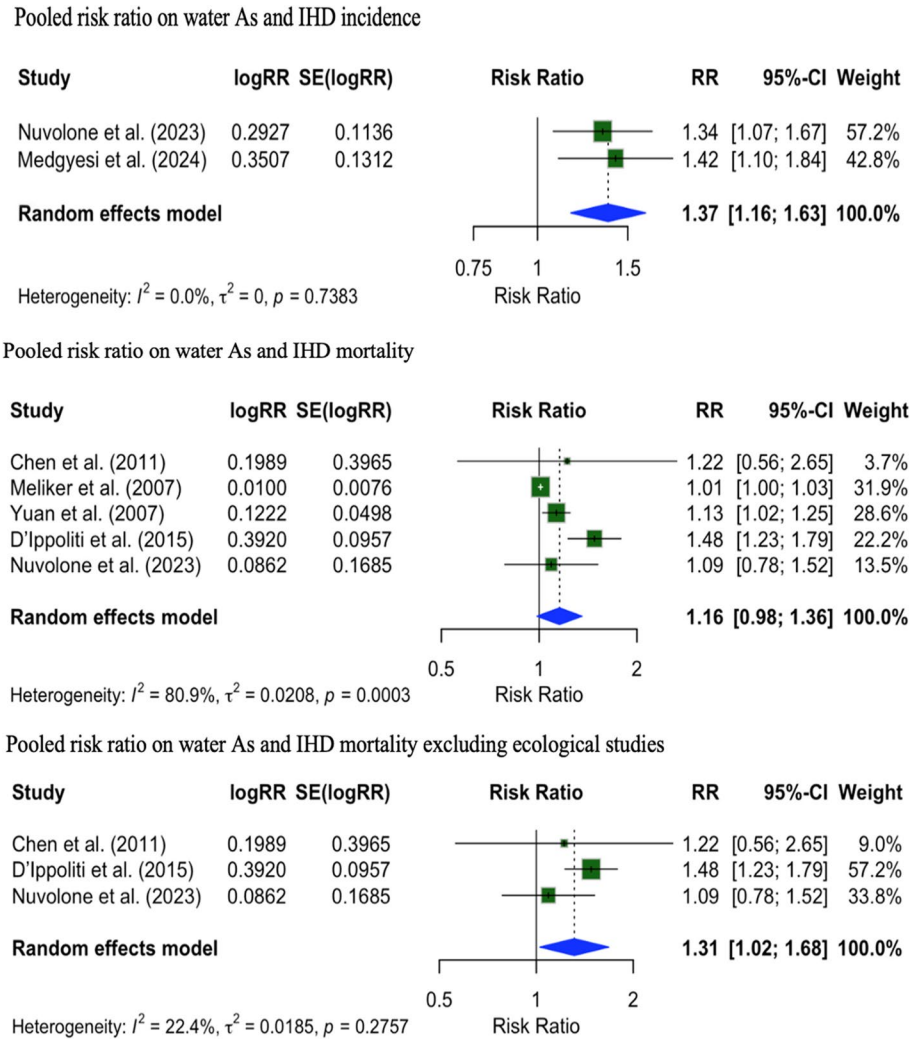

Fig. 3 Pooled risk ratios for water As and IHD incidence/mortality

findings were based on two studies on stroke incidence and six on stroke mortality [7]. Similarly, Xu et al [23] analyzed low water *As* levels and found no association with stroke mortality using data from seven studies [23]. These results are somewhat consistent with our findings, as no association was observed for stroke mortality with water *As* and we observed a suggestive association between stroke incidence and water *As.* Our analysis also identified a positive association between urinary *As* and stroke incidence based on two studies only, highlighting the need for further studies to explore this association and elucidate potential exposure pathways.

