

Review

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Genetic susceptibility to adverse arsenic-related cardiometabolic outcomes: a systematic review

<https://doi.org/10.1515/reveh-2025-0041>

Received March 31, 2025; accepted May 21, 2025;

published online June 27, 2025

Abstract: Millions of people worldwide are chronically exposed to environmental arsenic through drinking water, increasing their risk of various adverse cardiometabolic outcomes. To understand the inter-individual variation in arsenic susceptibility, this systematic review explores all epidemiological evidence on interactions between single nucleotide polymorphisms (SNPs) and arsenic exposure in relation to cardiometabolic health. Five electronic databases were searched until April 2023. From 42,202 retrieved publications, 18 candidate gene-environment (cGxE) studies were included, and no genome-wide association studies were found. Of 676 SNPs in 148 genes tested, 40 SNPs in 24 genes, 4 haplotypes and combined SNPs in *MCP-1/APOE*, were reported to statistically significantly interact with arsenic exposure. These genes were involved in arsenic

metabolism, oxidative stress or defence, DNA damage repair, endothelial (dys) function, inflammation or immune function, tumour suppressor activity, or were previously implicated in cardiometabolic disease pathways. Most studies did not explore the same SNPs (or strong proxies), and none of the identified SNP-arsenic interactions were replicated for the same arsenic species and cardiometabolic outcome. Whilst some SNPs are suggestive of influencing susceptibility to arsenic for various cardiometabolic outcomes, further research is needed to understand the interplay between arsenic and genetic variants, identify at-risk populations, and improve risk assessment.

Keywords: arsenic; cardiometabolic disease; genetic susceptibility; gene-environment; SNPs

Introduction

Environmental exposure to arsenic, one of the most abundant elements in the earth's crust, is increasingly recognised to elevate risk of adverse cardiovascular disease, hypertension and diabetes, with evidence being most conclusive at moderate to high levels of arsenic exposure [1–3]. Inter-individual variation in susceptibility to adverse arsenic-related health effects is influenced by the arsenic species (i.e., inorganic or organic, valency), concentration, and metabolism efficiency. The latter is shaped by biological factors (e.g., age, sex), lifestyle factors (e.g., nutritional status, physical activity) and potentially various genetic polymorphisms [4].

Several genetic studies – including genome-wide association [GWA] [5], linkage [6], and candidate gene studies [7] – have reported significant effects of variants near the arsenic methyltransferase (*AS3MT*) gene on arsenic metabolism and subsequent non-cardiometabolic disease outcomes, such as skin lesions and cancers [8]. Further candidate gene, linkage and exome-wide association studies suggest that additional genetic variants affecting arsenic metabolism and arsenic-related health outcomes likely exist, including genes critical for carbon-folate metabolism (e.g., forminotransferase

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cyclodeaminase [*FTCD*]) [9], genes involved in the classic arsenic methylation pathway (e.g., glutathione S-transferase omega [*GSTO*] [10], purine nucleoside phosphorylase [*PNP*] [11]), and genes involved in DNA damage repair (e.g., *MPO* [myeloperoxidase] [12], and *NBS1* [nibrin]) [13].

However, whilst one previous narrative review explored arsenic exposure, arsenic metabolism, and their interaction with genetic (and epigenetic) factors in relation to cancer outcomes [4], thus far, no study has systematically summarised the totality of evidence for the influence of genetic variations on arsenic-related cardiometabolic outcome susceptibility. Therefore, this systematic review aims to i) summarise all available epidemiological evidence exploring whether associations between environmental arsenic exposure and risk of adverse cardiometabolic outcomes change in the presence of common genetic variations, and ii) support the current understanding of the biomolecular mechanisms that may underpin arsenic-related cardiometabolic outcomes, based on the genetic variants proposed to be involved.

Methods

The study protocol was prospectively registered with PROSPERO (CRD42019146144). Findings are reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary Table 1) and Joanna Briggs Institute (JBI) guidelines [14, 15].

Search strategy and definitions

Five electronic databases were systematically searched using English search terms: PubMed, Web of Science, Scopus, EMBASE, and TOXLINE via TOXnet. Databases were searched from inception until 24 July 2019, with an updated search on 10 April 2023. Note, TOXLINE was excluded in the updated search as the database was retired in December 2019. Keywords used included indexed MeSH terms as well as free text terms related to ‘genetic polymorphism’, ‘genetic’, ‘arsenic’ and ‘arsenicals’ and were informed by previous publications [1, 16], and a medical information specialist (full search strategy in Supplementary Table 2). No restriction on the language or date was applied. Bibliographies of relevant publications (e.g., reviews, grey literature) and all included studies in the full-text screening were cross-referenced (forward and backward) to identify any additional eligible studies. The GWAS Catalog (<https://www.ebi.ac.uk/gwas/>) and Google Scholar were searched for additional studies fulfilling the inclusion criteria.

The exposure of interest was single nucleotide polymorphisms (SNPs): a single nucleotide change in the DNA sequence, comprising one of the most abundant types of genetic variation. No specific molecular processes, genes or SNPs were selected as a focus *a priori*, enabling the synthesis of all available evidence on common genetic variation(s) that may interact with arsenic exposure to impact arsenic-related cardiometabolic outcomes. Other variations in the DNA sequence, including other genetic variants (e.g., indels, microsatellites, repetitive elements), structural variation, and epigenetic variation were excluded. Haplotypes of linked SNPs within a chromosomal region were included.

This study included arsenic-related cardiometabolic diseases such as cardiovascular diseases (CVD, including coronary heart diseases [CHD], cerebrovascular diseases [CeD], peripheral arterial diseases [PAD], deep vein thrombosis [DVT]), diabetes mellitus (including type 1 [T1DM], type 2 [T2DM] and gestational [GDM]), hypertension, obesity, and metabolic syndrome. Subclinical cardiometabolic diseases (carotid atherosclerosis, arterial stiffness, ECG abnormality), and diagnostic markers (blood pressure [systolic, diastolic, pulse], blood glucose levels, carotid intima-media thickness [CIMT], HbA1c% levels) as continuous outcomes were included. Predictive biomarkers (e.g., asymmetric dimethylarginine (ADMA), fatty acid-binding protein 4 (FABP4) for CVDs) were excluded. Standard definitions following commonly used guidelines for the different cardiometabolic outcomes were applied (e.g., ACC/AHA [17] and ESC/ESH [18] guidelines for hypertension, or WHO [19], ADA [20], and NICE [21] guidelines for T2DM). Other diseases, such as skin lesions or cancer, were excluded, as were studies that only assessed the impact of SNPs on arsenic metabolism.

Study selection

Studies that met the inclusion criteria were: i) peer-reviewed quantitative epidemiological studies, ii) studies exploring whether one or more SNPs affects susceptibility to adverse cardiometabolic outcomes related to arsenic (i.e., whether a genetic variant is associated with higher or lower cardiometabolic risk when a person is exposed to arsenic), and iii) studies including arsenic species to which the general population is commonly environmentally exposed (i.e., inorganic arsenic [iAs] exposure or its metabolites [MMA, DMA], see Supplementary Table 3). Studies were excluded if they were studies that i) did not include a quantitative measure of arsenic exposure, ii) focused on forms of arsenic exposure uncommon in the general population such as medical therapy (e.g., melarsoprol treatment for parasitic infections, arsenic trioxide for leukemia), or intentional poisoning (homicide,

suicide), ii) were non-human (i.e., *in vitro*, animal studies), iii) had a secondary study design (e.g., reviews, meta-analyses), or that reported on data previously reported elsewhere, iv) were conference proceedings, case reports or case series, v) lacked an available full-text (after request of full-text from the authors), or vi) had overlapping study populations with another included study within this review (with exception of those studying a different cardiometabolic outcome and partially overlapping study populations). Studies on arsenic-exposed populations that did not include SNP-related arsenic susceptibility or SNP-arsenic interaction analyses were also excluded.

After the duplicates were removed in Endnote, abstracts and titles were blindly double-screened using Rayyan (<https://rayyan.ai/>). In this stage, all studies on SNPs in relation to arsenic-related disease or arsenic metabolism were included. Ambiguity in the inclusion and exclusion criteria was checked by conflict piloting after the first 500 records were screened, resulting in an inter-rater reliability kappa score of 98.6 %. In the second stage, full-texts were retrieved and double-screened, focusing only on arsenic-related adverse cardiometabolic outcomes as previously defined. Any disagreements between two reviewers were discussed until consensus was reached. To minimise bias, non-English records were included and translated/reviewed by a speaker of the language (i.e., Bengali, Dutch, French, Spanish, German, Serbian). However, few non-English studies were retrieved for full-text screening.

Data extraction

A data extraction tool was developed and pilot-tested on five randomly selected studies, and refined accordingly. Data were extracted by KvD, and verified by MJ. Data extracted included: first author, year of publication, study design, participant characteristics (country, age, sex, ethnicity and/or genetic ancestry), number of participants, years of follow-up (cohort studies), gene(s) and SNP(s) assessed (including their allele/genotype/haplotype frequencies), genotyping method, type of arsenic exposure (e.g., water, urinary or blood arsenic), method of arsenic exposure assessment, adverse cardiometabolic outcome (e.g., CVD, metabolic syndrome), outcome ascertainment method, measures of the combined effects (or interaction) of the SNPs and arsenic exposure on negative cardiometabolic outcomes (e.g., odds ratio [OR] estimates for interaction terms, joint ORs of the combined SNP-arsenic effect, relative excess risk due to the interaction [RERI], attributable proportion due to the interaction [AP], synergy index [SI], p-values for interaction [P_{int}]), variables adjusted for in the main statistical analyses,

and an open field to record additional information. When both p-values and Q-values (p-values adjusted for multiple comparisons) were reported, both were extracted, and results were discussed based on Q-values. When both unadjusted and adjusted measures of effect were reported, both were extracted, but the models that adjusted for the greatest number of confounders were discussed in the information synthesis. This approach was taken even when models adjusted for different variables across studies considering the adjusted effect estimates are more likely to be representative of the “true” effect than crude models.

To create an overview of all genes and SNPs assessed within the studies included review, an overview table was generated listing the corresponding gene, rsID, alleles, and consequence of the variation for each individual SNP (i.e., missense variant, synonymous variant, intron variant, noncoding transcript variant, 5' UTR variant, 3' UTR variant, 2KB upstream variant, 500B downstream variant) based on information in the included studies, the dbSNP database (<https://www.ncbi.nlm.nih.gov/snp/>) and the integrative database GeneCards (<https://www.genecards.org/>).

Individual study quality assessment

To allow for the incorporation of genetic and environmental components in individual study quality assessment, methodological quality was assessed using study design adapted versions of the quality assessment tool developed by Moon et al. 2017 for studies on environmental arsenic [1, 22] – and the Q-genie tool for the quality assessment of genetic association studies [23]. The tool was pilot-tested on five randomly selected studies, and refined accordingly. No overall score (e.g., good, fair, poor) was given as this can oversimplify important differences in bias, confounding, and overall quality of the different studies. Almost none of the studies explored the same SNP and cardiometabolic outcomes (Table 2, 3), therefore no overall assessment of the certainty of the body of evidence using Grading of Recommendations, Assessments, Development and Evaluation (GRADE) was performed.

Information synthesis

Due to the heterogeneity of included studies [i.e., genes/SNPs assessed, outcome assessed (e.g., CVD, DM, hypertension), and arsenic species assessed], data were descriptively synthesised, and no meta-analyses were performed. Studies were grouped and synthesised by the outcome of interest, and, where possible, further discussed by biochemical

processes relevant genes are involved in. Due to the limited number of (heterogenous) studies included, publication bias could not be assessed.

Results

42,202 publications were retrieved from the databases (Figure 1). After removing duplicates, 18,922 studies were screened by abstract and title, and 261 in full text. A total of 18 studies met the inclusion criteria, with summary characteristics reported in Table 1, individual study results in Table 2, and summary results in Table 3. Studies excluded in full-text screening and reason for exclusion are listed in Supplementary Table 4. Most studies were conducted in Taiwan ($n=7$) [24–30] and Bangladesh ($n=4$) [31–34], with others conducted in China ($n=3$) [35–37], Spain ($n=2$) [38, 39], Mexico [40], and the United States [41]. Included studies had a cross-sectional ($n=7$) [24, 33, 36–40], case-control ($n=5$) [26–28, 30, 35], cohort ($n=4$) [25, 29, 31, 41], or case-cohort ($n=1$) [34], design and included data from, among others, the HEALS [31, 33, 34], SHFS [41], Hortega [38, 39] and VALCAR [39] studies.

Study samples were relatively small ranging from 121 participants [29] up to 2,225 participants [34]. Most had gender parity in participants (i.e., 45–55 % women) [26, 27, 30, 31, 34, 38, 39], or included predominantly women (i.e., >55 % participants were women) [24, 25, 28, 29, 33, 35, 37, 40, 41], whilst two included predominantly men [32, 36]. All studies were conducted in adults, and were conducted as early as 1989 [28] up to 2018 [35].

Cardiometabolic outcomes

Studies reported on different cardiometabolic outcomes, including: hypertension or blood pressure (SBP, DBP, PP) [24, 28, 31, 36], metabolic syndrome [25], obesity [39], T2DM or insulin resistance [32, 35, 38, 40, 41], GDM [37], carotid atherosclerosis or CIMT [26, 27, 30, 33], CVD [34], CHD [34], stroke [34] or ECG abnormalities consistent with MI or ischemia, conduction defect, arrhythmia, arterial enlargement or ventricular hypertrophy or prolonged ventricular repolarization (Table 1) [29].

Hypertension and blood pressure (i.e., systolic, diastolic, pulse pressure) were assessed using a mercury or automated sphygmomanometer [24, 28, 31]. Hypertension was defined as $SBP \geq 130$ mmHg and/or $DBP \geq 80$ mmHg [24], or as $SBP \geq 140$ mmHg and/or $DBP \geq 90$ mmHg [28]. The studies on T2DM defined DM as fasting blood glucose (FBG) ≥ 126 mg/dL [38, 41], $HbA1c \geq 6.5$ % [32, 35, 38], self-reported physician

diagnosis or T2DM treatment [38], and 2-h post glucose ≥ 200 mg/dL [40], with homeostasis model assessment of insulin resistance (HOMA2-IR) computed using fasting glucose and insulin values [41]. GDM was defined at 24–28 weeks of pregnancy as $FBG \geq 5.1$ mmol/L, or 1 h plasma glucose (PG) ≥ 10 mmol/L and $2hPG \geq 8.5$ mmol/L after 75 g oral glucose tolerance test (OGTT) [37]. Carotid atherosclerosis was defined based on the intima-media thickness (>1 mm), plaque score (≥ 1), and maximum level of stenosis of the ECCA (≥ 50 %) [26, 27, 30]. CVD, CHD and stroke diagnoses were based on a validated verbal autopsy procedure [34], and obesity was defined as those with body mass index (BMI) values of ≥ 30 kg/m². Finally, metabolic syndrome cases were those with three or more of the following identified $FPG \geq 110$ mg/dL, triglycerides ≥ 150 mg/dL, $HDL \leq 40$ mg/dL for men or ≤ 50 mg/dL for women, $SBP \geq 130$ mmHg, $DBP \geq 85$ mmHg, and waist girth ≥ 90 cm for men ≥ 80 cm for women [34]. Studies focused predominantly on non-fatal outcomes, with only one of the studies focusing on fatal events (Table 1) [34].

Environmental arsenic exposure

Environmental arsenic exposure was measured in water [26–34, 40], spot morning [24, 41] or spot [25, 33–38] urine (adjusted [24, 25, 33, 34, 38, 41] or not adjusted for creatinine [35–37]), blood [31, 36], and blood plasma [39]. Most studies performed elemental analyses, with some performing speciation analyses (Table 1) [25, 33–35, 37, 38, 41]. In the SNP-arsenic-cardiometabolic disease analyses, most studies focused on total arsenic (tAs) or inorganic arsenic (iAs) [24, 26–36, 38–41] with only two studies including analyses exploring the interactions between SNP and arsenic metabolism markers: Primary methylation index [PMI] (defined by MMA/iAs) [25], Secondary Methylation Index (SMI) (defined by DMA/MMA) [25], $iAs\%$ [37], $MMA\%$ [25, 37], or $DMA\%$ [25, 37]. Studies reported predominantly on point arsenic exposure [24–27, 30–41] or cumulative arsenic exposure (CAE) [26, 28, 29], and for two studies it was assumed that multiple arsenic measurements were performed [28, 29].

Chemical analyses were performed using inductively couple plasma mass spectrometry (ICP-MS) [32, 36, 38, 39], high-performance liquid chromatography coupled to ICP-MS (HPLC-ICP-MS) [25, 33, 34, 37, 41], high-resolution ICP-MS (HR-ICP-MS) [31], anion exchange liquid chromatography coupled to ICP-MS (AEC-ICP-MS) [38], hydride generation atomic absorption spectroscopy AAS (HG-AAS) [26, 27, 30, 32, 40], graphite furnace AAS (GF-AAS) [24, 31, 33, 34], liquid chromatography-atomic fluorescence spectrometry (LC-

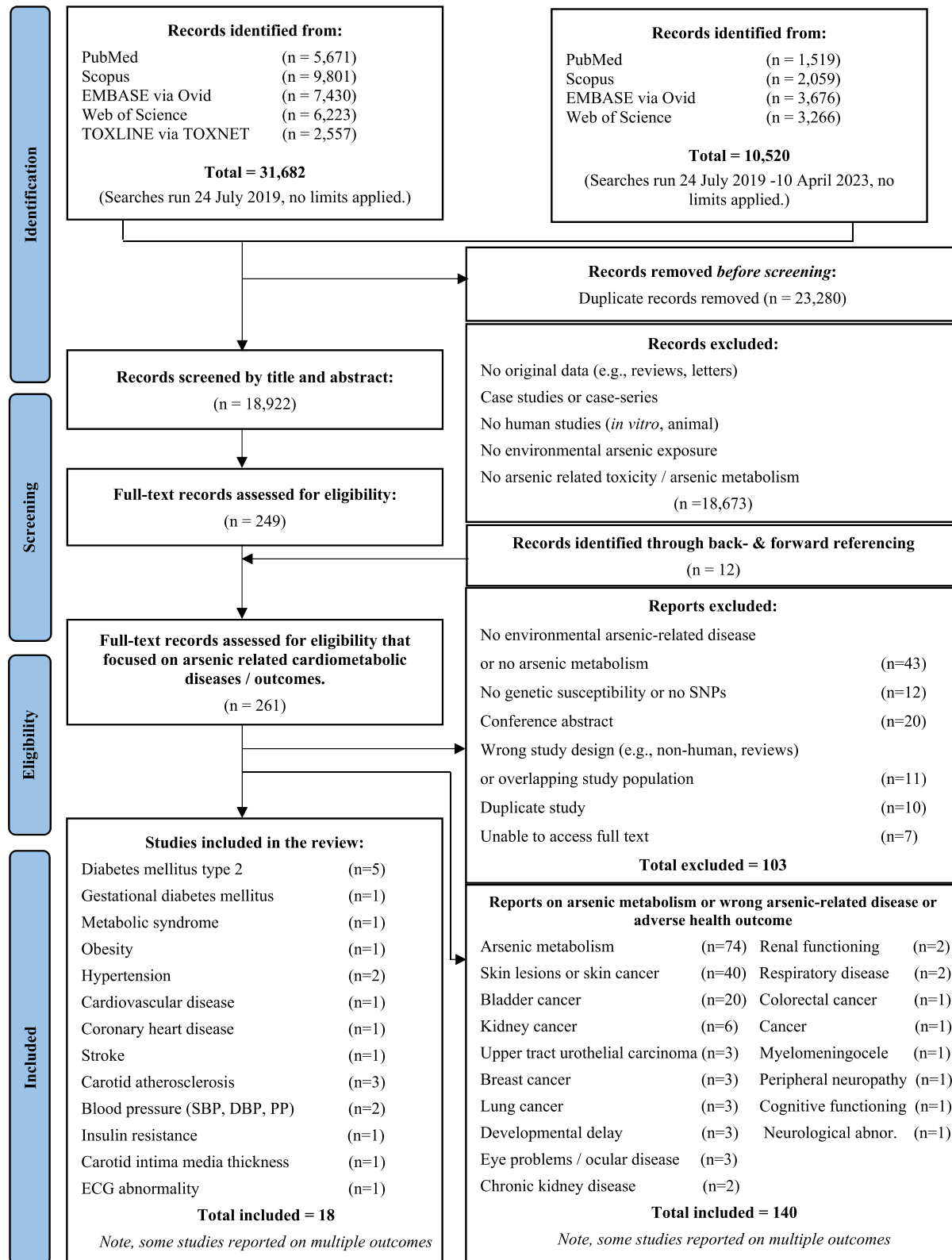


Figure 1: Study selection process using the PRISMA diagram.

Table 1: Study characteristics of studies exploring the association of single nucleotide polymorphisms (SNPs) with arsenic-induced cardio-metabolic disease.

Study	N	Women% (n)	Age	Location	Study design	Outcome	Outcome assessment	Arsenic assessment	Gene(s)	Genotyping	Study aim
Chen <i>et al.</i> 2012a	240 P: 36 C: 204	60 % (145)	56 ± 16.3 yr	12 villages in Nantou County, Taiwan	Cross-sectional Resident area ≥ 1 yr TP: NR	Hypertension	Resting BP (20-min) using sphygmomanometer SBP ≥ 130 DBP ≥ 85, HTN history treated with anti-HTN drugs	Urinary (spot morning) arsenic [As] (GF-AAS)	<i>SOD2</i> , <i>OGG1</i>	PCR-RFLP	Investigate whether individuals with different <i>SOD2</i> and <i>OGG1</i> genotypes have increased arsenic related hypertension risk.
Chen <i>et al.</i> 2012b	247 P: 111 C: 136	57 % (141) MetS 64.3 ± 7.9 yr	No MetS 60.4 ± 9.0 yr	Putai village, Taiwan	Cohort TP: 1990–2002/3	Metabolic syndrome	≥ 3 or more: FPG ≥ 110 mg/dL Trig ≥ 150 mg/dL HDL ≤ 40 mg/dL M ≤ 50 mg/dL W SBP ≥ 130 DBP ≥ 85 WG ≥ 90 cm M ≥ 80 cm W	Urinary (spot) arsenic [PMI, SMI, MMA%, DMA%] (HPLC-ICP-MS)	<i>AS3MT</i> , <i>GSTO1</i> , <i>GSTO2</i> (Note, results of publication only focus on <i>GSTO1</i>)	PCR-RFLP TaqMan SNP genotyping assay	Evaluate the association among arsenic methylation, genetic polymorphisms and MetS occurrence.
Drobná <i>et al.</i> 2012	255 P: NR C: NR	67 % (171)	34 ± 18 yr	Zimapan and Lagunera regions, Mexico	Cross-sectional Resident area ≥ 2 yr TP: NR	Diabetes mellitus type 2	OGTT 2h-PBG ≥ 200 mg/dL, FBG ≥ 126 mg/dL, physician diagnosis, diabetes treatment	Water arsenic [iAs] (HG-AAS)	<i>AS3MT</i>	TaqMan SNP genotyping assay	Assess the interaction between <i>AS3MT</i> polymorphism and iAs exposure on diabetes development.
Fan <i>et al.</i> 2022	938 P: 319 C: 619	66 % (620)	487 < 60 yr 451 ≥ 60 yr	Lv Liang City, Shanxi Province, China	Case-control TP: 2018	Diabetes mellitus type 2	HbA1c ≥ 6.5 %	Urinary (spot) arsenic [iAs] (LC-AFS)	<i>KEAP1</i>	Multiplex PCR	Explore whether T2DM is related to the low-to-moderate level arsenic exposure and <i>KEAP1</i> rs11545829 SNP.
Farzan <i>et al.</i> 2016	1,137 P: 432 C: 705	49 % (559)	Normal 37.4 ± 10.4 (Pre) HTN 43.1 ± 10.7	Araihazar, Bangladesh	Cohort (HEALS) Resident area ≥ 5 yrs TP: 2002/4–2007/9	Blood pressure (SBP, DBP, pulse pressure)	Resting BP (5-min) using automated sphygmomanometer	Water arsenic [iAs] (HR-ICP-MS)	<i>APOE</i> , <i>AS3MT</i> , <i>CBS</i> , <i>CYBA</i> , <i>GSTM1</i> , <i>GSTO1</i> , <i>GSTP1</i> , <i>GSTT1</i> , <i>HMOX1</i> , <i>ICAM1</i> , <i>IL6</i> , <i>MTHFR</i> , <i>NOS3</i> , <i>PNP</i> , <i>S1PR1</i> , <i>SOD2</i> , <i>TNF</i> , <i>VCAM1</i>	Illumina GoldenGate assay	Examine genetic susceptibility loci that may contribute to arsenic related increases in blood pressure.
Grau-Perez <i>et al.</i> 2017	395	19 % (77)	≤ 4 µg/L blood As 25.8 ± 6.6 yr > 4 µg/L 26.4 ± 5.8 yr	Zhongshan, Guangdong, China	Cross-sectional No change in living ≥ 1 yr TP: 2013/4	(Elevated) blood pressure (SBP, DBP)	Resting BP (no further details provided)	Blood arsenic [As] (ICP-MS)	<i>CCM3</i>	imLDR method	Investigate interaction effects between blood arsenic and <i>CCM3</i> polymorphism on blood pressure.
Grau-Perez <i>et al.</i> 2017	1,838 P: 255 C: 1,583	60 % (1,122)	36 (24–47) yr	Arizona, Oklahoma, North Dakota, South Dakota, United States	Cohort (SHFS) TP: 1998/99–2006/9	Diabetes mellitus type 2 Insulin resistance	FBG ≥ 126 mg/dL physician diagnosis, diabetes treatment IFG (100–126 mg/dL) and NFG < 100 mg/dL, HOMA2-IR	Urinary (morning spot) arsenic [iAs] (ICP-MS) [iAs, MMA, DMA] (HPLC-ICP-MS)	<i>AS3MT</i>	Illumina Cardio-Metabo DNA Analysis BeadChip	Study potential effect modification of the arsenic related diabetes association by <i>AS3MT</i> polymorphisms.

Table 1: (continued)

Study	N	Women% (n)	Age	Location	Study design	Outcome	Outcome assessment	Arsenic assessment	Gene(s)	Genotyping	Study aim
Grau-Perez <i>et al.</i> 2018	1,451	51 % (740)	Overall	Valladolid, Spain	Cross-sectional (Hortega study)	Diabetes mellitus type 2	FBG ≥ 126 mg/dL	Urinary (spot)	ABCA1, ACE, ADI-POQ, ADRB2, AGT, AGTR1, AGTRAP, APOA5, ATXN2L, BCS1L, CAT, CDKAL1, CETP, COX5A, COX5B, COX6B1, COX6B2, COX7A1, CRP, CYBA, CYP11B1, EDN1, EDN2, EDN3, EDNRA, EDNRB, ETV5, FABP2, FADS1, FADS2, FAIM2, FTO, GCLC, GCLM, GDF9, GNPDA2, GPX4, GPX6, GSR, GSS, IGF2BP2, IL10, IL10RA, IL10RB, IL18, IL18R1, IL18RAP, IL18R1, IL6, IL6R, IL1RL1, IL8, IL8RA, IL6ST, IL8, IL8RA, IL8RB, INSIG2, KCTD15, LAMA1, LIPC, LPL, MAF, MC4R, MPO, MSRA, MSRB2, MTCH2, NCF2, NCF4, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NEGR1, NOS1, NOS2A, NOS3, NOS5, NR3C2, OGG1, PON1, PPARA, PPARG, PPARGC1A, PRL, RAC2, REN, SCNN1A, SDHB, SDHD, SH2B1, SLC30A8, SOD1, SOD2, SOD3, TCF7L2, TNFA, TNFRSF1A, TNFRSF1B, TXN, TXN2, TXNRD1,	Oligo-ligation- assay SNPlex	Evaluate the interaction of arsenic and diabetes-related candidate polymorphisms as a potential determinant of T2DM.
	1,331		No DM				HbA1c ≥ 6.5 %	arsenic [tAs]			
	C:		48.5 $\pm$ 0.2 yr				physician diagnosis, diabetes treatment	(AEC-ICP-MS)			
	120		DM		7P: 2001/3						
			67.1 $\pm$ 1.4 yr								

Table 1: (continued)

Study	N	Women% (n)	Age	Location	Study design	Outcome	Outcome assessment	Arsenic assessment	Gene(s)	Genotyping	Study aim
Hsieh <i>et al.</i> 2007	479 P: 235 C: 244	53 % (255)	96: ≤55 yr 201: 55–65 yr 182: ≥65 yr	Lanyang Basin, Ilan County, Taiwan	Nested case-control TP: 1991/4–1997/8	Carotid atherosclerosis	Intima media thickness >1 mm plus one of: plaque score ≥1, stenosis of the ECCA >50 %	Water arsenic [As, CAE] (HG-AAS)	<i>TXNRD2, UCP1, UCP2, UCP3, UQCRB, WWOX, XDH</i> <i>MCP-1, APOE</i>	PCR-RFLP	Investigate the joint effects of arsenic exposure through drinking water and genetic polymorphism of APOE and MCP-1 on carotid atherosclerosis risk.
Hsieh <i>et al.</i> 2011	863 P: 384 C: 479	53 % (455)	Reference 59.2 ± 0.4 yr Cases 65.1 ± 0.4 yr	Lotung, Ilan County, Taiwan	Nested case-control TP: 1991/4–1997/8	Carotid atherosclerosis	Intima media thickness >1 mm plus one of: plaque score ≥1, stenosis of the ECCA >50 %	Water arsenic [As] (HG-AAS)	<i>AS3MT, GSTO1, GSTO2, PNP, PNP/GSTO haplotype(s)</i>	PCR-RFLP	Identify association between risk genotypes and development of carotid atherosclerosis in arsenic-exposed population.
Hsueh <i>et al.</i> 2005	292 P: 79 C: 213	61 % (177)	No HTN 46.2 ± 0.7 yr HTN 54.2 ± 0.8 yr	Homei, Fuhshing, & Hsinming, Taiwan	Nested case-control Resident area >6 months TP: 1989 - NR	Hypertension	Health examination (not further details); or antihypertensive drug use SBP ≥140 DBP ≥90	Water arsenic [CAE] (previous reports) [42]	<i>CYBA, SOD2, NOS3, CAT</i>	PCR-RFLP	Assess the association of 4 genetic polymorphisms with arsenic-related hypertension.
Liang <i>et al.</i> 2023	385 P: 86 C: 299	100 % (385)	Overall 29 (26–33) yr Non-GDM 29 (26–32) yr GDM 31 (28–34) yr	Beichen district, Tianjin, China	Cross-sectional Resident area ≥6 yr TP: 2017/18	Gestational diabetes mellitus	75 g OGTT at 24–28 weeks FBG ≥5.1 mmol/L or 1hPG ≥10 mmol/L or 2hPG ≥8.5 mmol/L	Urinary (spot) arsenic [As%], MMA%, DMA%] (HPLC-ICP-MS)	<i>AS3MT, N6AMT1</i>	Hi-SNP genotyping (3-round multiplex PCR with NGS)	Explore the individual and combined effects of <i>N6AMT1</i> and <i>AS3MT</i> SNPs with arsenic metabolism on GDM.
Liao <i>et al.</i> 2009	121 P: 79 C: 42	61 % (74)	ECG normal 62 ± 7.3 yr ECG abnormal 64.9 ± 8.7 yr	Homei, Fuhshing, and Hsinming, Taiwan	Cohort Live ≥5 days a week in area TP: 1993–2002	ECG abnormality	12-Lead ECG (MI or ischemia, conduction defect, arrhythmias, atrial enlargement or ventricular hypertrophy, prolonged ventricular repolarization)	Water arsenic [CAE] (previous reports)	<i>AS3MT, GSTO1, GSTO2, PON1, PON2</i>	TaqMan SNP Genotyping Assay; PCR-RFLP	Investigate possible contribution of genetic factors, and long-term arsenic exposure to CVD development.
Martínez-Barquero <i>et al.</i> 2015	1,970 P: 468	51 % (1,006)	VALCAR 46.4 ± 14.9 yr	Valencia & Valladolid, Spain	Cross-sectional (VALCAR)	Obesity, BMI	BMI value was ≥30 kg/m ²	Blood plasma arsenic [As] (ICP-MS)	<i>EDN1, EDN2, EDN3, EDNR4, EDNR8</i>	Oligo-ligation-assay SNPlex	Assess whether arsenic modulates the effect of <i>EDNR8</i>

Table 1: (continued)

Study	N	Women% (n)	Age	Location	Study design	Outcome	Outcome assessment	Arsenic assessment	Gene(s)	Genotyping	Study aim
	C: 1,502		Hortega 54.4 ± 19.3 yr		Hortega study TP: 2001/3						genetic polymorphisms in obesity development.
Pan <i>et al.</i> 2013	919 P: 83 C: 836	39 % (361)	No DM 33.5 ± 11.7 yr DM 39.8 ± 10.8 yr	Pabna district, Bangladesh	Follow-up of a skin-lesion case control TP: 2001/3–2009/11	Diabetes mellitus type 2 % HbA1c levels	HbA1c ≥6.5 %	Water arsenic [As] (ICP-MS)	ADAMT59, BCL11A, CDC123, CDKN2A, CDKN2B, CENTD2, IDE, KCNQ1, KMG2, LGR5, NOTCH2, PRC1, SLC30A8, TCF2, THADA, TSPAN8, WFS1	Sequenome MassARRAY iPLEX	Evaluate interaction between SNPs in diabetes genes and water arsenic exposure T2DM risk.
Wang <i>et al.</i> 2007	605 P: 279 C: 326	52 % (316)	110–55 yr 258: 55–65 yr 237: ≥65 yr	Lanyang Basin, Ilan County, Taiwan	Case-control TP: 1991/4–1997/98	Carotid atherosclerosis	Intima media thickness >1 mm, plaque score ≥1, stenosis of the ECCA >50 %	Water arsenic (HG-AAS)	GSTM1, GSTT1, GSTP1, P53	PCR-RFLP	Explore the joint effects water arsenic exposure and genetic polymorphisms on risk of carotid atherosclerosis.
Wu <i>et al.</i> 2014	1,078	60.9 %	38 (27–52) yr	Araihazar, Bangladesh	Cross-sectional (HEALS) Resident area ≥5 yr TP: 2000/2 – 2012	Carotid intima-media thickness	Carotid sonography using the SonoSite MicroMaxx ultrasound machine	Water arsenic [tAs] (HPLC-ICP-MS) Urinary (spot) arsenic [tAs] (GF-AAS)	GSTM1, GSTT1, GSTO1, GSTP1, MTHFR, CBS, PNPAS3MT, HMOX1, NOS3, SOD2, CYBA, APOE, TNF, IL6, ICAM1, S1PR1, VCAM1	Illumina GoldenGate assay	Evaluate whether the association between arsenic exposure and cIMT differs by 207 SNPs.
Wu <i>et al.</i> 2015	2,225 CVD: 447 CHD: 238 Str: 165 C: 1,375	53 % (1,181)	Sub-cohort 38.6 ± 9.7 yr CVD 47.4 ± 9.7 yr CHD 45.4 ± 9.2 yr Stroke 50.8 ± 8.9 yr	Araihazar, Bangladesh	Case-cohort (HEALS) Resident area ≥5 yr TP: 2000/2 – 2012	CVD, CHD, Stroke (mortality)	Validated verbal autopsy	Water arsenic [tAs] (ICP-MS) Urinary (spot) arsenic [tAs] (GFAAS) [As ³⁺ , As ⁵⁺ , MMA, DMA] (HPLC-ICP-MS)	APOE, AS3MT, CBS, CYBA, GSTM1, GSTO1, GSTP1, GSTT1, HMOX1, ICAM1, IL6, MTHFR, NOS3, PNP, S1PR1, SOD2, TNF, VCAM1	Illumina GoldenGate assay	Investigate whether associations between arsenic exposure and CVD risk are modified by genetic polymorphism in 18 genes.

AAS, atomic absorption spectroscopy; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; MeTS, metabolic syndrome; DM, diabetes mellitus; ECCA, extracranial carotid artery; ECG, electrocardiogram; FBG, fasting blood glucose; GDM, gestational diabetes mellitus; GFAAS, graphite furnace atomic absorption; HDL, high density lipoprotein; HEALS, health effects of arsenic longitudinal study; HG-AAS, hydride generation atomic absorption spectroscopy; HOMA2-IR, homeostasis model assessment insulin resistance; HPLC-ICP-MS, high-performance liquid chromatography ICP-MS; HR-ICP-MS, high-performance ICP-MS; HTN, hypertension; ICP-MS, inductively coupled plasma mass spectrometry; IFG, impaired fasting glycaemia; MeTS, metabolic syndrome; MI, myocardial infarction; NR, not clearly reported; OGTT, oral glucose tolerance test; PCR-RFLP, polymerase chain reaction restriction fragment length polymorphism; SBP, systolic blood pressure; SHFS, strong heart family study; SNP, single nucleotide polymorphism; T2DM, Type 2 diabetes mellitus; TP, time period; Trig, triglycerides; WG, waist girth. *Note*, abbreviations of relevant genes can be found in Supplementary Table 4.

Table 2: Summary results of studies exploring the association of single nucleotide polymorphisms (SNPs) with arsenic-related cardiometabolic outcomes (i.e., studies assessing environmental arsenic-SNP interaction with cardiometabolic outcomes).