Our findings provide strong evidence for an association between water *As* and IHD incidence with RR of 1.37 (1.16–1.63) and almost 0% heterogeneity, indicating high consistency across studies. For IHD mortality, the overall risk estimate was elevated (RR = 1.16 (0.98–1.36)) and heterogeneity was high (80.9%). However, after excluding ecological studies, the association became stronger (RR = 1.31 (1.02–1.68)), and heterogeneity was reduced to 22%, suggesting that study design may have influenced the pooled estimate. These findings are consistent with the US EPA IRIS review [70], which highlights strong epidemiological evidence linking *As* exposure to IHD morbidity and mortality across multiple case–control and cohort studies in diverse populations [71, 72]. These results reinforce the growing consensus that exposure to water *As* is a risk factor for circulatory diseases such as IHD.

Understanding the role of influential studies is crucial, as they significantly shape pooled estimates and overall interpretation. These studies often feature large sample sizes, high-quality methods, or robust analyses, which can strongly impact effect sizes and their direction. For stroke incidence, the positive association between urine *As* and stroke incidence is driven by two large prospective

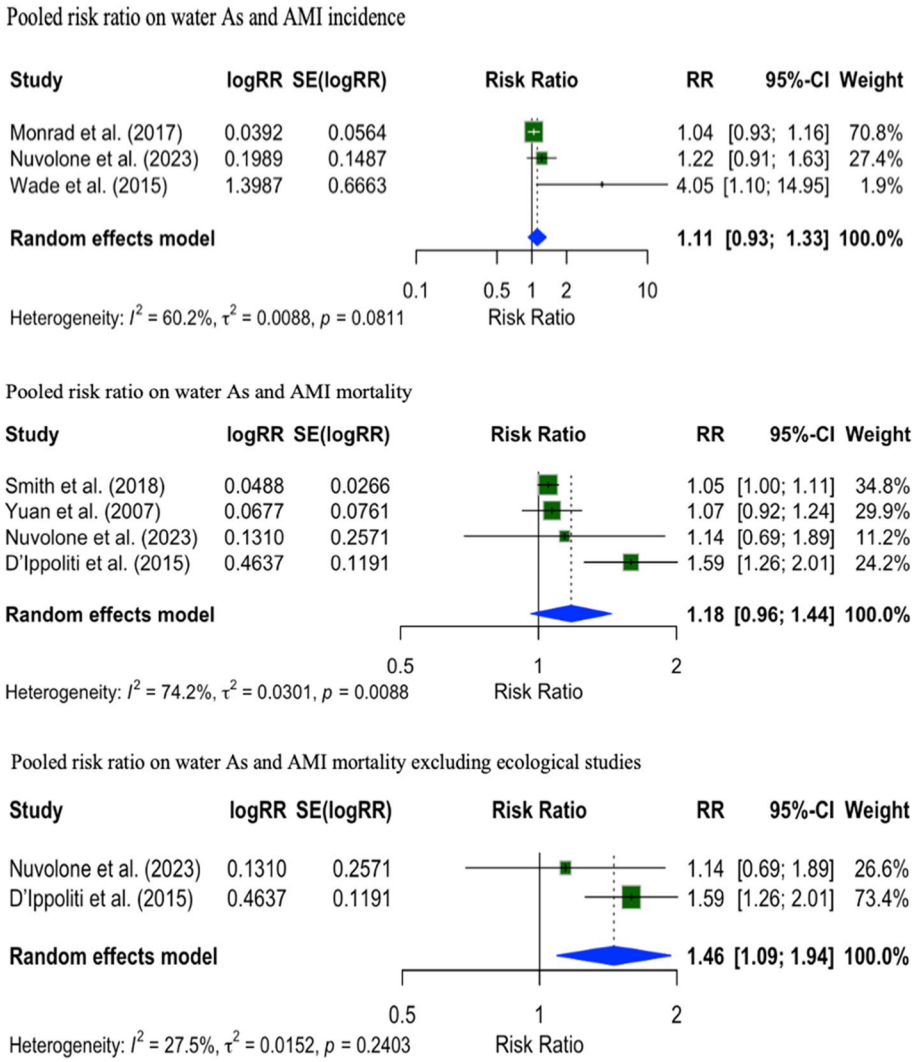

Fig. 4 Pooled risk ratio of water As and AMI incidence/mortality

studies. Among these, the study by Moon et al. [55] carries 78% of the weight with a tighter confidence interval, highlighting its substantial influence on the pooled estimates. In the case of water *As* and stroke incidence, three prospective cohort studies collectively drive the findings of a suggestive association with individual study weights of 23% [62], 22% [59], and 19% [64]. For IHD incidence, the association is driven by two large prospective studies [59, 64], both characterized by substantial sample sizes.

The increased risk of AMI mortality among men was primarily driven by two ecological studies, Smith et al [44] and Yuan et al [45] with a combined weight of 63%. Removing these studies results in a stronger association but greater heterogeneity and a wider confidence interval. The influence of both prospective and ecological studies emphasizes the importance of study design, sample size, and statistical precision in interpreting the results.

Another factor influencing the As-CVD association might be variability in *As* exposure and CVD assessment methods across studies. Differences in measurement techniques and exposure assignment were observed in both urinary and water *As* studies. In studies assessing urinary *As,* some measured total *As* while others included speciation to distinguish between inorganic and organic forms. Adjustment methods also varied, with some only applying creatinine