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
Chen <i>et al.</i> 2012a Hypertension, (HTN) Urinary arsenic (µg/g creatinine)	<i>SOD2</i> (rs4880)	Val-Val	≤ 8 µg/g	OR 1.0 (ref.)		51/69	Both <i>SOD2</i> and <i>OGG1</i> genotypes may be prone to increased
		Val-Val	> 8 µg/g	OR 3.1 (1.2–7.9)	<0.05	15/11	arsenic-related hypertension risk.
		Val-Ala / Ala-Ala	≤ 8 µg/g	OR 1.2 (0.6–2.4)	–	26/34	Adjusted for age, gender, urinary Pb levels, renal disease history
		Val-Ala / Ala-Ala	> 8 µg/g	OR 4.2 (1.7–10.3)	<0.01	22/12	and <i>SOD2</i> genotype (only <i>OGG1</i>).
	<i>OGG1</i> (rs1052133)	Ser-Cys/Ser-Ser	≤ 8 µg/g	OR 1.0 (ref.)		48/63	
		Ser-Cys/Ser-Ser	> 8 µg/g	OR 3.2 (1.4–7.4)	<0.01	25/17	
		Cys-Cys	≤ 8 µg/g	OR 1.0 (0.5–2.0)	–	29/40	
Chen <i>et al.</i> 2012b Metabolic syndrome (MetS) Urinary arsenic metabolites (PMI, SMI, MMA%, DMA%)	<i>GSTO1</i> (rs4925)	Cys-Cys	> 8 µg/g	OR 3.4 (1.1–10.7)	<0.05	12/6	
		AA	PMI high	OR 1.0 (ref.)		24/48	Findings suggest that decreasing MMA% and PMI and increasing
		AD + DD	PMI high	OR 1.32 (0.61–2.90)	0.48	20/30	DMA% and SMI are associated with increased MetS risk, which
		AA	PMI low	OR 2.03 (1.03–4.01)	0.04	42/44	may be marginally modified by the <i>GSTO1</i> genotype.
	AD + DD	AA	PMI low	OR 4.00 (1.65–9.71)	0.002	24/13	Adjusted by age and betel nut chewing.
		AA	SMI low	OR 1.0 (ref.)	–	20/57	Study did not report on <i>GSTO2</i> or <i>AS3MT</i> polymorphisms results.
		AD + DD	SMI low	OR 2.91 (1.29–6.57)	0.01	22/23	High and low PMI, SMI, MMA% and DMA% were not clearly
		AA	SMI high	OR 4.65 (2.22–9.73)	<0.001	46/35	defined.
		AD + DD	SMI high	OR 3.87 (1.62–9.26)	0.002	22/20	
	AA	AA	MMA% high	OR 1.0 (ref.)		22/55	
		AD + DD	MMA% high	OR 2.35 (1.07–5.15)	0.03	23/24	
		AA	MMA% low	OR 3.36 (1.66–6.79)	<0.001	44/37	
		AD + DD	MMA% low	OR 3.24 (1.37–7.66)	0.007	21/19	
Drobná <i>et al.</i> 2012 Diabetes mellitus type 2 (T2DM) Water arsenic, ppb	<i>AS3MT</i> (rs11191439)	AA	DMA% low	OR 1.0 (ref.)		23/57	
		AD + DD	DMA% low	OR 1.86 (0.83–4.18)	0.13	17/22	
		AA	DMA% high	OR 3.44 (1.69–6.99)	<0.001	43/35	
		AD + DD	DMA% high	OR 3.54 (1.59–7.87)	0.002	27/21	
		TT	<52 ppb	OR 1.0 (ref.)		–	– Carriers of rs11191439 (greater than additive) and rs17881215
	TC + CC	TC + CC	<52 ppb	OR 3.47 (0.8–17.0)	–	–	– (approximately multiplicative) genotypes may be more likely to
		TC + CC	≥52 ppb	OR 5.68 (1.95–17.0)	–	–	– develop arsenic-related T2DM. Little indication of consistent as-
		TC + CC	≥52 ppb	OR 11.4 (2.2–58.8)	–	–	– sociation with any of the other 4 (rs3740393, rs3740390,
		GG	<52 ppb	OR 1.0 (ref.)		–	– rs10748835, <i>VNTR</i> variants) genotypes and T2DM.
		GC + CC	<52 ppb	OR 1.97 (0.23–12.5)	–	–	– Adjusted for age, sex, hypertension, and obesity.
Fan <i>et al.</i> 2022 Diabetes mellitus type 2 (T2DM) Urinary arsenic (µg/g creatinine)	<i>KEAP1</i> (rs11545829)	GG	≥52 ppb	OR 4.60 (1.6–15.0)	–	–	– 95% CI not clearly reported for all categories, nor number of
		GC + CC	≥52 ppb	OR 8.8 (1.6–47.3)	–	–	– cases and controls in each group, or the <i>P</i> value. Cursive 95% CI
		GG + GA	µg/g (cont)	OR 10.12 (2.89–35.41)	<0.05	300/548	estimated based on Figure 1. ³
		AA	µg/g (cont)	OR 10.67 (0.20–564.83)			There was no statistically significant multiplicative nor additive
				RERI AP	>0.05 <i>P</i> _{int} 0.73	19/71	interaction between rs11545829 and urinary arsenic on T2DM risk. Adjusted for cigarette smoking, alcohol drinking, gender, age, hypertension, and BMI.

Table 2: (continued)

Study	Gene	Genotype	Arsenic µg/LI (cont)	β_{int}	MoA 95% CI	P (Q)	Ca/Co	Comments
Farzan et al. 2016 Systolic blood pressure (SBP) Water arsenic, µg/l	<i>APOE</i> (rs429358)	Dominant model		β_{int}	0.26 (−0.08–0.59)	0.14 (0.78)	–	– From the 235 SNPs, 44 SNPs showed an interaction with water
		Recessive model		β_{int}	2.05 (0.57–3.54)	0.01 (0.34)	–	– arsenic for one or more blood pressure outcomes. The <i>CYBA</i>
	<i>CBS</i> (rs234709)	Dominant model		β_{int}	0.34 (0.06–0.62)	0.02 (0.54)	–	– (rs3794624) polymorphism was the only one statistically signifi-
		Recessive model		β_{int}	0.49 (−1.00–1.97)	0.52 (0.94)	–	– cant after FDR adjustment.
	<i>CBS</i> (rs2014564)	Dominant model		β_{int}	0.28 (0.01–0.56)	0.04 (0.67)	–	– Adjusted for sex, age at enrolment, BMI, smoking status,
		Recessive model		β_{int}	0.17 (−0.12–0.46)	0.25 (0.86)	–	– educational attainment, and diabetes at baseline.
	<i>CBS</i> (rs2124459)	Dominant model		β_{int}	0.40 (0.12–0.68)	0.01 (0.34)	–	– Coefficients are in relation to each SNP, time and well arsenic
		Recessive model		β_{int}	0.41 (−1.12–1.95)	0.60 (0.96)	–	– concentration in the different genetic models. P-values are for
	<i>CBS</i> (rs234701)	Dominant model		β_{int}	0.29 (0.02–0.57)	0.04 (0.67)	–	– interaction.
		Recessive model		β_{int}	0.12 (−0.18–0.41)	0.44 (0.93)	–	– Three models were run for dominant, recessive, and additive --
	<i>CYBA</i> (rs3794624)	Dominant model		β_{int}	0.02 (−0.29–0.33)	0.90 (0.99)	–	– additive models were not shown as they were similar to domi-
		Recessive model		β_{int}	2.43 (0.78–4.08)	0.004 (0.34)	–	– nant models.
	<i>GSTM1</i> (rs4147567)	Dominant model		β_{int}	0.60 (0.17–1.03)	0.01 (0.34)	–	– Number of study participants for each model were not reported.
	<i>GSTM1</i> (rs749174)	Dominant model		β_{int}	0.29 (0.02–0.52)	0.04 (0.67)	–	–
		Recessive model		β_{int}	0.43 (−1.11–1.97)	0.58 (0.96)	–	–
	<i>GSTT1</i> (rs4630)	Dominant model		β_{int}	0.10 (−0.33–0.52)	0.66 (0.98)	–	–
Diastolic blood pressure, (DBP) Water arsenic, µg/l		Recessive model		β_{int}	1.07 (0.11–2.03)	0.03 (0.67)	–	–
	<i>IL6</i> (rs1524107)	Dominant model		β_{int}	0.34 (0.08–0.60)	0.01 (0.47)	–	–
		Recessive model		β_{int}	0.10 (−0.81–1.01)	0.83 (0.98)	–	–
	<i>NOS3</i> (rs743506)	Dominant model		β_{int}	−0.10 (−0.36–0.16)	0.45 (0.93)	–	–
		Recessive model		β_{int}	0.72 (0.04–1.40)	0.04 (0.67)	–	–
	<i>STPR1</i> (rs3753194)	Dominant model		β_{int}	−0.04 (−0.29–0.22)	0.78 (0.98)	–	–
		Recessive model		β_{int}	0.45 (0.02–0.88)	0.04 (0.67)	–	–
	<i>SOD2</i> (rs5746123)	Dominant model		β_{int}	0.33 (0.02–0.64)	0.04 (0.67)	–	–
		Recessive model		β_{int}	0.18 (−0.75–1.12)	0.70 (0.98)	–	–
	<i>APOE</i> (rs429358)	Dominant model		β_{int}	0.06 (−0.15–0.27)	0.56 (0.99)	–	–
		Recessive model		β_{int}	0.95 (0.03–1.88)	0.04 (0.82)	–	–
	<i>AS3MT</i> (rs9527)	Dominant model		β_{int}	0.22 (0.02–0.42)	0.03 (0.74)	–	–
		Recessive model		β_{int}	−1.30 (−2.65–0.04)	0.06 (0.88)	–	–
	<i>AS3MT</i> (rs4290163)	Dominant model		β_{int}	0.26 (0.03–0.49)	0.03 (0.74)	–	–
		Recessive model		β_{int}	−0.60 (−1.63–0.42)	0.25 (0.88)	–	–
	<i>GSTM1</i> (rs4147567)	Dominant model		β_{int}	0.36 (0.09–0.63)	0.01 (0.74)	–	–
	<i>GSTM1</i> (rs6591256)	Dominant model		β_{int}	0.24 (0.08–0.40)	0.003 (0.70)	–	–
		Recessive model		β_{int}	0.20 (−0.06–0.46)	0.14 (0.88)	–	–
	<i>GSTM1</i> (rs1695)	Dominant model		β_{int}	0.30 (0.04–0.57)	0.02 (0.74)	–	–
	<i>HMOX1</i> (rs5755718)	Dominant model		β_{int}	0.26 (0.04–0.48)	0.02 (0.74)	–	–
		Recessive model		β_{int}	0.16 (−0.11–0.43)	0.24 (0.88)	–	–

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95 % CI	P (Q)	Ca/Co	Comments
Pulse pressure, PP Water arsenic, µg/L	<i>HMOX1</i> (rs8139532)	Dominant model	β_{int}	0.29 (0.07–0.52)	0.01 (0.74)	–	–
	<i>HMOX1</i> (rs16995662)	Dominant model	β_{int}	0.25 (0.03–0.48)	0.03 (0.74)	–	–
	<i>HMOX1</i> (rs2269534)	Dominant model	β_{int}	0.25 (0.03–0.48)	0.03 (0.74)	–	–
	<i>IL6</i> (rs2069840)	Dominant model	β_{int}	–0.11 (–0.29–0.07)	0.24 (0.88)	–	–
	<i>IL6</i> (rs13306435)	Recessive model	β_{int}	0.59 (0.07–1.10)	0.02 (0.74)	–	–
	<i>IL6</i> (rs1554606)	Dominant model	β_{int}	0.19 (0.01–0.36)	0.04 (0.82)	–	–
	<i>IL6</i> (rs1474347)	Recessive model	β_{int}	–0.37 (–1.12–0.37)	0.33 (0.92)	–	–
	<i>IL6</i> (rs1554606)	Dominant model	β_{int}	0.28 (0.04–0.52)	0.02 (0.74)	–	–
	<i>IL6</i> (rs1474347)	Recessive model	β_{int}	–0.60 (–1.63–0.42)	0.25 (0.88)	–	–
	<i>NOS3</i> (rs3918198)	Dominant model	β_{int}	0.19 (0.03–0.34)	0.02 (0.74)	–	–
	<i>NOS3</i> (rs1799983)	Recessive model	β_{int}	0.02 (–0.46–0.49)	0.94 (0.99)	–	–
	<i>NOS3</i> (rs1799983)	Dominant model	β_{int}	0.25 (0.02–0.47)	0.03 (0.74)	–	–
	<i>PNP</i> (rs17882836)	Dominant model	β_{int}	0.30 (0.07–0.52)	0.01 (0.74)	–	–
	<i>TNF</i> (rs4248159)	Recessive model	β_{int}	0.04 (–0.13–0.21)	0.65 (0.99)	–	–
	<i>APOE</i> (rs429358)	Dominant model	β_{int}	0.21 (0.02–0.40)	0.03 (0.74)	–	–
	<i>AS3MT</i> (rs4290163)	Dominant model	β_{int}	0.21 (0.02–0.40)	0.03 (0.74)	–	–
	<i>AS3MT</i> (rs10509761)	Recessive model	β_{int}	0.22 (–0.01–0.44)	0.06 (0.62)	–	–
	<i>CBS</i> (rs6586281)	Dominant model	β_{int}	1.08 (0.11–2.06)	0.03 (0.52)	–	–
	<i>CBS</i> (rs234701)	Recessive model	β_{int}	0.34 (0.10–0.58)	0.01 (0.45)	–	–
	<i>CBS</i> (rs706208)	Dominant model	β_{int}	–0.30 (–1.39–0.78)	0.58 (0.90)	–	–
	<i>CBS</i> (rs3788050)	Recessive model	β_{int}	0.11 (–0.05–0.28)	0.18 (0.79)	–	–
	<i>CBS</i> (rs234709)	Dominant model	β_{int}	0.32 (0.06–0.58)	0.02 (0.49)	–	–
	<i>CBS</i> (rs2124459)	Recessive model	β_{int}	0.23 (0.05–0.40)	0.01 (0.46)	–	–
			β_{int}	–0.10 (–0.31–0.12)	0.38 (0.88)	–	–
			β_{int}	0.21 (0.03–0.39)	0.02 (0.49)	–	–
			β_{int}	0.06 (–0.13–0.25)	0.54 (0.90)	–	–
			β_{int}	0.19 (0.01–0.38)	0.04 (0.57)	–	–
			β_{int}	–0.06 (–0.27–0.15)	0.59 (0.91)	–	–
			β_{int}	0.12 (–0.10–0.34)	0.27 (0.85)	–	–
			β_{int}	0.69 (0.19–1.18)	0.007 (0.45)	–	–
			β_{int}	0.23 (0.05–0.41)	0.01 (0.47)	–	–
			β_{int}	0.32 (–0.69–1.33)	0.53 (0.90)	–	–
			β_{int}	0.26 (0.07–0.44)	0.01 (0.45)	–	–
			β_{int}	0.17 (–0.88–1.21)	0.76 (0.95)	–	–

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95 % CI	P (Q)	Ca/Co	Comments
	CBS (rs2849727)	Dominant model	β_{int}	0.20 (0.02–0.37)	0.03 (0.53)	-	-
		Recessive model	β_{int}	0.53 (-0.47–1.53)	0.30 (0.86)	-	-
	CBS (rs9983620)	Dominant model	β_{int}	0.01 (-0.16–0.17)	0.95 (0.98)	-	-
		Recessive model	β_{int}	0.39 (0.01–0.76)	0.04 (0.57)	-	-
	CYBA (rs3794624)	Dominant model	β_{int}	0.01 (-0.19–0.21)	0.90 (0.98)	-	-
		Recessive model	β_{int}	2.10 (1.01–3.20)	<0.001 (0.05)	-	-
	CYBA (rs13306296)	Dominant model	β_{int}	0.03 (-0.21–0.15)	0.74 (0.94)	-	-
		Recessive model	β_{int}	1.02 (0.22–1.81)	0.01 (0.47)	-	-
	GSTM1 (rs4147567)	Dominant model	β_{int}	0.30 (0.01–0.58)	0.04 (0.57)	-	-
		Recessive model	β_{int}	0.20 (0.02–0.38)	0.03 (0.49)	-	-
	IL6 (rs2069845)	Dominant model	β_{int}	0.49 (-0.54–1.52)	0.35 (0.88)	-	-
		Recessive model	β_{int}	0.18 (0.004–0.35)	0.04 (0.57)	-	-
	IL6 (rs1524107)	Dominant model	β_{int}	-0.05 (-0.89–0.78)	0.90 (0.98)	-	-
		Recessive model	β_{int}	0.26 (0.08–0.43)	0.004 (0.45)	-	-
	IL6 (rs1554606)	Dominant model	β_{int}	-0.02 (-0.63–0.58)	0.94 (0.98)	-	-
		Recessive model	β_{int}	0.29 (0.04–0.54)	0.02 (0.49)	-	-
	MTHFR (rs9651118)	Dominant model	β_{int}	-0.32 (-1.40–0.76)	0.56 (0.90)	-	-
		Recessive model	β_{int}	-0.04 (-0.21–0.14)	0.69 (0.93)	-	-
	NOS3 (rs743506)	Dominant model	β_{int}	0.48 (0.03–0.94)	0.04 (0.55)	-	-
		Recessive model	β_{int}	-0.03 (-0.20–0.14)	0.72 (0.94)	-	-
	NOS3 (rs1808593)	Dominant model	β_{int}	0.49 (0.04–0.94)	0.03 (0.53)	-	-
		Recessive model	β_{int}	0.22 (0.03–0.40)	0.02 (0.49)	-	-
	PNP (rs17882836)	Dominant model	β_{int}	0.10 (-0.09–0.29)	0.30 (0.86)	-	-
		Recessive model	β_{int}	0.28 (0.08–0.48)	0.01 (0.45)	-	-
	PNP (rs1617940)	Dominant model	β_{int}	-0.05 (-0.22–0.12)	0.58 (0.90)	-	-
		Recessive model	β_{int}	0.47 (0.01–0.92)	0.04 (0.57)	-	-
	SOD2 (rs10370)	Dominant model	β_{int}	0.04 (-0.13–0.22)	0.61 (0.91)	-	-
		Recessive model	β_{int}	0.32 (0.06–0.58)	0.02 (0.47)	-	-
	SOD2 (rs12526686)	Dominant model	β_{int}	0.23 (0.05–0.40)	0.01 (0.46)	-	-
		Recessive model	β_{int}	-0.16 (-0.38–0.07)	0.17 (0.78)	-	-
	TNF (rs1800630)	Dominant model	β_{int}	0.26 (0.08–0.43)	0.01 (0.45)	-	-
		Recessive model	β_{int}	-0.08 (-0.34–0.17)	0.52 (0.90)	-	-
	TNF (rs3179060)	Dominant model	β_{int}	0.20 (0.02–0.38)	0.03 (0.53)	-	-
		Recessive model	β_{int}	0.22 (0.04–0.39)	0.02 (0.47)	-	-
	VCAM1 (rs3176877)	Dominant model	β_{int}	-0.13 (-0.34–0.09)	0.26 (0.85)	-	-
		Recessive model	β_{int}	-0.02 (-0.20–0.15)	0.78 (0.95)	-	-

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
Gao et al. 2018 Systolic blood pressure, SBP Blood arsenic, µg/l	<i>VCAM1</i> (rs3783617)	Recessive model		β_{int} 0.48 (0.03–0.94)	0.04 (0.55)	–	–
	<i>VCAM1</i> (rs3917016)	Dominant model		β_{int} 0.24 (0.03–0.46)	0.02 (0.49)	–	–
	<i>CCM3</i> (rs9818496)	Recessive model		β_{int} –0.20 (–0.95–0.56)	0.60 (0.91)	–	–
		CC	0–4 µg/l	OR 1.0 (ref.)	–	–	Interactions between the rs9818496, rs3804610 and rs6784267 <i>CCM3</i> genotypic variants and blood arsenic increased the hazard of increased SBP.
		CC	>4 µg/l	OR 1.62 (0.53–2.82)	–	–	–
		CT + TT	0–4 µg/l	OR 1.35 (0.75–2.57)	–	–	–
		CT + TT	>4 µg/l	OR 2.68 (1.35–5.55)	–	–	–
		Interaction (multiplicative)		OR_{int} 1.50 (1.15–1.95)	0.003	–	Adjusted for age, gender, BMI, smoking status, alcohol use status, education level, BG, TG, TC, HDL, LDL, and CRP.
	<i>CCM3</i> (rs3804610)	TT	0–4 µg/l	OR 1.0 (ref.)	–	–	Number of study participants in each category not reported.
		TT	>4 µg/l	OR 1.62 (0.53–2.82)	–	–	–
		CT + CC	0–4 µg/l	OR 1.35 (0.75–2.57)	–	–	–
		CT + CC	>4 µg/l	OR 2.68 (1.35–5.55)	–	–	–
		Interaction (multiplicative)		OR_{int} 1.50 (1.15–1.95)	0.003	–	–
	<i>CCM3</i> (rs6784267)	CC	0–4 µg/l	OR 1.0 (ref.)	–	–	–
Diastolic blood pressure, DBP Blood arsenic, µg/l		CC	>4 µg/l	OR 1.46 (0.87–2.41)	–	–	–
		CT + TT	0–4 µg/l	OR 1.29 (0.71–2.23)	–	–	–
		CT + TT	>4 µg/l	OR 1.82 (1.09–2.44)	–	–	–
		Interaction (multiplicative)		OR_{int} 1.31 (1.08–1.59)	0.006	–	–
	<i>CCM3</i> (rs9818496)	CC	0–4 µg/l	OR 1.0 (ref.)	–	–	–
		CC	>4 µg/l	OR 1.32 (0.72–2.95)	–	–	–
		CT + TT	0–4 µg/l	OR 1.27 (0.42–3.84)	–	–	–
		CT + TT	>4 µg/l	OR 1.57 (0.93–2.88)	–	–	–
		Interaction (multiplicative)		OR_{int} 1.31 (0.87–1.90)	0.067	–	–
	<i>CCM3</i> (rs3804610)	TT	0–4 µg/l	OR 1.0 (ref.)	–	–	–
		TT	>4 µg/l	OR 1.32 (0.72–2.95)	–	–	–
		CT + CC	0–4 µg/l	OR 1.27 (0.42–3.84)	–	–	–
		CT + CC	>4 µg/l	OR 1.57 (0.93–2.88)	–	–	–
		Interaction (multiplicative)		OR_{int} 1.31 (0.87–1.90)	0.067	–	–
Grau-Perez et al. 2017 Diabetes mellitus type 2 (T2DM) Urinary arsenic (µg/g creatinine) & metabolism markers (iAs%, MMA%, DMA%) HOMA2-IR	<i>CCM3</i> (rs6784267)	CC	0–4 µg/l	OR 1.0 (ref.)	–	–	–
		CC	>4 µg/l	OR 1.40 (0.86–2.59)	–	–	–
		CT + TT	0–4 µg/l	OR 1.33 (0.91–2.40)	–	–	–
		CT + TT	>4 µg/l	OR 1.54 (0.96–2.98)	–	–	–
		Interaction (multiplicative)		OR_{int} 1.28 (1.06–1.55)	0.052	–	–
	<i>AS3MT</i> (rs12768205)	GG	As 75th v 25th	HR 1.14 (0.86–1.51)	P_{int} 0.79	121/809	Results found no interaction between genetic polymorphisms, iAs exposure, arsenic metabolism with diabetes risk.
		GA	As 75th v 25th	HR 1.14 (0.86–1.49)	111/639	111/639	Adjusted for gender, age, education, BMI, smoking status, WC,
		AA	As 75th v 25th	HR 1.39 (0.79–2.44)	20/138	20/138	GFR, estimated vitamin B ₂ , vitamin B ₆ and folate, <i>AS3MT</i> genotype
	<i>AS3MT</i> (rs12768205)	GG	iAs% v MMA%	GMR 0.98 (0.76–1.26)	P_{int} 0.82	120/776	and FG levels at baseline.
		GA	iAs% v MMA%	GMR 1.02 (0.81–1.28)	108/616	108/616	GMRs were estimated per 5% increase in arsenic metabolism
		AA	iAs% v MMA%	GMR 0.88 (0.49–1.57)	20/134	20/134	markers.
		GG		GMR 1.05 (0.87–1.27)	P_{int} 0.77	120/776	

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
Urinary arsenic metabolism markers	<i>AS3MT</i> (rs12768205)	GA	MMA% v DMA%				The association between iAs% and DMA% with HOMA2-IR differed by the AS3MT genetic variant. Adjusted for sex, age, education, BMI, smoking status, WC, GFR, ΣAs concentration, estimated vitamin B ₁₂ , vitamin B ₆ , and folate, AS3MT genotype and FG levels at baseline.
			MMA% v DMA%	GMR 1.04 (0.82–1.31)		108/616	
		AA	MMA% v DMA%	GMR 0.84 (0.47–1.51)		20/134	
			MMA% v iAs%	GMR 0.97 (0.84–1.12)	P _{int} 0.76	120/776	
		GA	DMA% v iAs%	GMR 0.95 (0.84–1.09)		108/616	
	<i>AS3MT</i> (rs12768205)	AA	DMA% v iAs%	GMR 1.08 (0.77–1.54)		20/134	
		GG	iAs% v MMA%	GMR 1.12 (1.04–1.20)	P _{int} 0.03	775	
		GA	iAs% v MMA%	GMR 1.04 (0.98–1.12)		616	
	<i>AS3MT</i> (rs12768205)	AA	iAs% v MMA%	GMR 1.04 (0.92–1.16)		134	
		GG	MMA% v DMA%	GMR 0.93 (0.89–0.99)	P _{int} 0.15	775	
Grau-Perez et al. 2018 Diabetes mellitus type 2 (T2DM) Urinary arsenic (μg/g creatinine)	<i>AS3MT</i> (rs12768205)	GA	MMA% v DMA%	GMR 0.90 (0.84–0.97)		616	The study indicates suggestive evidence for a differential association of arsenic related T2DM and genetic polymorphisms in <i>IL8RA</i> , <i>TXN</i> , <i>NR3C2</i> , <i>COX5A</i> and <i>GCLC</i> . Tests for interaction were obtained from linear regression models with arsenic as a continuous variable. Only includes genes with top interaction P-values. Note, no polymorphism was significant after correcting for multiple testing (Bonferroni significance level 0.002) Adjusted for age, sex, education, urinary cotinine levels, smoking status, alcohol consumption, fish consumption, residence place and arsenobetaine.
		AA	MMA% v DMA%	GMR 0.83 (0.73–0.92)		134	
		GG	DMA% v iAs%	GMR 0.98 (0.95–1.02)	P _{int} 0.03	775	
		GA	DMA% v iAs%	GMR 1.02 (0.99–1.06)		616	
		AA	DMA% v iAs%	GMR 1.06 (0.98–1.14)		134	
	<i>IL8RA</i> (rs1008563) Additive	TT	80th v 20th	OR 2.26 (2.18–2.34)	P _{int} 0.004	40/329	
			80th v 20th				
			80th v 20th				
		TC		OR 3.38 (3.29–3.46)		46/608	
		CC		OR 5.04 (4.69–5.42)		27/313	
	<i>IL8RA</i> (rs1008562) Additive	CC	80th v 20th	OR 2.48 (2.40–2.56)	P _{int} 0.01	49/451	
		CG	80th v 20th	OR 3.48 (3.39–3.58)		44/602	
		GG	80th v 20th	OR 4.89 (4.48–5.33)		20/207	
		AA	80th v 20th	OR 4.19 (4.01–4.38)	P _{int} 0.004	71/732	
		AG + GG	80th v 20th	OR 2.48 (2.38–2.58)		47/566	
	<i>TXN</i> (rs4135168) Dominant <i>NR3C2</i> (rs13117325) Additive	GG	80th v 20th	OR 3.87 (3.73–4.02)	P _{int} 0.007	48/572	
		GA	80th v 20th	OR 2.82 (2.76–2.88)		46/554	
		AA	80th v 20th	OR 2.06 (1.93–2.19)		18/138	
		TT	80th v 20th	OR 2.70 (2.63–2.76)	P _{int} 0.01	82/779	
		TC + CC	80th v 20th	OR 4.65 (4.30–5.03)		33/492	
Urinary arsenic (μg/g creatinine)	<i>GCLC</i> (rs11415624) Dominant Additive	DD	80th v 20th	OR 3.80 (3.67–3.93)	P _{int} 0.01	58/585	
		DA	80th v 20th	OR 2.73 (2.67–2.79)		54/574	
		AA	80th v 20th	OR 1.96 (1.84–2.09)		8/164	

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
Hsieh et al. 2007 Carotid atherosclerosis Water arsenic, µg/L Cumulative water arsenic, mg/lyr	COX5A (rs1133322)	TC + TT	80th v 20th	OR 3.44 (3.36–3.53)	P_{int} 0.01	96/978	
	Recessive	CC	80th v 20th	OR 2.03 (1.90–2.17)		21/323	
	MCP-1	0	≤10 µg/L	OR 1.0 (ref.)		1/5	Those with two risk genotypes of APOE (AG or GG) and MCP-1 (ε4 allele) and high arsenic exposure have strikingly highest risk for the development carotid atherosclerosis, showing significant joint effect of arsenic exposure and risk genotypes of APOE and MCP-1.
	(rs1024611)	1	≤10 µg/L	OR 2.7 (0.3–28.1)	–	13/24	
	APOE	2	≤10 µg/L	OR 5.1 (0.3–89.5)	–	3/2	
	(rs429358, rs7412)	0	>10 µg/L	OR 4.2 (0.4–41.5)	–	37/53	
		1	>10 µg/L	OR 5.8 (0.6–54.7)	–	140/135	
		2	>10 µg/L	OR 10.3 (1.0–102.5)	<0.05	41/25	0 = non-risk polymorphisms of the 2 genes, 1=at least one risk polymorphism, 2=two risk polymorphisms.
	MCP-1	0	≤0.2 mg/L/yr	OR 1.0 (ref.)		1/7	
	(rs1024611)	1	≤0.2 mg/L/yr	OR 6.4 (0.7–59.0)	0.05–0.1	22/25	Adjusted for age and gender.
Hsieh et al. 2011 Carotid atherosclerosis Water arsenic, µg/l	APOE	2	≤0.2 mg/L/yr	OR 10.1 (0.6–173.1)	–	3/2	
	(rs429358, rs7412)	0	>0.2 mg/L/yr	OR 7.0 (0.8–62.1)	0.05–0.1	37/50	
		1	>0.2 mg/L/yr	OR 8.6 (1.0–73.4)	<0.05	131/134	
		2	>0.2 mg/L/yr	OR 15.7 (1.7–141.2)	<0.05	41/25	
	PNP (rs1049564)	ht1GC/ht3AC	≤50 µg/L	OR 1.0 (ref.)		–	– PNP, AS3MT, and GSTO polymorphisms may exacerbate the for-
	(rs1130650)	ht2AT	≤50 µg/L	OR 0.85 (0.31–2.35)	0.76 (0.76)	–	– mation of atherosclerosis in individuals with high levels of arsenic
		ht1GC/ht3AC	>50 µg/L	OR 1.38 (0.99–1.91)	0.06 (0.09)	–	– concentration in well water (>50 µg/L).
	AS3MT	ht2AT	>50 µg/L	OR 2.08 (1.32–3.30)	0.002 (0.006)	–	– The polymorphism of the two PNP gene loci are listed in this
	(rs11191439)	TT	≤50 µg/L	OR 1.0 (ref.)		–	– order: rs1049564, rs1130650.
		TC	≤50 µg/L	OR 1.49 (0.16–14.17)	0.73 (0.073)	–	– The polymorphisms of the three GSTO gene loci are listed in this
Hsueh et al. 2005 Hypertension (HTN) Water (cumulative) arsenic (mg/l-yr)		TT	>50 µg/L	OR 1.57 (0.99–2.49)	0.05 (0.075)	–	– order: rs4925, rs2297235 and rs156697.
	GSTO (rs4925)	ht1CAA/ht3CAG	>50 µg/L	OR 2.63 (1.00–6.92)	0.05 (0.075)	–	– Adjusted for age, gender, cigarette smoking, alcohol consump-
	GSTO2 (rs2297235, rs156697)	ht2AGG	≤50 µg/L	OR 1.0 (ref.)		–	– tion, HTN, cholesterol, FG, and BMI.
		ht1CAA/ht3CAG	≤50 µg/L	OR 1.01 (0.40–2.56)	0.98 (0.98)	–	– Number of study participants in each category not reported.
		ht2AGG	>50 µg/L	OR 1.54 (1.11–2.14)	0.01 (0.03)	–	
	CYBA	CC	>50 µg/L	OR 1.62 (1.05–2.50)	0.03 (0.045)	–	
	(rs4673)	CC	<10.5 mg/l-yr	OR 1.0 (ref.)		7/73	Results suggest that the CYBA, SOD2, and NOS3 polymorphism
		CT + TT	≥10.5 mg/l-yr	OR 3.8 (1.5–9.6)	<0.05	47/76	may play a role in arsenic related hypertension, but no CAT
		CT + TT	<10.5 mg/l-yr	OR 3.0 (0.5–19.2)	>0.05	2/8	polymorphisms.
	SOD2	CT + TT	≥10.5 mg/l-yr	OR 3.7 (0.9–15.6)	>0.05	7/7	Adjusted for age, gender, triglycerides and LDL-cholesterol
Hsueh et al. 2005 Hypertension (HTN) Water (cumulative) arsenic (mg/l-yr)		TT	<10.5 mg/l-yr	OR 1.0 (ref.)		3/57	
	(rs4880)	TT	≥10.5 mg/l-yr	OR 5.7 (1.6–20.9)	<0.05	33/56	
		TC + CC	<10.5 mg/l-yr	OR 4.5 (1.0–21.4)	>0.05	6/24	
		TC + CC	≥10.5 mg/l-yr	OR 9.0 (2.3–35.0)	<0.05	21/25	
	CAT	CC	<10.5 mg/l-yr	OR 1.0 (ref.)		8/73	
	(rs1001179)	CC	≥10.5 mg/l-yr	OR 3.5 (1.4–8.6)	<0.05	51/75	
		CT	<10.5 mg/l-yr	OR 1.5 (0.2–14.9)	>0.05	1/8	
		CT	≥10.5 mg/l-yr	OR 2.4 (0.5–11.6)	>0.05	3/8	
	NOS3	GG	<10.5 mg/l-yr	OR 1.0 (ref.)		8/65	
	(rs1799983)	GG	≥10.5 mg/l-yr	OR 2.7 (1.1–6.7)	<0.05	44/69	

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
Liang et al. 2023 Gestational diabetes mellitus, GDM Urinary arsenic metabolites (iAs%, MMA%, DMA%)	<i>N6AMT1</i> (rs1997605)	GT + TT	<10.5 mg/l-yr	OR 0.4 (0.1–4.1)	>0.05	1/14	
		GT + TT	≥10.5 mg/l-yr	OR 3.7 (1.2–11.7)	<0.05	10/13	
		GA + AA	>19.37 iAs%	OR 1.0 (ref.)			Results suggest that polymorphisms in <i>N6AMT1</i> (rs1997605, rs1003671) could contribute to the differential arsenic susceptibility of individuals to GDM.
		GA + AA	≤19.37 iAs%	OR 1.04 (0.52–2.08)	0.917		
		GG	>19.37 iAs%	OR 1.58 (0.72–3.43)	0.253		The additive interactions between <i>N6AMT1</i> rs1997605 GG genotypes and lower iAs% or higher DMA% were statistically significant.
		GG	≤19.37 iAs%	OR 3.23 (1.42–7.39)	0.005		
			RERI 1.62 (–0.81–4.05)		–		
			AP 0.50 (0.01–0.99)		–		
			SI 3.64 (0.34–39.51)		–		
					–		rs1003671 GG genotypes and lower iAs% or higher DMA%.
	<i>N6AMT1</i> (rs1997605)	GA + AA	>1.11 MMA%	OR 1.0 (ref.)			No significant combined effects were observed between <i>AS3MT</i> SNPs and urinary As metabolism indicators on GDM risk.
		GA + AA	≤1.11 MMA%	OR 1.07 (0.54–2.13)	0.839		
		GG	>1.11 MMA%	OR 1.66 (0.77–3.57)	0.193		Adjusted for age, ethnicity, education, pre-pregnancy body mass index, serum folate, B ₁₂ , homocysteine (Hcy), urinary total
		GG	≤1.11 MMA%	OR 3.30 (1.43–7.61)	0.005		arsenic, urinary arsenobetaine (AsB), and <i>AS3MT</i> .
			RERI 1.56 (–0.95–4.07)		–		
			AP 0.47 (–0.03–0.98)		–		
			SI 3.13 (0.40–24.71)		–		
					–		
					–		
					–		
	<i>N6AMT1</i> (rs1003671)	GA + AA	≤79.62 DMA%	OR 1.0 (ref.)			
		GA + AA	>79.62 DMA%	OR 1.04 (0.52–2.08)	0.917		
		GG	≤79.62 DMA%	OR 1.56 (0.71–3.39)	0.265		
		GG	>79.62 DMA%	OR 3.30 (1.45–7.51)	0.004		
			RERI 1.71 (–0.76–4.17)		–		
			AP 0.52 (0.04–0.99)		–		
			SI 3.87 (0.34–44.42)		–		
					–		
					–		
					–		
	<i>N6AMT1</i> (rs1003671)	GA + AA	>19.37 iAs%	OR 1.0 (ref.)			
		GA + AA	≤19.37 iAs%	OR 1.14 (0.61–2.13)	0.672		
		GG	>19.37 iAs%	OR 1.51 (0.42–5.47)	0.532		
		GG	≤19.37 iAs%	OR 5.40 (1.50–19.46)	0.010		
			RERI 3.75 (–3.11–10.61)		–		
			AP 0.70 (0.19–1.20)		–		
			SI 6.76 (0.21–213.06)		–		
					–		
					–		
					–		
	<i>N6AMT1</i> (rs1003671)	GA + AA	>1.11 MMA%	OR 1.0 (ref.)			
		GA + AA	≤1.11 MMA%	OR 1.28 (0.70–2.34)	0.421		
		GG	>1.11 MMA%	OR 3.01 (0.89–10.24)	0.077		
		GG	≤1.11 MMA%	OR 2.96 (0.82–10.63)	0.097		
			RERI –0.34 (–5.37–4.70)		–		
			AP –0.11 (–1.91–1.69)		–		
			SI 0.85 (0.08–9.27)		–		
					–		
					–		
					–		
	<i>N6AMT1</i> (rs1003671)	GA + AA	≤79.62 DMA%	OR 1.0 (ref.)			
		GA + AA	>79.62 DMA%	OR 1.16 (0.62–2.13)	0.646		
		GG	≤79.62 DMA%	OR 1.52 (0.42–5.50)	0.528		
		GG	>79.62 DMA%	OR 5.43 (1.51–19.55)	0.010		

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
AS3MT (rs1046778)		TC + CC	>19.37 iAs%	RERI 3.76 (−3.13–10.66)	–	–	–
				AP 0.69 (0.18–1.20)	–	–	–
				SI 6.62 (0.23–194.10)	–	–	–
				OR 1.0 (ref.)	–	–	–
		TC + CC	≤19.37 iAs%	OR 1.68 (0.84–3.34)	0.140	–	–
				OR 1.57 (0.71–3.51)	0.267	–	–
		TT	≤19.37 iAs%	OR 1.56 (0.58–4.18)	0.380	–	–
				RERI −0.70 (−2.63–1.24)	–	–	–
		TC + CC	>1.11 MMA%	AP −0.45 (−1.90–1.00)	–	–	–
				SI 0.44 (0.04–5.49)	–	–	–
				OR 1.0 (ref.)	–	–	–
				OR 1.72 (0.87–3.40)	0.118	–	–
AS3MT (rs1046778)		TC + CC	≤1.11 MMA%	OR 1.63 (0.74–3.60)	0.225	–	–
				OR 1.58 (0.56–4.45)	0.390	–	–
		TT	≤1.11 MMA%	RERI −0.78 (−2.79–1.24)	–	–	–
				AP −0.49 (−2.03–1.04)	–	–	–
		TC + CC	≤79.62 DMA%	SI 0.43 (0.03–5.53)	–	–	–
				OR 1.0 (ref.)	–	–	–
				OR 1.68 (0.85–3.33)	0.133	–	–
				OR 1.58 (0.71–3.51)	0.264	–	–
		TT	>79.62 DMA%	OR 1.55 (0.58–4.16)	0.380	–	–
				RERI −0.71 (−2.64–1.23)	–	–	–
		TC + CC	>19.37 iAs%	AP −0.45 (−1.91–1.00)	–	–	–
				SI 0.44 (0.04–5.45)	–	–	–
				OR 1.0 (ref.)	–	–	–
				OR 1.07 (0.48–2.38)	0.864	–	–
AS3MT (rs1191453)		TC + CC	≤19.37 iAs%	OR 0.92 (0.44–1.93)	0.825	–	–
				OR 1.85 (0.81–4.24)	0.144	–	–
		TT	≤19.37 iAs%	RERI 0.86 (−0.40–2.12)	–	–	–
				AP 0.47 (−0.10–1.03)	–	–	–
		TC/CC	>1.11 MMA%	SI −102.09 (NaN–NaN)	–	–	–
				OR 1.0 (ref.)	–	–	–
				OR 1.64 (0.73–3.70)	0.233	–	–
				OR 1.41 (0.66–2.99)	0.370	–	–
		TT	≤1.11 MMA%	OR 1.91 (0.81–4.54)	0.140	–	–
				RERI −0.13 (−1.75–1.48)	–	–	–
		TC + CC	≤79.62 DMA%	AP −0.07 (−0.93–0.79)	–	–	–
				SI 0.87 (0.18–4.30)	–	–	–
				OR 1.0 (ref.)	–	–	–
				OR 1.20 (0.54–2.67)	0.651	–	–