correction, while others also adjusted for AsB to account for dietary sources, potentially impacting comparability. Similarly, water *As* exposure was assigned using different methodologies, ranging from direct well water sampling to municipal supply estimates and historical reconstructions. Some studies incorporated temporal variability in exposure, accounting for fluctuations in *As* concentrations over time, whereas others assumed stable exposure levels, which may introduce

misclassification and affect dose–response estimates. For CVD outcome ascertainment, inconsistent diagnostic approaches, such as self-reported data, reliance on non-validated health records, or differences in the methods used to measure specific CVD outcomes (stroke, IHD, AMI, or HF), can introduce errors into the classification of disease status [73, 74]. Such outcome misclassification where objective clinical confirmation is lacking, could lead to an underestimation or overestimation of the true associations between *As* and CVD outcomes. The lack of uniform diagnostic protocols across studies contributes to the heterogeneity in findings and may complicate the interpretation of the cumulative evidence. The inconsistencies in both exposure and outcome definitions highlight the need for standardized methodologies to estimate *As*-CVD relationships. Future research should prioritize harmonization of exposure assessment techniques and CVD case definitions to improve comparability, reduce bias, and ensure more reliable risk estimates for public health decision-making.

The association between *As* and CVD outcomes, including stroke, IHD, AMI, and HF, might be mediated through mechanisms such as oxidative stress, endothelial dysfunction, epigenetic aberrations, enzyme activity modifications, and signaling pathway dysregulation [26, 75, 76]. Endothelial dysfunction, a key target of *As* toxicity, disrupts the balance between vasoconstriction and vasodilation, leading to vascular abnormalities and increased risks of stroke, myocardial infarction, hypertension, and HF [26]. Urinary *As* is associated with serum expression of specific microRNAs, key regulators of cellular processes essential for cardiac function [77]. Atypical miRNA expression can disrupt cellular homeostasis, contributing to *As*-induced diseases such as CVD, and diabetes [78]. Circulating miRNAs also serve as potential prognostic biomarkers for risk stratification in AMI, diastolic dysfunction, HF, and atherosclerosis [69, 79]. Moreover, *As* exposure stiffens the aorta and major arteries, causing them to lose compliance. This stiffening increases the workload on the left ventricle, requiring greater effort to pump blood into the stiffened arteries and can lead to left ventricular hypertrophy [39]. Notably, ventricular hypertrophy leads towards HF.