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
Liao et al. 2009 ECG abnormality Water (cumulative) arsenic (ppm-yr)	<i>PON1</i> (rs662, rs705379) <i>PON2</i> (rs7493)	TT	≤79.62 DMA%	OR 1.03 (0.49–2.16)	0.937	-	Participants with high cumulative arsenic exposure and carrying the R-C-S haplotype was linked to increased ECG abnormality risk (synergistic effect). <i>PON</i> R-C-S refers to the <i>PON1</i> (rs662), <i>PON1</i> (rs705379), <i>PON2</i> (rs7493) haplotype. Note, none of the eight included polymorphism reached statistical significance in univariate models. Adjusted by age, gender and cigarette smoking. From the 8 polymorphisms analysed, an association for two <i>EDNRB</i> polymorphism with obesity was found. A positive association for the two SNPs with obesity risk in those with higher arsenic exposure. Haplotype analysis indicates that there was a lower risk for obesity in individuals with higher arsenic levels, but no association for medium or low arsenic levels. Haplotype construction uses rs5351, rs3759475. Adjusted for age and sex. Number of study participants in each haplotype category not reported.
		TT	≤79.62 DMA%	OR 1.87 (0.81–4.30)	0.140	-	
	PON R-C-S -		RERI	0.64 (-0.68–1.96)	-	-	
			AP	0.34 (-0.28–0.97)	-	-	
			SI	3.75 (0.01–940.13)	-	-	
			OR	1.0 (ref.)	-	3/22	
	PON R-C-S +		OR	1.57 (0.19–13.00)	0.319	2/8	
			OR	4.27 (0.83–22.08)	0.632	11/17	
	PON R-C-S +		OR	19.19 (1.86–197.76)	0.014	4/2	
Martínez-Barquero et al. 2015 Obesity Blood plasma arsenic (nmol/L)	<i>EDNRB</i> (rs5351)	GG	≥50 nmol/L	OR 1.0 (ref.)	-	42/115	From the 8 polymorphisms analysed, an association for two <i>EDNRB</i> polymorphism with obesity was found. A positive association for the two SNPs with obesity risk in those with higher arsenic exposure. Haplotype analysis indicates that there was a lower risk for obesity in individuals with higher arsenic levels, but no association for medium or low arsenic levels. Haplotype construction uses rs5351, rs3759475. Adjusted for age and sex. Number of study participants in each haplotype category not reported.
		AG + AA	≥50 nmol/L	OR 0.51 (0.32–0.82)	0.005	54/265	
		GG	20–50 nmol/L	OR 1.0 (ref.)	-	37/133	
		AG + AA	20–50 nmol/L	OR 0.70 (0.43–1.13)	0.15	49/256	
		GG	≤20 nmol/L	OR 1.0 (ref.)	-	29/123	
		AG + AA	≤20 nmol/L	OR 0.70 (0.41–1.20)	0.20	46/272	
	<i>EDNRB</i> (rs3759475)	CC	≥50 nmol/L	OR 1.0 (ref.)	-	44/120	
		CT + TT	≥50 nmol/L	OR 0.53 (0.33–0.85)	0.009	54/256	
		CC	20–50 nmol/L	OR 1.0 (ref.)	-	35/132	
		CT + TT	20–50 nmol/L	OR 0.77 (0.47–1.25)	0.30	52/259	
		CC	≤20 nmol/L	OR 1.0 (ref.)	-	29/126	
		CT + TT	≤20 nmol/L	OR 0.70 (0.41–1.21)	0.20	46/268	
	<i>EDNRB</i> (rs5351, rs3759475)	GC	≥50 nmol/L	OR 1.0 (ref.)	-	-	
		AT	≥50 nmol/L	OR 0.53 (0.37–0.76)	<0.001	-	
		AC	≥50 nmol/L	OR 0.66 (0.13–3.28)	0.62	-	
		GT	≥50 nmol/L	OR 0.78 (0.09–6.72)	0.82	-	
		GC	20–50 nmol/L	OR 1.0 (ref.)	-	-	
		AT	20–50 nmol/L	OR 0.84 (0.59–1.20)	0.34	-	
		AC	20–50 nmol/L	OR 0.69 (0.08–6.05)	0.74	-	
Pan et al. 2013 Diabetes mellitus type 2 (T2DM) Water arsenic, µg/l	<i>ADAMTS9</i> rs17070905 rs17070967 rs6766801 rs2058703 rs1051055 rs12126	GT	20–50 nmol/L	OR 2.00 (0.49–8.11)	0.33	-	Three SNPs showed a significant interaction with arsenic increasing T2DM risk. When using a subset of the population with exposure <148 µg/L water arsenic only the gene-environment interaction with <i>NOTCH2</i> rs699780 remained significant. Adjusted for age, sex, BMI, smoking, skin lesions, using piecewise regression models.
		GC	≤20 nmol/L	OR 1.0 (ref.)	-	-	
		AT	≤20 nmol/L	OR 0.82 (0.56–1.19)	0.29	-	
		AC + GT	≤20 nmol/L	OR 0.30 (0.04–2.52)	0.27	-	
		rs17070905		P-value for interaction	0.076 (0.063)	957	
		rs17070967		in the study	0.096 (0.063)	adults,	
	<i>BCL11A</i> <i>CDC123</i>	rs6766801		population	0.113 (0.063)	83 T2DM	
		rs2058703			0.101 (0.063)	exposure <148 µg/L water arsenic only the gene-environment interaction with <i>NOTCH2</i> rs699780 remained significant.	
		rs1051055			0.008 (0.033)	Adjusted for age, sex, BMI, smoking, skin lesions, using piecewise regression models.	
		rs12126			0.017 (0.052)		

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
	CDKN2A	rs3088440			0.088 (0.063)		Q-values are calculated using FDR adjustment for the P-value of interaction.
	CDKN2B	rs1063192			0.138 (0.067)		
		rs3217986			0.078 (0.063)		
		rs3217992			0.938 (0.319)		
	CENTD2	rs11603334			0.024 (0.061)		
	IDF	rs4646954			0.136 (0.067)		
	KCNQ1	rs1057128			0.107 (0.063)		
		rs10798			0.093 (0.063)		
		rs8234			0.144 (0.067)		
	KMG2	rs343092			0.123 (0.065)		
	LGR5	rs17109924			0.090 (0.063)		
	NOTCH2	rs1043964			0.438 (0.168)		
		rs699779			0.096 (0.063)		
		rs699780			0.003 (0.021)		
		rs7527186			0.059 (0.063)		
		rs835575			0.115 (0.063)		
PRC1		rs835576			0.044 (0.063)		
		rs12911192			0.243 (0.109)		
		rs14280			0.960 (0.319)		
		rs7601			0.465 (0.168)		
SLC30A8		rs10282940			0.348 (0.146)		
		rs11558471			0.553 (0.194)		
TCF2		rs2466293			0.317 (0.138)		
		rs1058166			0.454 (0.168)		
		rs10962			0.115 (0.063)		
		rs2688			0.003 (0.021)		
THADA		rs1549723			0.046 (0.063)		
		rs17031056			0.384 (0.156)		
TSPAN8		rs1051334			0.052 (0.063)		
	WFS1	rs1801208			0.111 (0.063)		
% HbA1c levels Water arsenic, µg/l		rs1801212			0.110 (0.063)		
		rs734312			0.449 (0.168)		
	ADAMTS9	rs17070905		P-value for interaction	0.091 (0.449)	No significant interactions were shown for SNPs with arsenic on T2DM risk.	
		rs17070967		in the study	0.136 (0.449)	Adjusted for age, sex, BMI, smoking, skin lesions, using piece-wise regression models.	
		rs6766801		population	0.144 (0.449)	Q-values are calculated using FDR adjustment for the P-value of interaction.	
	BCL11A	rs2058703			0.553 (0.68)		
	CDC123	rs1051055			0.354 (0.621)		
		rs12126			0.786 (0.745)		
	CDKN2A	rs3088440			0.681 (0.698)		

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA	95 % CI	P (Q)	Ca/Co	Comments
Wang et al. 2007 Carotid atherosclerosis Water arsenic (µg/L)	CDKN2B	rs1063192				0.498 (0.677)		
		rs3217986				0.931 (0.793)		
		rs3217992				0.992 (0.816)		
		rs11603334				0.707 (0.698)		
	CENTD2	rs4646954				0.417 (0.621)		
	IDE	rs1057128				0.248 (0.621)		
	KCNQ1	rs10798				0.086 (0.449)		
		rs8234				0.017 (0.353)		
	KMG42	rs343092				0.161 (0.457)		
	LGR5	rs17109924				0.29 (0.621)		
	NOTCH2	rs1043964				0.326 (0.621)		
		rs699779				0.541 (0.353)		
		rs699780				0.023 (0.68)		
		rs7527186				0.376 (0.621)		
		rs835575				0.093 (0.449)		
		rs835576				0.078 (0.449)		
	PRC1	rs12911192				0.571 (0.68)		
		rs14280				0.861 (0.792)		
		rs7601				0.714 (0.698)		
	SLC30A8	rs10282940				0.905 (0.793)		
	rs11558471				0.655 (0.698)			
	rs2466293				0.123 (0.449)			
TCF2	rs1058166				0.365 (0.621)			
	rs10962				0.645 (0.698)			
	rs2688				0.491 (0.677)			
THADA	rs1549723				0.385 (0.621)			
	rs17031056				0.587 (0.68)			
TSPAN8	rs1051334				0.137 (0.449)			
WFS1	rs1801208				0.411 (0.621)			
	rs1801212				0.351 (0.621)			
	rs734312				0.939 (0.793)			
Wang et al. 2007 Carotid atherosclerosis Water arsenic (µg/L)	GSTP1 (rs1695)	Ile/Ile	≤50 µg/L	OR	1.0 (ref.)			Results of this study suggest that there is a joint effect of arsenic exposure and GSTP1 and P53 (synergistic effect) genotypic variants on the risk of carotid atherosclerosis.
		Ile/Val + Val/Val	≤50 µg/L	OR	1.9 (0.9–4.0)	> 0.05		Adjusted for age and gender.
		Ile/Ile	>50 µg/L	OR	2.7 (1.6–4.5)	<0.01		Number of study participants (patients/controls) in each category not reported.
		Ile/Val + Val/Val	>50 µg/L	OR	6.0 (3.3–10.7)	<0.001		
	TP53 (rs1042522)	Arg/Arg	≤50 µg/L	OR	1.0 (ref.)			
		Arg/Pro + Pro/Pro	≤50 µg/L	OR	0.9 (0.5–1.9)	> 0.05		
		Arg/Arg	>50 µg/L	OR	1.4 (0.7–3.0)	> 0.05		
		Arg/Pro + Pro/Pro	>50 µg/L	OR	3.1 (1.7–5.7)	<0.001		
		0	≤50 µg/L	OR	1.0 (ref.)			
		1	≤50 µg/L	OR	1.0 (0.4–2.2)	> 0.05		

Results of this study suggest that there is a joint effect of arsenic exposure and GSTP1 and P53 (synergistic effect) genotypic variants on the risk of carotid atherosclerosis.

Adjusted for age and gender.

Number of study participants (patients/controls) in each category not reported.

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
Wu et al. 2014 Carotid intima-media thickness Water arsenic (µg/L)	No. variant genotypes of GSTP1 and P53	2	≤50 µg/L	OR 1.9 (0.7–5.3)	> 0.05	–	–
		0	>50 µg/L	OR 1.4 (0.6–3.3)	> 0.05	–	–
		1	>50 µg/L	OR 2.8 (1.3–6.0)	<0.01	–	–
		2	>50 µg/L	OR 6.1 (2.7–13.9)	<0.001	–	–
	APOE (rs7256173)	Dominant	µg/L (cont)	β _{int} 49.6 (21.6, 77.6)	0.0005	–	– Nine SNPs (APOE, AS3MT, PNP, TNF) had a nominally statistically significant interaction with well-water (or urinary) arsenic in cIMT.
		Additive	µg/L (cont)	β _{int} 2.0 (–6.1, 10.1)	0.63	–	–
		Dominant	µg/L (cont)	β _{int} –2.1 (–11.9, 7.8)	0.68	–	–
		Recessive	µg/L (cont)	β _{int} 21.0 (1.0, 41.0)	0.039	–	– Coefficient of multiplicative interaction between a 1-standard-deviation increase (96.7 µg/L) in arsenic and each SNP.
	AS3MT (rs11191442)	Additive	µg/L (cont)	β _{int} 2.9 (–5.1, 10.9)	0.47	–	–
		Dominant	µg/L (cont)	β _{int} –1.6 (–11.4, 8.2)	0.75	–	– Adjusted for sex, age at cIMT measurement, BMI, smoking status, educational attainment, SBP, diabetes status at baseline, and change in urinary arsenic level between visits.
		Recessive	µg/L (cont)	β _{int} 23.8 (4.4, 43.2)	0.016	–	–
		Additive	µg/L (cont)	β _{int} 2.8 (–5.2, 10.9)	0.49	–	–
	AS3MT (rs3740392)	Dominant	µg/L (cont)	β _{int} –1.8 (–11.7, 8.1)	0.73	–	–
		Recessive	µg/L (cont)	β _{int} 23.6 (4.2, 43.1)	0.017	–	– Number of study participants (patients/controls) not reported.
		Additive	µg/L (cont)	β _{int} 8.5 (–2.8, 19.8)	0.14	–	–
		Dominant	µg/L (cont)	β _{int} 6.3 (–6.8, 19.4)	0.34	–	–
	PNP (rs17886095)	Recessive	µg/L (cont)	β _{int} 40.4 (3.4, 77.4)	0.032	–	–
		Dominant	µg/L (cont)	β _{int} 35.0 (4.1, 65.9)	0.027	–	–
		Additive	µg/L (cont)	β _{int} 8.9 (–0.8, 18.6)	0.071	–	–
		Dominant	µg/L (cont)	β _{int} 13.5 (1.6, 25.4)	0.026	–	–
	TNF (rs3790064)	Recessive	µg/L (cont)	β _{int} –0.4 (–27.6, 26.9)	0.98	–	–
		Dominant	µg/L (cont)	β _{int} 24.7 (0.6, 48.7)	0.044	–	–
		Additive	µg/L (cont)	β _{int} –4.0 (–15.2, 7.2)	0.48	–	–
		Dominant	µg/L (cont)	β _{int} –0.9 (–13.4, 11.7)	0.89	–	–
Carotid intima-media thickness Water arsenic (µg/L)	APOE (rs7256173)	Recessive	µg/L (cont)	β _{int} –47.3 (–90.4, –4.2)	0.032	–	–
		CC	< 40.4 µg/L	β _{int} 1.0 (ref.)	–	504	Adjusted for sex, age at cIMT measurement, BMI, smoking status, educational attainment, SBP, diabetes status at baseline, and change in urinary arsenic level between visits.
		CC	≥ 40.4 µg/L	β _{int} 8.7 (–1.4, 18.8)	–	504	–
		CT + TT	< 40.4 µg/L	β _{int} –8.1 (–40.4, 24.1)	–	25	–
	AS3MT (rs10883790)	CT + TT	≥ 40.4 µg/L	β _{int} 46.0 (10.7, 81.3)	–	21	Only total number of participants in each category was reported.
		CA + AA	< 40.4 µg/L	β _{int} 1.0 (ref.)	–	490	–
		CA + AA	≥ 40.4 µg/L	β _{int} 8.0 (–2.3, 18.3)	–	483	–
		CC	< 40.4 µg/L	β _{int} –5.4 (–32.2, 21.4)	–	37	–
	AS3MT (rs11191442)	CC	≥ 40.4 µg/L	β _{int} 35.8 (9.2, 62.4)	–	38	–
		TT + TA	< 40.4 µg/L	β _{int} 1.0 (ref.)	–	488	–
		TT + TA	≥ 40.4 µg/L	β _{int} 7.8 (–2.5, 18.1)	–	479	–
		AA	< 40.4 µg/L	β _{int} –5.8 (–32.5, 21.0)	–	37	–
	AS3MT (rs3740392)	AA	≥ 40.4 µg/L	β _{int} 38.3 (12.1, 64.5)	–	39	–
		AA + AG	< 40.4 µg/L	β _{int} 1.0 (ref.)	–	489	–
		AA + AG	≥ 40.4 µg/L	β _{int} 7.2 (–3.1, 17.5)	–	487	–
		GG	< 40.4 µg/L	β _{int} –5.1 (–31.6, 21.3)	–	38	–
	GG	≥ 40.4 µg/L	β _{int} 40.9 (14.4, 67.5)	–	38	–	–

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
Carotid intima-media thickness Urinary arsenic (µg/g creatinine)	<i>APOE</i> (rs7256173) <i>AS3MT</i> (rs10883790)	Dominant	µg/g (cont)	β_{int}	0.021	-	- Coefficient of multiplicative interaction between a 1-standard-deviation increase (345.2 µg/g creatinine) in arsenic and each SNP.
		Additive	µg/g (cont)	β_{int}	0.22	-	-
		Dominant	µg/g (cont)	β_{int}	0.67	-	-
		Recessive	µg/g (cont)	β_{int}	0.008	-	- Adjusted for sex, age at cIMT measurement, BMI, smoking status, educational attainment, SBP, diabetes status at baseline, and change in urinary arsenic level between visits.
	<i>AS3MT</i> (rs11191442)	Additive	µg/g (cont)	β_{int}	0.18	-	-
		Dominant	µg/g (cont)	β_{int}	0.57	-	-
		Recessive	µg/g (cont)	β_{int}	0.009	-	- Number of study participants (patients/controls) not reported.
		Additive	µg/g (cont)	β_{int}	0.23	-	-
	<i>AS3MT</i> (rs3740392)	Dominant	µg/g (cont)	β_{int}	0.69	-	-
		Recessive	µg/g (cont)	β_{int}	0.004	-	-
		Additive	µg/g (cont)	β_{int}	0.16	-	-
		Dominant	µg/g (cont)	β_{int}	0.29	-	-
	<i>PNP</i> (rs17886095) <i>PNP</i> (rs17882804)	Recessive	µg/g (cont)	β_{int}	0.086	-	-
		Dominant	µg/g (cont)	β_{int}	0.64	-	-
		Additive	µg/g (cont)	β_{int}	0.072	-	-
		Dominant	µg/g (cont)	β_{int}	0.14	-	-
Carotid intima-media thickness Urinary arsenic (µg/g creatinine)	<i>APOE</i> (rs7256173) <i>AS3MT</i> (rs10883790)	Recessive	µg/g (cont)	β_{int}	0.030	-	-
		Dominant	µg/g (cont)	β_{int}	0.96	-	-
		Additive	µg/g (cont)	β_{int}	0.95	-	-
		Dominant	µg/g (cont)	β_{int}	0.97	-	-
	<i>AS3MT</i> (rs10883790)	Recessive	µg/g (cont)	β_{int}	0.84	-	-
		CC	< 183 µg/g	β	1.0 (ref.)	508	Adjusted for sex, age at cIMT measurement, BMI, smoking status, educational attainment, SBP, diabetes status at baseline, and change in urinary arsenic level between visits.
		CT + TT	≥ 183 µg/g	β	7.9 (-2.2, 18.1)	514	Only total number of participants in each category was reported.
		CT + TT	< 183 µg/g	β	7.5 (-24.2, 39.2)	26	-
	<i>AS3MT</i> (rs10883790)	CT + AA	≥ 183 µg/g	β	27.9 (-6.6, 62.4)	22	-
		CA + AA	< 183 µg/g	β	1.0 (ref.)	486	-
		CA + AA	≥ 183 µg/g	β	5.9 (-4.4, 16.2)	501	-
		CC	< 183 µg/g	β	-2.9 (-27.2, 21.3)	46	-
	<i>AS3MT</i> (rs11191442)	CC	≥ 183 µg/g	β	40.7 (11.6, 69.9)	31	-
		TT + TA	< 183 µg/g	β	1.0 (ref.)	483	-
		TT + TA	≥ 183 µg/g	β	5.7 (-4.6, 16.0)	498	-
		AA	< 183 µg/g	β	-0.2 (-24.1, 23.8)	47	-
Wu et al. 2015 Cardiovascular disease (CVD) Water arsenic, µg/l	<i>AS3MT</i> (rs3740392)	AA	≥ 183 µg/g	β	40.4 (11.4, 69.5)	31	-
		AA + AG	< 183 µg/g	β	1.0 (ref.)	484	-
		AA + AG	≥ 183 µg/g	β	5.7 (-4.5, 16.0)	506	-
		GG	< 183 µg/g	β	0.4 (-23.3, 24.2)	48	-
	<i>ICAM1</i> (rs281432)	GG	≥ 183 µg/g	β	44.1 (14.6, 73.6)	30	-
		CG + CC	< 45 µg/L	HR	1.0 (ref.)	143/500	From 170 SNPs explored, multiplicative interactions were statistically significant for CVD after multiple testing corrections for <i>ICAM1</i> (rs2781432) and <i>VCAM1</i> (rs3176867).
		GG	< 45 µg/L	HR	1.35 (0.84-2.18)	43/173	-
		CG + CC	≥ 45 µg/L	HR	1.67 (1.14-2.43)	185/520	-
		GG	≥ 45 µg/L	HR	2.98 (1.87-4.77)	73/151	Adjusted for sex, age, BMI, smoking status, educational
					P_{int} 0.40		

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
Cardiovascular disease (CVD) Water arsenic, µg/L	<i>VCAM1</i> (rs13176867)	TC + TT CC	< 45 µg/L HR	1.0 (ref.) 0.89 (0.56–1.41)	P_{int} 0.04	166/594 16/65	attainment, SBP, diabetes status, and change in urinary arsenic between visits.
		TC + TT CC	≥ 45 µg/L HR	1.30 (0.83–2.05)		222/609	
		TC + TT CC	≥ 45 µg/L HR	2.13 (1.37–3.31)		27/42	
	<i>APOE</i> rs405509	AA vs. AC + CC	µg/L (cont)	HR 1.09 (0.78, 1.53)	0.021 (0.287)	–	Coefficient of multiplicative interaction between a 1-SD increase
	rs7259620	GG vs. AG + AA	µg/L (cont)	HR 1.35 (0.96, 1.89)	0.041 (0.324)	–	(101.3 µg/L) in arsenic and each SNP.
	<i>AS3MT</i> rs1046778	TC + CC vs. TT	µg/L (cont)	HR 1.22 (0.87, 1.72)	0.038 (0.324)	–	Adjusted for sex, age, BMI, smoking status, educational attainment, SBP, diabetes status, and change in urinary arsenic between visits.
	rs10748839	TC + CC vs. TT	µg/L (cont)	HR 1.34 (0.91, 2.00)	0.046 (0.324)	–	
	rs10786719	AG + GG vs. AA	µg/L (cont)	HR 1.28 (0.87, 1.90)	0.046 (0.324)	–	
	rs11191454	AG + GG vs. AA	µg/L (cont)	HR 1.27 (0.87, 1.84)	0.016 (0.287)	–	P-values from tests for multiplicative interactions between a 1-SD
	rs12573221	AC + CC vs. AA	µg/L (cont)	HR 1.18 (0.81, 1.71)	0.040 (0.324)	–	increase well-water arsenic and SNPs.
	rs4290163	GT + TT vs. GG	µg/L (cont)	HR 1.25 (0.85, 1.84)	0.036 (0.324)	–	
	rs9527	GG vs. GA + AA	µg/L (cont)	HR 1.00 (0.63, 1.61)	0.041 (0.324)	–	
	<i>CBS</i> rs1005585	AG + GG vs. AA	µg/L (cont)	HR 1.03 (0.67, 1.58)	0.006 (0.274)	–	
	rs3788050	GT + TT vs. GG	µg/L (cont)	HR 1.10 (0.73, 1.66)	0.015 (0.287)	–	
	rs8132811	CT + TT vs. CC	µg/L (cont)	HR 1.01 (0.71, 1.45)	0.002 (0.141)	–	
	<i>GSTO1</i> rs1147611	CA + AA vs. CC	µg/L (cont)	HR 1.65 (1.16, 2.36)	0.026 (0.296)	–	
Coronary heart disease, (CHD) Water arsenic, µg/L	rs11509438	GA + AA vs. GG	µg/g (cont)	HR 1.70 (1.19, 2.41)	0.024 (0.295)	–	
	rs2282326	AC + CC vs. AA	µg/L (cont)	HR 1.66 (1.17, 2.36)	0.041 (0.324)	–	
	<i>ICAM1</i> rs281432	GG vs. CG + CC	µg/L (cont)	HR 1.82 (1.31, 2.54)	9.4×10^{-7} (0.0002)	–	
	<i>NOS3</i> rs1800783	TA + AA vs. TT	µg/L (cont)	HR 1.06 (0.75, 1.50)	0.022 (0.287)	–	
	rs6951150	CT + TT vs. CC	µg/L (cont)	HR 1.04 (0.73, 1.48)	0.012 (0.287)	–	
	<i>SOD2</i> rs2758331	CA + AA vs. CC	µg/L (cont)	HR 1.07 (0.72, 1.59)	0.021 (0.287)	–	
	rs2758334	TC + CC vs. TT	µg/L (cont)	HR 0.96 (0.66, 1.41)	0.009 (0.287)	–	
	rs8031	TA + AA vs. TT	µg/L (cont)	HR 1.02 (0.68, 1.51)	0.046 (0.324)	–	
	<i>VCAM1</i>						
	rs3176867	CC vs. TC + TT	µg/L (cont)	HR 1.34 (0.95, 1.87)	0.0004 (0.035)	–	
	rs3176871	GG vs. GA + AA	µg/L (cont)	HR 0.55 (0.32, 0.95)	0.018 (0.287)	–	
	rs3765685	AA vs. AG + GG	µg/L (cont)	HR 1.20 (0.83, 1.74)	0.014 (0.287)	–	
	<i>AS3MT</i> (rs1046778)	TC+CC vs. TT	µg/L (cont)	HR 1.25 (0.84–1.85)	0.043 (0.315)	–	Coefficient of multiplicative interaction between a 1-SD increase
	(rs11191454)	AG+GG vs. AA	µg/L (cont)	HR 1.33 (0.88–2.01)	0.036 (0.290)	–	(101.3 µg/L) in arsenic and each SNP.
	(rs12573221)	AC+CC vs. AA	µg/L (cont)	HR 1.17 (0.76–1.78)	0.007 (0.257)	–	Adjusted for sex, age, BMI, smoking status, educational attainment, SBP, diabetes status, and change in urinary arsenic between visits.
	<i>CBS</i>	AG+GG vs. AA	µg/L (cont)	HR 0.93 (0.55–1.58)	0.009 (0.257)	–	
	(rs1005585)						
	(rs11700748)	TC+TT vs. CC	µg/L (cont)	HR 1.04 (0.68–1.58)	0.018 (0.257)	–	P-values from tests for multiplicative interactions between a 1-SD
	(rs2124459)	TC+CC vs. TT	µg/L (cont)	HR 1.08 (0.67–1.73)	0.050 (0.321)	–	increase well-water arsenic and SNPs.
	(rs2849727)	TC+TT vs. CC	µg/L (cont)	HR 1.08 (0.72–1.61)	0.050 (0.321)	–	
	(rs3788050)	GT+TT vs. GG	µg/L (cont)	HR 0.96 (0.58–1.58)	0.018 (0.257)	–	
	(rs706208)	TC+CC vs. TT	µg/L (cont)	HR 1.02 (0.67–1.56)	0.031 (0.275)	–	

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95% CI	P (Q)	Ca/Co	Comments
Stroke Water arsenic (µg/L)	<i>GSTO1</i> (rs1147611)	CA+AA vs. CC	µg/L (cont)	HR 1.72 (1.13–2.60)	0.028 (0.275)	-	-
	(rs11509438)	GA+AA vs. GG	µg/L (cont)	HR 2.07 (1.36–3.15)	0.028 (0.275)	-	-
	(rs2282326)	AC+CC vs. AA	µg/L (cont)	HR 1.74 (1.15–2.63)	0.036 (0.290)	-	-
	<i>ICAM1</i> (rs281432)	GG vs. CG+CC	µg/L (cont)	HR 1.56 (1.04–2.34)	0.007 (0.257)	-	-
	<i>IL6</i> (rs2069835)	TC+CC vs. TT	µg/L (cont)	HR 1.27 (0.77–2.12)	0.031 (0.275)	-	-
	<i>MTHFR</i> (rs12121543)	CA+AA vs. CC	µg/L (cont)	HR 0.92 (0.61–1.39)	0.016 (0.257)	-	-
	(rs17421462)	GG vs. GA+AA	µg/L (cont)	HR 0.80 (0.47–1.36)	0.029 (0.275)	-	-
	(rs1801131)	AC+CC vs. AA	µg/L (cont)	HR 0.92 (0.59–1.43)	0.015 (0.257)	-	-
	<i>NOS3</i> (rs1800783)	TA+AA vs. TT	µg/L (cont)	HR 0.94 (0.63–1.39)	0.015 (0.257)	-	-
	(rs6951150)	TC+TT vs. CC	µg/L (cont)	HR 0.96 (0.65–1.44)	0.014 (0.257)	-	-
	<i>SOD2</i> (rs2758334)	TC+CC vs. TT	µg/L (cont)	HR 0.96 (0.61–1.51)	0.042 (0.315)	-	-
	<i>VCAM1</i> (rs1409419)	CC vs. TC+TT	µg/L (cont)	HR 0.83 (0.56–1.24)	0.027 (0.275)	-	-
	(rs2209627)	AA vs. AG+GG	µg/L (cont)	HR 0.70 (0.40–1.23)	0.008 (0.257)	-	-
	(rs3176867)	CC vs. TC+TT	µg/L (cont)	HR 1.51 (1.01–2.26)	0.027 (0.275)	-	-
	(rs3176871)	GG vs. GA+AA	µg/L (cont)	HR 0.48 (0.27–0.88)	0.011 (0.257)	-	-
	(rs3176878)	CC vs. TC+TT	µg/L (cont)	HR 0.78 (0.45–1.35)	0.014 (0.257)	-	-
	(rs3917014)	GG vs. AG+AA	µg/L (cont)	HR 1.55 (0.87–2.73)	0.003 (0.260)	-	-
	<i>ASMT</i> (rs10786719)	AG+GG vs. AA	µg/L (cont)	HR 1.16 (0.64–2.08)	0.050 (0.440)	-	Coefficient of multiplicative interaction between a 1-SD increase (101.3 µg/L) in arsenic and each SNP.
	(rs11191439)	TT vs. TC+CC	µg/L (cont)	HR 0.82 (0.38–1.76)	0.044 (0.440)	-	Adjusted for sex, age, BMI, smoking status, educational attainment, SBP, diabetes status, and change in urinary arsenic between visits.
	<i>CBS</i> (rs8132811)	CT+TT vs. CC	µg/L (cont)	HR 0.97 (0.57–1.64)	0.021 (0.440)	-	P-values from tests for multiplicative interactions between a 1-SD increase well-water arsenic and SNPs.
<i>GSTO1</i> (rs1147611) <i>ICAM1</i> (rs281432)	(rs1147611)	CA+AA vs. CC	µg/L (cont)	HR 1.64 (0.99–2.73)	0.027 (0.440)	-	-
	(rs281432)	GG vs. CG+CC	µg/L (cont)	HR 1.85 (1.14–3.01) (0.14)	8.3 × 10⁻⁵ (0.14)	-	-
	<i>NOS3</i> (rs1800779)	AG+GG vs. AA	µg/L (cont)	HR 1.36 (0.84–2.20)	0.034 (0.440)	-	-
	(rs1800783)	TA+AA vs. TT	µg/L (cont)	HR 1.10 (0.69–1.76)	0.013 (0.440)	-	-
	(rs3793342)	CT+TT vs. CC	µg/L (cont)	HR 1.29 (0.79–2.12)	0.023 (0.440)	-	-
	(rs3918169)	AG+GG vs. AA	µg/L (cont)	HR 1.18 (0.73–1.92)	0.031 (0.440)	-	-
	(rs6951150) <i>VCAM1</i>	CT+TT vs. CC	µg/L (cont)	HR 1.01 (0.63–1.62)	0.002 (0.193)	-	-

Table 2: (continued)

Study	Gene	Genotype	Arsenic	MoA 95 % CI	P (Q)	Ca/Co	Comments
Cardiovascular disease, (CVD) Urinary arsenic (µg/g creatinine)	(rs3176867) <i>AS3MT</i>	CC vs. TC+TT	µg/L (cont)	HR 1.23 (0.76–1.99)	0.007 (0.377)	–	–
	(rs12573221)	AC+CC vs. AA	µg/g (cont)	HR 0.99 (0.64–1.54)	0.011 (–)	–	Coefficient of multiplicative interaction between a 1-SD increase (322 µg/g) in arsenic and each SNP.
	(rs4290163)	GT+TT vs. GG	µg/g (cont)	HR 1.11 (0.72–1.70)	0.011 (–)	–	Adjusted for sex, age, BMI, smoking status, educational attainment, SBP, diabetes status, and change in urinary arsenic between visits.
	(rs1005585) <i>CBS</i>	AG+GG vs. AA	µg/g (cont)	HR 1.02 (0.63–1.64)	4.3×10^{-7} (–)	–	–
	(rs3788050)	GT+TT vs. GG	µg/g (cont)	HR 1.09 (0.69–1.73)	1.1×10^{-6} (–)	–	–
Coronary heart disease (CHD) Urinary arsenic (µg/g creatinine)	(rs8132811) <i>ICAM1</i>	CT+TT vs. CC	µg/g (cont)	HR 1.00 (0.65–1.54)	0.002 (–)	–	P-values from tests for multiplicative interactions between a 1-SD increase well-water arsenic and SNPs.
	(rs281432) <i>SOD2</i>	GG vs. CG+CC	µg/g (cont)	HR 1.68 (1.12–2.52)	0.014 (–)	–	–
	(rs2758331)	CA+AA vs. CC	µg/g (cont)	HR 0.97 (0.63–1.50)	0.010 (–)	–	–
	(rs2758334)	TC+CC vs. TT	µg/g (cont)	HR 0.86 (0.56–1.31)	0.005 (–)	–	–
	(rs8031) <i>AS3MT</i>	TA+AA vs. TT	µg/g (cont)	HR 0.90 (0.59–1.38)	0.008 (–)	–	–
Stroke Urinary arsenic (µg/g creatinine)	(rs12573221) <i>CBS</i>	AC+CC vs. AA	µg/g (cont)	HR 1.03 (0.63–1.69)	0.035 (–)	–	–
	(rs1005585)	AG+GG vs. AA	µg/g (cont)	HR 1.01 (0.57–1.79)	0.0003 (–)	–	–
	(rs3788050) <i>ICAM1</i>	GT+TT vs. GG	µg/g (cont)	HR 1.02 (0.59–1.79)	0.0009 (–)	–	–
	(rs1409419)	CC vs. TC+TT	µg/g (cont)	HR 0.84 (0.54–1.31)	0.002 (–)	–	–
	(rs2209627)	AA vs. AG+GG	µg/g (cont)	HR 0.57 (0.29–1.14)	0.043 (–)	–	–
Stroke Urinary arsenic (µg/g creatinine)	(rs3176878) <i>CBS</i>	CC vs. TC+TT	µg/g (cont)	HR 0.62 (0.31–1.25)	0.050 (–)	–	–
	(rs8132811) <i>ICAM1</i>	CT+TT vs. CC	µg/g (cont)	HR 0.89 (0.49–1.63)	0.003 (–)	–	–
	(rs281432)	GG vs. CG+CC	µg/g (cont)	HR 1.60 (0.87–2.93)	0.005 (–)	–	–

Most studies only presented the results of statistically significant SNPs and thus these have been included here. Q-values are adjusted p-values after FDR correction. A, adenine; AP, attributable proportion due to the interaction; BG, blood glucose; β_{int} , coefficient for interaction; BMI, body mass index; C, cytosine; Ca, cases; CHD, coronary heart disease; CI, confidence interval; cIMT, carotid intima-media thickness; Co, controls; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; DMA, dimethylated arsenic; ECG, electrocardiogram; FDR, false discovery rate; G, guanine; GMR, geometric mean ratio; HDL, high-density lipoprotein; HOMA2-IR, homeostatic model assessment insulin resistance; HR, heart rate; HTN, hypertension; LDL, low-density lipoprotein; MoA, measure of association; MMA, monomethylated arsenic; OR, odds ratio; OR_{int}, odds ratio for interaction; Pb, lead; P_{int}, p-value for interaction; PMI, primary methylation index; Ppb, parts per million; RERI, relative excess risk due to interactions; SBP, systolic blood pressure; SD, standard deviation; SI, synergy index; SMI, secondary methylation index; SNP, single nucleotide polymorphism; SNV, small nucleotide variant; T, thymine; TC, total cholesterol; TG, triglycerides; T2DM, Type 2 diabetes mellitus; WC, waist circumference. Abbreviations of relevant genes can be found in Supplementary Table 5. The bold MAO and P/Q values are considered statistically significant.

Table 3: Single nucleotide polymorphisms (SNPs) associated with arsenic-related cardiometabolic disease.