Strengths and limitations

The strengths and limitations of this work warrant thorough consideration. The review incorporated two popular metrics of *As* exposure (urine biomarker and drinking water) in association with specific CVD outcomes such as stroke, IHD, AMI and HF.

A significant strength of this review is its inclusion of both peer-reviewed published articles and grey literature, such as unpublished dissertations, which are frequently neglected in previous reviews. By incorporating grey literature, this review ensures a more comprehensive and balanced analysis, addressing key issues often overlooked in studies that rely solely on published research; reviews excluding grey literature are prone to (a) overrepresenting studies with significant or positive findings, (b) inflating effect size estimates, and (c) impair precision and generalizability of effect size estimations [80]. This broader approach enhances the reliability and validity of our findings, providing a more accurate reflection of the relationship between *As* exposure and CVD outcomes.

This review includes all papers that met the inclusion criteria, regardless of their study design. This stands in contrast to previous reviews and meta-analyses that excluded studies due to cross-sectional design, ecological design, or fewer than three *As* categories [7]. We did not include biomarkers such as toenails, blood serum, or hair as potential sources of *As* exposure. Literature suggests that, alongside urine, toenails are a prominent biomarker for *As* since they provide more stable measurements over time [22]. While this study focused on water and urine *As* for methodological consistency, future studies should consider whether there are enough studies that use alternative biomarkers (toenail, blood, hair) to provide additional insights into *As* metabolism and its CVD effects.

This review primarily relied on observational epidemiological investigations, which are susceptible to unknown confounding variables, thereby limiting the ability to establish causal relationships. To address this, future research must be meticulously designed to explore the health implications of CVD in relation to the intensity and duration of low-to-moderate *As* exposure.

Another limitation of this study is the inconsistency in *As* exposure evaluation and CVD outcome determination among the included studies. Divergences in exposure categories (highest vs lowest exposure groups), measurement methodologies, and outcome definitions constrained comparability and may have resulted in misclassification. This heterogeneity likely resulted in discrepancies in risk estimations and hindered the application of a uniform exposure–response model. We were hoping to calculate relative risks in specific exposure ranges (5–10 µg/l) but unfortunately there was too much variability in exposure groupings across studies to be able to assess risk in specific exposure ranges. Future research that can define exposure thresholds and outcome definitions, or implement dose–response methodologies, would improve risk assessment.

Conclusion

This systematic review strengthens the evidence of an association between low-to-moderate *As* exposure and CVD outcomes by incorporating recently published

studies and implementing a rigorous analytical framework. Through separate analyses on water *As* and urine *As*, sex-stratified analyses, and multiple sensitivity analyses to assess influence of study design, this review provides a detailed synthesis of the epidemiological evidence. The findings indicate an association between low-to-moderate concentrations of *As* in urine and stroke incidence. We also observe associations between water *As* and IHD incidence, and associations with IHD and AMI mortality strengthened after excluding ecological studies. Sex- stratified analyses suggested consistently elevated risks from water *As* among men and women.

Approximately 33% of all deaths in the United States are attributed to CVD, with an estimated 1.5 million adults experiencing heart attacks or strokes each year [31]. These events result in premature deaths and impose a significant financial burden on healthcare systems. From apublic health perspective, even a slight increase in the risk of CVD linked to *As* exposure could have substantial implications for both individual and community health. Given the uncertain associations observed for AMI, and HF, future research should be strategically designed to investigate relationships between low-to-moderate *As* exposure and CVD outcomes. The insights from this review are particularly relevant for re-evaluating regulatory risk assessment, and public health policy considerations.

Abbreviations

As	Arsenic
AMI	Acute myocardial infarction
CVD	Cardiovascular Disease
DMA	Dimethylarsinic acid
HF	Heart Failure
iAs	Inorganic Arsenic
IHD	Ischemic Heart Disease
RR	Relative Risk
MMA	Monomethylarsonic acid

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01184-5.

Supplementary Material 1.

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Authors' contributions
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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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