Significant SNP-arsenic	Arsenic and disease	Risk ^(b)	Non-significant results reported ^(c)	Gene (product) function ^(d)
AS3MT				
rs17881215	W + DM [40]	↑	–	Arsenic metabolism; transfer of methyl group from SAM to arsenical
rs11191439	W + DM [40]	↑	W + CA [0.05 (0.075)] [27] W + CVD/CHD/Stroke [0.044 (0.440)] [34] ^(a) CW + ECG ab [29] W/U + CIMT [33] U + MetS [25]	
rs12768205	U[iAs% vs. MMA%] + IR [41] U[DMA% vs. iAs%] + IR [41]	↑	U[iAs% vs. MMA%] + DM [41] U[DMA% vs. iAs%] + DM [41]	
rs10883790	W/U + CIMT [33]	↑	W + CVD/CHD/Stroke [34]	
rs11191442	W/U + CIMT [33]	↑	W + CVD/CHD/Stroke [34]	
rs3740392	W/U + CIMT [33]	↑	W + CVD/CHD/Stroke [34]	
rs4919694	W/U + CIMT [33]	↑	W + CVD/CHD/Stroke [34]	
APOE				
rs7256173	W/U + CIMT [33]	↑	W + CVD/CHD/Stroke [34]	Inflammation/endothelial function; catabolism of triglyceride-rich lipoprotein constituent
CCM3				
rs9818496	W + SBP [36]	↑	W + DBP [36]	Cell apoptosis; vascular development / angiogenesis; implicated in influencing cardiovascular-related physiological response
rs3804610	W + SBP [36]	↑	W + DBP [36]	
rs6784267	W + SBP [36]	↑	W + DBP [36]	
CDC123				
rs1051055	W + DM [32]	↑	W + % HbA1c [32]	Cell division cycle; implicated in T2DM
COX5A				
rs1133322	U + DM [38]	↑	–	Oxidative phosphorylation; component of cytochrome C oxidase; implicated in T2DM
CYBA				
rs3794624	W + PP [31]	↑	W + SBP [<i>P</i> 0.004 (0.34)] ^(a) [31] W + CVD/CHD/Stroke [34] W/U + CIMT [33]	Oxidative stress/defence; encodes the light, alpha subunit of Cytochrome B
rs4673	CW + HTN [28]	↑	–	
EDNRB				
rs3759475	B + Ob [39]	↓	U + T2DM [38]	Inflammation/endothelial function; located primarily in vascular endothelial cells with a role in vasoconstriction, vasodilation, and cell proliferation
rs5351	B + Ob [39]	↓	U + T2DM [38]	
GCLC				
rs11415624	U + DM [38]	↑	–	Oxidative stress/defence; glutathione synthesis; first rate limiting enzyme of glutathione synthesis
GSTO1				
rs4925	U (PMI, SMI, MMA%, DMA%) + MetS [25] W + CA [27]	↑	CW + ECG ab [29] W + CVD/CHD/Stroke [34] W/U + CIMT [33]	Arsenic metabolism; glutathione-dependent thiol transferase and dehydroascorbate reductase activities; reduces MMA and DMA
GSTP1				
rs1695	W + CA [30]	↑	W + DBP [<i>P</i> 0.02 (0.74)] ^(a) [31] W + CVD/CHD/Stroke [34]	Arsenic metabolism; conjugation of reduced glutathione to a wide number of hydrophobic electrophiles;

Table 3: (continued)

Significant SNP-arsenic	Arsenic and disease	Risk ^(b)	Non-significant results reported ^(c)	Gene (product) function ^(d)
ICAM1				
rs281432	W + CVD/Stroke [34]	↑	W + CHD [<i>P</i> 0.007 (0.257)] ^(a) [34] U + CVD/Stroke/CHD [34]	Inflammation/endothelial function; encodes cell adhesion molecules
IL8RA				
rs1008563	U + DM [38]	↑	–	Implicated in T2DM; receptor to interleukin-8; activation of neutrophils
rs1008562	U + DM [38]	↑	–	
NOS3				
rs1799983	CW + HTN [28]	↑	W + DBP [<i>P</i> 0.01 (0.74)] ^(a) [31]	Oxidative stress/defence; production of nitric oxide (NO) which is implicated in vascular smooth muscle relaxation, angiogenesis, blood clotting
NOTCH2				
rs699780	W + DM [32]	↑	W + % HbA1c [32]	Cell fate decision; development; immune function
NR3C2				
rs13117325	U + DM [38]	↑	–	Cellular sodium ion homeostasis; implicated in T2DM; encodes the mineralocorticoid receptor
rs2137335	U + DM [38]	↑	–	
NGAMT1				
rs1997605	U (iAs%, MMA%, DMA%+ GDM [37]	↑	–	Arsenic metabolism; methyltransferase; involved in converting MMA to DMA
rs1003671	U (iAs%, MMA%, DMA%+ GDM [37]	↑	–	
OGG1				
rs1052133	U + HTN [24]	↑	U + T2DM [38]	DNA repair; glycosylase removing premutagenic 8-oxo-G – a base by-product of ROS exposure
PNP				
rs17886095	W/U + CIMENT [33]	↑	W + CVD/CHD/Stroke [34]	Arsenic metabolism; catalyses the phosphorylation of purine nucleosides; arsenic reductase
rs17882804	W/U + CIMENT [33]	↑	W + CVD/CHD/Stroke [34]	
rs3790064	W/U + CIMENT [33]	↑	W + CVD/CHD/Stroke [34]	
TP53				
rs1042522	W + CA [30]	↑	–	Tumour suppressor; protects vascular smooth muscle from apoptosis; implicated in atherosclerosis
SOD2				
rs4880	U + HTN [24]	↑	U + T2DM [38]	Oxidative stress/defence; ROS scavenger in mitochondria; binds to superoxide by-products of oxidative phosphorylation
	CW + HTN [28]	↑		
TCF2				
rs2688	W + DM [32]	↑	W + % HbA1c [32]	Nephron development, embryonic pancreas development; implicated in T2DM
TNF				
rs3093661	W + CIMENT [33]	↑	W + CVD/CHD/Stroke [34]	Inflammation/endothelial function; encodes multifunctional proinflammatory cytokine
rs3790064	W + CIMENT [33]	↑	U + CIMENT [33] U + CIMENT [33]	

Table 3: (continued)

Significant SNP-arsenic	Arsenic and disease	Risk ^(b)	Non-significant results reported ^(c)	Gene (product) function ^(d)
TXN rs4135168	U + DM [38]	↑	–	Oxidative stress/defence; cellular redox homeostasis;
VCAM1 rs3176867	W + CVD [34]	↑	W + CHD [<i>P</i> 0.027 (0.275)] ^(a) / Stroke [<i>P</i> 0.007 (0.377)] ^(a) [34] U + CIMT [33]	Inflammation/endothelial function; mediates leukocyte-endothelial cell adhesion and signal transduction; may have a role in CA
Haplotypes				
PON R-C-S haplotype [PON1 (rs662), PON1 (rs705379), PON2 (rs7493)]	CW + ECG ab [29]	↑	–	Serum esterase/lactonase with antioxidant action on HDL; protective atherosclerosis
PNP A-T haplotype (rs1049564, rs1130650)	W + CA [27]	↑	–	Arsenic metabolism; catalyses the phosphorolysis of purine nucleosides; arsenic reductase
GST A-G-G haplotype [GSTO1 (rs925), GSTO2 (rs2297235, rs156697)]	W + CA [27]	↑	–	Arsenic metabolism; glutathione-dependent thiol transferase and dehydroascorbate reductase activities; reduces MMA and DMA
EDRNB A-T haplotype (rs5351, rs3759475)	B + Ob [39]	↓	–	Inflammation/endothelial function; located primarily in vascular endothelial cells with a role in vasoconstriction, vasodilation, and cell proliferation
MCP-1 (rs1024611), APOE (rs429358, rs7412)	W + CA [26]	↑	–	Inflammation/endothelial function; catabolism of triglyceride-rich lipoprotein constituent (<i>APOE</i>); chemotactic response and mobilization of intracellular calcium (<i>MCP-1</i>)

B, blood; CA, carotid atherosclerosis; CHD, coronary heart disease; CVD, cardiovascular disease; CW, cumulative water arsenic; DBP, diastolic blood pressure; DM, diabetes mellitus; DMA, dimethylated arsenic; ECG, electrocardiogram; HDL, high-density lipoprotein; HTN, hypertension; IR, insulin resistance; MetS, metabolic syndrome; Ob, obesity; PMI, primary methylation index; ROS, reactive oxygen species; SAM, S-Adenosyl methionine; SBP, systolic blood pressure; SMI, secondary methylation index; U, urine, W, water. ^(a) Here the P (Q) values are presented with Q referring to the p-value adjusted for multiple testing. ^(b) Refers to whether there is a positive or negative association between the arsenic-SNV interaction and disease of interest. ^(c) Here, studies are listed that investigated a same SNV for which a significant interaction effect was reported in one study – but that reported non-significant interaction effects (before and/or after adjustment for multiple testing). ^(d) Information described in this column is based on information provided in the referenced included articles as well as the dbSNP database (<https://www.ncbi.nlm.nih.gov/snp/>) and the integrative database GeneCards (<https://www.genecards.org/>). ↓ Arsenic exposed individuals had lower disease risk in those carrying the variant compared to those carrying the wildtype. ↑ Arsenic exposed individuals had higher disease risk in those carrying the variant compared to the wildtype. – Indicates that there was no other study that explored this unique SNP. Details on each individual SNP can be found in supplementary Table 5.

AFS) [35] or results from previous reports (without detail on the chemical analyses performed) [28, 29].

From the 18 included studies, some were conducted in areas with high arsenic exposure (i.e., at least one category or the mean was reported or estimated to be $>100 \mu\text{g/L}$ arsenic in water, or the study area was reported to be an arsenic-rich or arsenic hyperendemic area) [28–34, 36, 38, 39] and others in areas with low-moderate arsenic exposure (i.e., at least one category was reported or estimated to be $<100 \mu\text{g/L}$ arsenic in water, or the study area was reported to have low or moderate environmental arsenic exposure) [24–27, 30–41]. Several studies required participants to have a minimum length of residence or unchanged life circumstances to be included in the study (i.e., living in the study area for ≥ 1 year [24, 36], ≥ 2 years [40], ≥ 5 years [31, 33, 34] or ≥ 6 years [37], or residing in the study area for ≥ 5 days in the week [29]), whilst other studies followed participants over time or assumed exposure was constant (Table 1).

Genes and single nucleotide polymorphisms

Across studies, 676 unique SNPs in 148 genes were explored. supplementary Table 5 provides an overview of all studied SNPs including alleles and the consequence of the genetic variation. All studies used a hypothesis-driven candidate gene approach selecting candidate genes based on i) their involvement in arsenic metabolism [25, 27, 29–31, 33, 34, 37, 40, 41], ii) their role in oxidative stress or endogenous defence against reactive oxygen species (ROS) [24, 28], iii) their role related to T2DM metabolic pathways [32, 35, 38], iv), their role in the development of atherosclerosis [26, 29, 30], or v) their role in the endothelin system relevant to obesity [39], vi) if genes have been reported to modify associations between arsenic and CVD in previous epidemiological studies [31, 34], vii) genes where arsenic exposure has been associated with gene products known as risk factors or predictors for CVD [31, 34] or impaired vascular development [36], and ix) if genes have been related to arsenic exposure in animal, *in vitro*, or epidemiologic studies, and are known to play a key role in CVD risk [33].

Genotyping was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) [24–28, 30], the TaqMan SNP Genotyping Assay [25, 29, 40], the Illumina GoldenGate assay [31, 33, 34], the oligo-ligation-assay SNPlex [38, 39], the Illumina Cardio-Metabo DNA Analysis BeadChip (MetaboChip) [41], the Sequenom MassARRAY iPLEX [32], a multiplex PCR [35], a high throughput-SNP approach (3-rounds of multiplex PCR with NGS) [37], or using the Improved Multiple Ligase Detection Reaction (iMLDR) method (Table 1) [36].

Quality assessment of the individual studies

Most of the included studies [24–30, 32, 36, 37, 40] have sample sizes of less than 1000 participants or had a relatively low frequency of the variant allele, which greatly limits the power to detect modest genetic effect sizes. All studies are candidate gene-environment studies, which increases the likelihood of false positive results. Overall, studies varied between the potential for bias, confounding and representativeness of the study population (supplementary Tables 6–8). Within the studies based on cohorts, there was a lack of clarity on the adequacy of the follow-up of participants as well as on the independence of loss to follow-up by exposure group.

In the interaction analyses, most studies adjusted for at least age [24–41], gender or sex [24, 26–36, 38–41], smoking status [27, 29, 31–36, 38, 41], BMI [27, 31–37, 41], and educational attainment [31, 33, 34, 36–38, 41], whilst some further adjusted for hypertension or blood pressure [27, 33–35, 40], diabetes status or blood glucose [27, 31, 33, 34, 36, 41], alcohol use [27, 35, 36, 38], total cholesterol [27, 36], low-density lipoprotein cholesterol (LDL) [28, 36], high-density lipoprotein cholesterol (HDL) [36], triglycerides [28, 36], waist circumference [41], glomerular filtration rate (GFR) [41], C-reactive protein (CRP) [36], ethnicity [37], place of residence [38], betel nut chewing [25], fish consumption [38], obesity [40], renal disease history [24], skin lesions [32], serum folate [37], urinary cotinine levels [38], homocysteine [37], vitamin B2 [41], B6 [41] or B₁₂ [37], change in creatinine between visits [34], urinary lead levels [24], arsenobetaine [37, 38], (change in) urinary total arsenic [33, 37], *AS3MT* polymorphism [37, 41], and *SOD2* polymorphism [24].

Hypertension and blood pressure

The four studies exploring SNPs in arsenic-related hypertension or blood pressure, explored the following candidate genes: *APOE*, [31] *AS3MT*, [31] *CAT*, [28] *CBS*, [31] *CCM3*, [36] *CYBA*, [28, 31] *GSTM1*, [31] *GSTO1*, [31] *GSTP1*, [31] *GSTT1*, [31] *HMOX1*, [31] *ICAM1*, [31] *IL6*, [31] *MTHFR*, [31] *NOS3*, [28, 31] *OGG1*, [24] *PNP*, [31] *SIPR1*, [31] *SOD2*, [24, 28, 31] *TNF*, [31] and *VCAM1* [31]. See supplementary Table 5 for abbreviations, alleles and consequences, and Table 2 for individual study results). Compared to participants with low urinary arsenic exposure ($<8 \mu\text{g/g}$ creatinine) who were *SOD2* or *OGG1* reference allele homozygotes, those that were *SOD2* (rs4880-C) or *OGG1* (rs1052133-G) allele homozygotes or heterozygotes did not have a significantly higher odds of hypertension at low urinary arsenic levels. However, people with higher urinary arsenic levels ($\geq 8 \mu\text{g/g}$ creatinine) and the

reference *SOD2* [OR 3.1, 95%CI: 1.2–7.9] or *OGG1* homozygous alleles [OR 3.2, 95%CI: 1.4–7.4] had a significantly higher hypertension odds relative to the low urinary arsenic reference, which was even higher in participants who carried the *SOD2* (rs4880-C) [OR 4.2, 95%CI: 1.7–10.3, $p < 0.01$] or *OGG1* (rs1052133-G) [OR 3.4, 95 % CI: 1.1–10.7, $p < 0.05$] alleles [24]. Findings from Hsueh et al. 2007 on CAE further supported these results for the *SOD2* rs4880-C allele: hypertension odds for participants with high water CAE (≥ 10.5 mg/l-year) carrying the SNP was significantly higher (OR 9.0, 95 % CI: 2.3–35.0, $p < 0.05$) compared to *SOD2* reference allele homozygotes and low CAE (< 10.5 mg/l-yr), whilst the higher hypertension odds for participants with the reference alleles and high CAE was lower at OR 5.7 (95%CI: 1.6–20.9, $p < 0.05$). Furthermore, both *NOS3* and *CYBA* variants were suggested to play a role in susceptibility to arsenic-related hypertension, but not *CAT* (Table 2 for details) [28]. Evidence from the HEALS study on 235 SNPs in 18 genes [31] found that 44 SNPs interacted with water arsenic for one or more blood pressure outcomes, including SNPs in the aforementioned genes *SOD2* (analyses did not include rs4880 or another strong proxy for rs4880 [24, 28]), *NOS3* (of which one of the same SNPs as Hsueh et al. [rs1799983 [28]]) and *CYBA* (analyses did not include rs4673 or another strong proxy [28]) [31]. However, after FDR adjustment, the only variant that had a statistically significant interaction ($Q < 0.05$) with water arsenic and annual pulse pressure was *CYBA* (rs3794624-A) in recessive genetic models (β_{123} 2.10 mmHg, 95 % CI: 1.01–3.20) (Table 2) [31]. Finally, one study on variants in *CCM3* identified interactions between rs9818496, rs3804610 and rs6784267 and arsenic exposure with higher systolic blood pressure (Table 2) [36].

Diabetes mellitus type 2 and gestational diabetes mellitus

Studies on SNPs in arsenic-related T2DM included 128 unique candidate genes (supplementary Table 5) [32, 35, 38, 40, 41]. Two studies that solely focused on different SNPs in the key enzyme catalysing the transfer of methyl groups to arsenic, *AS3MT*, indicated that carriers of two SNPs (rs10748835, rs11191439) were more likely to develop arsenic-related DM (greater than additive with water arsenic ≥ 52 ppb and rs11191439-T alleles, approximately multiplicative with water arsenic ≥ 52 ppb and rs17881215-C alleles) compared to those carrying reference homozygous alleles [40], and that the association between iAs% and DMA% with HOMA2-IR varied depending on the *AS3MT* (rs12768205) genetic variant (Table 2) [41]. A follow-up of a cancer case-control study found statistically significant

interactions (after correction for multiple comparisons) between *CDC123* (rs1051055), *NOTCH2* (rs699780), and *TCF2* (rs2688) – and a nominally significant interaction in *THADA* (rs1549723) with arsenic-related T2DM when using piecewise linear regression in the interaction model [32]. However, when assessing the subset of participants exposed to water arsenic < 148 $\mu\text{g/L}$, only *NOTCH2* (rs699780) remained significant [32]. Interestingly, a non-monotonic dose-response association was found in participants with the *NOTCH2* rs699780-C heterozygous or homozygous alleles – whilst the dose-response association in the reference allele homozygotes was approximately linear [32]. Furthermore, a study on 354 SNPs found no significant interactions with total urinary arsenic and the included SNPs after correction for multiple testing. However, some nominally significant interactions were observed: *IL8RA* (rs1008563 [p-value 0.004], rs1008562 [p-value 0.01]), *TXN* (rs4135168 [p-value 0.004]), *NR3C2* (rs13117325 [p-value 0.007], rs2137335 [p-value 0.01]), *COX5A* (rs1133322 [p-value 0.01]) and *GCLC* (rs11415624 [p-value 0.01]) (Table 2) [38].

One cross-sectional study on the combined effects of *N6AMT1* and *AS3MT* SNPs and arsenic exposure on GDM odds found no statistically significant combined effects between *AS3MT* SNPs and arsenic metabolism markers [37]. Odds of GDM were greater among those carrying the *N6AMT1* rs1997605-G/ rs100367-G homozygous alleles and lower urinary iAs%, lower MMA% and greater DMA% compared to those carrying the reference homozygous and heterozygous alleles. However, additive statistically significant interactions were only found between *N6AMT1* rs1997605/rs1003671 risk genotypes and lower iAs% or higher DMA% (Table 2) [37].

Carotid atherosclerosis and carotid intima-media thickness

Four studies explored genetic susceptibility to arsenic in relation to carotid atherosclerosis [26, 27, 30] or CIMT [33] in genes encoding well-known proteins involved in arsenic metabolism (*AS3MT*, [27, 33] *PNP* [27, 33] and members of the glutathione S-transferase (GST) superfamily of enzymes [*GSTM1*, [30, 33] *GSTO1*, [27, 33] *GSTO2*, [27] *GSTP1*, [30, 33] *GSTT1*, [30, 33]]), oxidative stress (*HMOX1*, [33] *NOS3*, [33] *SOD2*, [33] *CYBA* [33]), or inflammation and endothelial function (*APOE*, [33] *TNF*, [33] *IL6*, [33] *ICAM1*, [33] *S1PR1*, [33] *VCAM1* [33]), as well as a tumour-suppressive gene *TP53* [30] (which may play a role in vascular apoptosis), and the combined effect of variants in *APOE* and *MCP-1* [26].

While none were statistically significant after adjusting for multiple testing, there were 9 SNPs in *APOE*, *AS3MT*, *PNP* and *TNF* that had a nominally statistically significant interaction with water arsenic in CIMT (Table 2), with joint presence of the risk genotype and arsenic exposure having a much greater difference in CIMT in comparison to the risk genotype or high arsenic exposure alone [33]. In genotype and haplotype analyses, participants with water arsenic exposure >50 µg/L had a significant or nominally significant interaction for carotid atherosclerosis risk with the *PNP* A-T haplotype (listed rs1049564, rs1130650) [OR 2.08; 95%CI, 1.32–3.30, P_{int} 0.006], the *AS3MT* rs11191439 genotypic variant (OR 2.63, 95%CI: 1.00–6.92, P_{int} 0.075), and the *GST* A-G-G haplotype (listed rs662, rs705379, rs7493) [OR 1.62; 95 % CI, 1.05–2.50, P_{int} 0.045] compared to a reference of arsenic exposure <50 µg/L and the reference haplotype/genotype [27]. Those who had both risk genotypes of *APOE* and *MCP-1* and had either high water arsenic exposure (>10 µg/L) or high cumulative arsenic exposure (>0.22 mg/L-year), likewise, had higher odds compared to participants who carried reference genotypes and had low arsenic exposure, with ORs of 10.3 (1.0–102.5) and 15.7 (1.7–141.2) respectively [26]. Further analyses indicate that participants with the *GSTP1* rs1695 or *TP53* rs1042522 exposed to water arsenic >50 µg/L had significantly higher odds of carotid atherosclerosis, with ORs of 6.0 (95%CI: 3.3–10.7) and 3.1 (95%CI: 1.7–5.7) [highly significant synergistic effect] respectively, compared to participants with the reference alleles and water arsenic ≤50 µg/L – whilst participants below ≤50 µg/L arsenic exposure had no significant difference in risk and those at >50 µg/L arsenic exposure with reference alleles had lower ORs of 2.7 (95%CI: 1.5–4.5) for *GSTP1* and 1.4 (95%CI: 0.7–3.0) for *TP53* respectively (Table 2) [30].

Metabolic syndrome

One study focused on metabolic syndrome and the *GSTO1* rs4925 SNP [25], which was the only study to explore SNP-arsenic-disease interactions utilising arsenic metabolism markers PMI, SMI, MMA% and DMA% (other studies only explored tAs or iAs). The study findings suggest that participants with lower PMI and the *GSTO1* rs4925-D homozygous plus heterozygous alleles had significantly higher odds of MetS (OR 4.00, 95%CI: 1.65–9.71, $p=0.002$) compared to those with higher PMI and reference homozygous alleles – with those exposed to lower PMI and carrying reference alleles

having lower MetS odds (OR 2.03, 95%CI: 1.03–4.01, $p=0.04$) [25]. Lower MMA%, and higher SMI or DMA% were also associated with MetS – with some suggestive evidence that the association may be modified by *GSTO1* genotype (Table 2) [25].

Obesity

One study focused on arsenic-related obesity and genetic variation in genes of the Endothelin (EDN) system (*EDN1*, *EDN2*, *EDN3*, *EDNRA*, *EDNRB*), selected as i) endothelin is able to regulate adiponectin levels (thus may impact obesity), and ii) EDN receptors have been reported as potential factors mediating arsenic-related adipocyte dysfunction [39]. Two SNPs in the *EDNRB* gene (rs3759475, rs5351) had lower odds of obesity in participants carrying the *EDNRB* variant alleles compared to the reference homozygous alleles at high blood arsenic levels (≥50 nmol/L), with ORs of 0.51 (95 % CI: 0.32–0.82) and 0.53 (95%CI: 0.33–0.85) for those carrying rs5351-A and rs3759475-C homozygous plus heterozygous alleles respectively [39]. However, the associations were not statistically significant at medium (20–50 nmol/L) or low (≤20 nmol/L) arsenic levels (Table 2) [39].

Cardiovascular disease and ECG abnormalities

The two studies with a focus on arsenic with CVD (including CHD, stroke) or ECG abnormalities (in line with MI or ischemia, conduction defect, arrhythmia, atrial enlargement or ventricular hypertrophy, prolonged ventricular repolarization) included the following candidate genes: *APOE*, [34] *AS3MT*, [29, 34] *CBS*, [34] *CYBA*, [34] *GSTM1*, [34] *GSTO1*, [29, 34] *GSTO2* [29] *GSTP1*, [34] *GSTT1*, [34] *HMOX1*, [34] *ICAM1*, [34] *IL6*, [34] *MTHFR*, [34] *NOS3*, [34] *PNP*, [34] *PON1*, [29] *PON2* [29], *S1PR1*, [34] *SOD2*, [34] *TNF*, [34] and *VCAM1*. [34] A constructed *PON* R-C-S haplotype [*PON1* (rs662), *PON1* (rs705379), *PON2* (rs7493)] had synergistic interaction effects with cumulative arsenic exposure and ECG abnormalities. Illustratively, those with the R-C-S haplotype and cumulative arsenic exposure >14.7 ppm-yr had a statistically significant ($p=0.014$) higher odds (OR 19.19, 95%CI: 1.86–197.76) when compared to those without the R-C-S haplotype exposed to ≤14.7 ppm-yr cumulative arsenic, whilst those with the R-C-S haplotype and ≤14.7 ppm-yr cumulative arsenic exposure and those without the haplotype and >14.7 ppm-yr

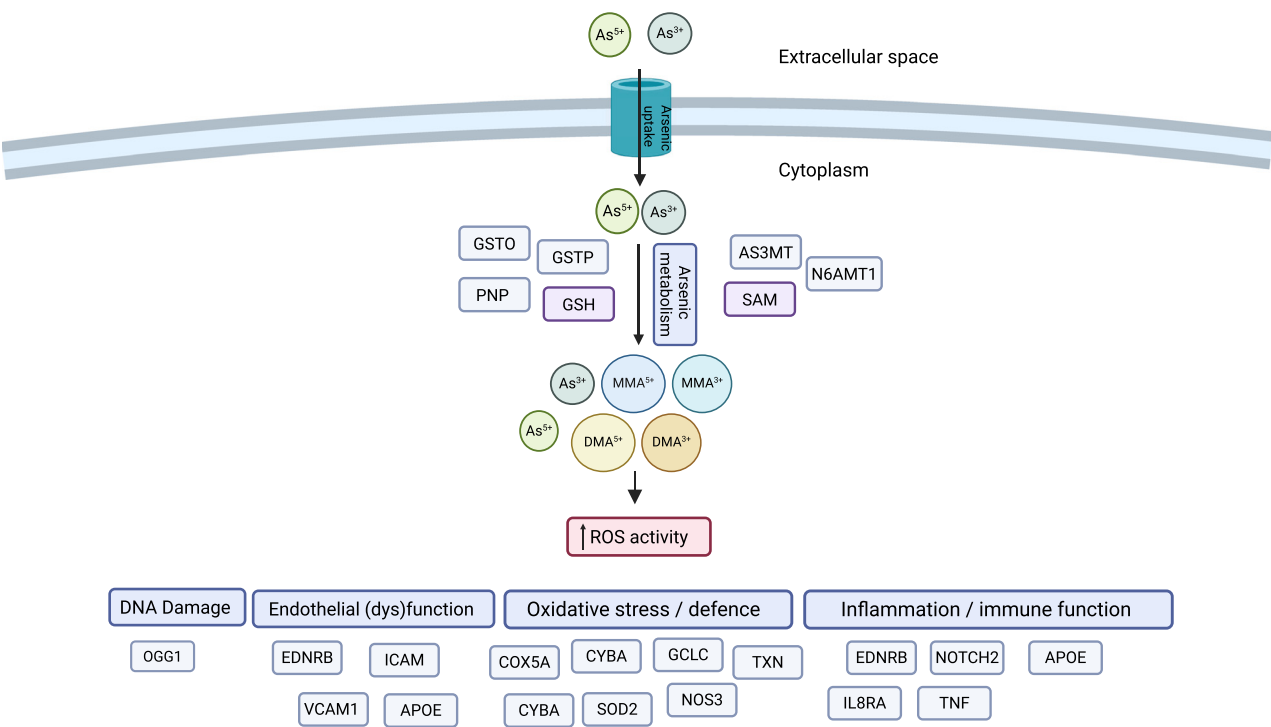


Figure 2: Genes and molecular pathways reported to interact with arsenic exposure to affect risk of arsenic-related adverse cardiometabolic outcomes. After ingestion, iAs (predominantly iAs^{5+} in drinking water) is absorbed in the gastro-intestinal tract and undergoes a series of reduction-oxidation and methylation steps to generate monomethylated arsenic (MMA) and, subsequently, dimethylated arsenic (DMA) species, whereby DMA^{5+} is the human biomethylation end-product. Biological mechanisms underlying adverse cardiometabolic outcomes have largely been hypothesised to be related to an increase in reactive oxygen species (ROS) activity. Different molecular pathways (arsenic metabolism, DNA damage, endothelial (dys)function, oxidative stress / defence, inflammation / immune function) are in dark blue and genes for which SNPs were identified to interact with arsenic exposure on risk adverse arsenic-related cardiometabolic outcomes are in light blue/grey (Table 3).

cumulative arsenic exposure did not have any statistically significant higher odds of ECG abnormality (OR 1.57, 95%CI: 0.19–13.00; and 4.27, 95%CI: 0.83–22.08 respectively) [29]. Furthermore, a case-cohort study nested in HEALS found only two (out of 170) SNPs had statistically significant multiplicative interactions for water arsenic related CVD. Participants with the *ICAM* (rs281432) and *VCAM1* (rs3176867) variant alleles and $\geq 45 \mu\text{g/L}$ water arsenic exposure had adjusted hazard ratios (aHRs) of 2.98 (95%CI: 1.87–4.77) and 2.13 (95%CI: 1.37–3.31) respectively compared with those carrying the reference *ICAM* and *VCAM1* alleles and $<45 \mu\text{g/L}$ water arsenic exposure. These aHRs were higher than participants with $\geq 45 \mu\text{g/L}$ not carrying the variants, who had aHRs of 1.67 (95%CI: 1.14–2.43) and 1.30 (95%CI: 0.83–2.05) for *ICAM* and *VCAM1* respectively (Table 2) [34].

Overall results

Table 3 summarises all the SNPs which were found to have statistically significant interactions with arsenic exposure in

relation to cardiometabolic outcomes. Other studies exploring the same SNP but reporting a non-significant result (for the same or a different cardiometabolic outcome), were also listed to provide appropriate context. For each gene (product) information is provided on the biological roles and processes the gene (product) is thought to be involved in (Figure 2, Table 3).

Discussion

To our knowledge, this is the first systematic review synthesising the evidence on genetic susceptibility to adverse arsenic-related cardiometabolic outcomes (i.e., genetic interactions with arsenic exposure). Across 676 SNPs in 148 genes assessed in 18 candidate gene studies, 40 SNPs in 24 genes, 4 haplotypes and combined SNPs in *MCP-1/APOE*, were indicative of SNP-arsenic interactions associated with adverse cardiometabolic outcomes. Polymorphisms that were reported to significantly interact with arsenic in relation to cardiometabolic outcomes or to result in higher/lower

susceptibility to arsenic, were predominantly affecting genes involved in arsenic metabolism (*AS3MT*, *GSTO1*, *GSTP1*, *N6AMT1*, *PNP*), oxidative stress or defence (*COX5A*, *CYBA*, *GCLC*, *NOS3*, *SOD2*, *TXN*), DNA damage repair (*OGG1*), endothelial (dys)function, inflammation or immune function (*APOE*, *EDNRB*, *NOTCH2*, *IL8RA*, *ICAM*, *MCP-1*, *TNF*, *VCAM1*), tumour suppressor activity (*TP53*), or have been previously implicated in influencing the cardiovascular related physiological response (*CCM3*), diabetes mellitus (*CDC123*, *COX5A*, *ILRA8*, *NR3C2*, *TCF2*), or atherosclerosis (*PON*, *TP53*). Importantly, most SNPs were only investigated in a single study and only one SNP (*SOD2* rs4880) had been tested for replication with the same cardiometabolic outcome (hypertension), albeit different arsenic exposure metrics (urinary arsenic [24], water CAE [28]). Overall, there is a lack of high-quality studies exploring the interactions between genetic variations and environmental arsenic exposure in relation to cardiometabolic diseases, as well as a shortage of replicated findings across existing studies.

In 2012 the first genome-wide association study (GWAS) on arsenic-related toxicity phenotypes was performed in the HEALS study [43], identifying two genetic variants in *AS3MT* (rs9527, rs11191527) that had independent associations with arsenic metabolism (appearing to impact DMA production [44]), of which one (rs9527) was also shown to interact with arsenic to influence incident skin lesion risk [43]. A more recent HEALS GWAS reported suggestive evidence for an additive interaction with arsenic for a protein-altering variant of forminotransferase cyclodeaminase [*FTCD*] (rs61735836) – a SNP located in a gene important for histidine catabolism which generates one-carbon units [9]. These studies provide evidence for the relevance of arsenic metabolism in arsenic toxicity phenotypes, as well as the involvement of the one-carbon/folate cycle in arsenic metabolism and toxicity [9, 43, 45]. However, the candidate genes studies identified in this review reported only nominally significant SNP-arsenic interactions for *AS3MT* (rs9527) and for SNPs in other genes involved in arsenic metabolism in relation to CVD and DBP (which did not remain significant after multiple comparisons adjustment) [31, 34], no significant arsenic-SNP interaction for *AS3MT* (rs11191527) with CVD [34], and did not include *FTCD* (rs61735836) in any study. Nevertheless, the current finding that multiple SNPs in *A3SMT* interact with arsenic exposure in relation to cardiometabolic outcomes [33, 40, 41], coupled with existing epidemiological and experimental evidence on the role of arsenic metabolism in disease progression [46, 47], suggests that genetic variants in the arsenic metabolism pathway likely modulate arsenic's effect on cardiometabolic disease. Involvement of the exact genetic variants influencing

arsenic metabolism need to be further confirmed in studies with substantially greater power to detect interaction effects relevant to cardiometabolic health.

Within this study, several genes related to oxidative stress have been proposed to be involved in the differential susceptibility to arsenic-related cardiometabolic disease. For example, in two studies *CYBA*, which encodes a subunit of the NADPH oxidase involved in ROS generation, was found to have a significant interaction with arsenic exposure in relation to hypertension and blood pressure [28, 31]. Interestingly, *in vitro* studies have indicated that NADPH oxidase activity and subcellular localisation can also be influenced by arsenic [48, 49]. Furthermore, two other studies identified potential interaction effects between *SOD2*, a superoxide dismutase, and arsenic in relation to hypertension [24, 28] – suggesting *SOD2* may limit mitochondrial defence capacity against ROS. Considering that arsenic is able to induce the generation of ROS, and ROS has been implicated in atherosclerosis and CVD development [50], it seems biologically plausible that genetic variants affecting oxidative stress may influence the effect of arsenic on cardiometabolic outcomes [34].

Importantly, all gene-arsenic studies identified, focused on candidate gene SNPs that were selected *a priori*, which should be evaluated with caution [51–53]. By selecting genes *a priori*, the roles of other (unknown) SNPs potentially relevant for arsenic susceptibility cannot be included. Notably, in well-powered GWAS analyses of complex phenotypes, robust, replicable, signals were often different from genes hypothesised to be related to an outcome in candidate gene studies [54–56]. Thus, candidate genes previously hypothesised to be implicated in a disease have often shown limited evidence for association in well-powered large GWAS. In absence of additional supporting evidence, this may suggest that candidate genes hypothesised to influence arsenic susceptibility in relation to cardiometabolic disease may not be “truly” associated with arsenic-related cardiometabolic disease [51, 52]. Furthermore, the gene-arsenic candidate gene studies described in this review are likely substantially underpowered to observe “true” associations of the small effect sizes in complex traits or diseases (candidate gene-environment studies [cGxE] studies often assume larger effect sizes than appropriate when basing the effect size on the environmental exposure of the effect) [52]. Whilst this may seem to be in contrast with the statistically significant findings reported in this review, candidate gene studies are simultaneously inherently prone to false positives as they focus on a small number of variants out of millions of possibilities. Given this low prior probability, strong statistical evidence is required – including the use of appropriate multiple testing thresholds and replication of

findings across different studies [51, 52, 57]. Yet, across the included studies there was a complete lack of replication of observed SNP-arsenic interactions for the same cardiometabolic outcome, and multiple testing adjustments were often only made for all SNPs included in the study instead of all plausible genetic variants. Studies that did explore the same SNP but on different outcomes or arsenic species did not consistently report results in the same direction. Thirdly, cGxE studies are often marred by statistical inaccuracies that most cGxE studies do not account for: i) transformations of the arsenic exposure scale can alter evidence of multiplicative interaction terms [51], ii) covariate-gene and covariate-arsenic terms are often not included in models, preventing the proper adjustment of the impact of covariates on interaction terms [51], and iii) multiple comparisons may make erroneous inferences more likely which needs to properly adjusted for [51], 52.

Limitations in the ascertainment of arsenic exposure can also influence uncertainty levels when assessing the arsenic-SNP interactions. For example; i) the use of environmental media may not accurately reflect “true” arsenic exposure due to the exclusion of other exposure routes, ii) studies using elemental analysis instead of speciation analysis may not accurately account for arsenic species considered non-toxic (e.g., arsenobetaine), iii) studies that measured arsenic at one time-point without taking into consideration changes in exposure may have an inaccurate perception of “true” chronic exposure, or iv) studies that measured arsenic at a community, county or state level or estimated arsenic based on a geographical location may not accurately reflect individual exposure. Such potential exposure misclassifications could result in the underestimation of the assessed associations if the misclassification was non-differential by the outcome of interest.

This systematic review has various limitations. First, the available evidence was limited in quality and replication, complicating robust information synthesis and preventing the performance of meta-synthesis. The lack of GWAS of SNP-arsenic interactions on cardiometabolic outcomes has prevented robust discovery. Secondly, most studies were conducted in Taiwan and Bangladesh. This may influence the generalisability of results across different study populations as different populations may have different genetic ancestry, and demographic histories including arsenic exposure. Likewise, the lack of ethnically diverse populations may risk missing genetic variations that increase arsenic tolerance. For example, some Andean populations that have been exposed to arsenic over the past 7000 years are reported to carry genetic variations that increase arsenic metabolism efficiency and reduce susceptibility [58, 59]. Thirdly, whilst this systematic

review was not able to formally assess the influence of publication bias, the presence of publication bias (i.e., lack of publication of negative or null results, including unpublished results in publications that were published) is likely increasing the number of false-positive gene-arsenic findings [51, 52]. Despite this, this systematic review has several strengths, including a broad definition of cardiometabolic outcomes, a detailed comprehensive search strategy to gather available evidence, and no restriction in terms of language or publication date.

Conclusions

There is a lack of high-quality studies examining the interplay between genetic variations and environmental arsenic exposure in relation to cardiometabolic diseases, along with a lack of replicated results across current research. Variants proposed to contribute to differential arsenic susceptibility were found in genes related to arsenic metabolism, oxidative stress and defense, endothelial function, DNA repair, tumor suppression, inflammation or immune response, or were previously linked to cardiometabolic diseases. Whilst the involvement of many of these pathways appear biologically plausible, further research in large prospective cohort studies that use genome wide GxE analyses and are conducted in ethnographically diverse cohorts, combined with *in vivo* and *in vitro* studies that identify or confirm the functional impacts of identified SNPs, are needed to further understand the interplay between arsenic and genotypic variants in relation to cardiometabolic disease. Furthermore, considering the polygenic nature of cardiometabolic outcomes and the low statistical power in single marker GWAS, further research should consider the use of genome-wide composite measures (polygenic scores [PGSs]) in GxE analyses. [60].

Research ethics: Not applicable.

Informed consent: Not applicable.

Author contributions: KRvD conceived the presented idea and developed the research protocol with support from AB and CW. KRvD conducted the literature searches with support from a medical librarian. KRvD conducted all title and abstract screening, full-text screening, data extraction, and quality assessment. JK, MJ and NK acted as second screeners, data extractors and quality assessors. KRvD drafted the initial manuscript, tables, and figures with support of all other co-authors. AB and CW provided critical feedback and guidance throughout the project. All authors reviewed the manuscript and contributed intellectually to the project.

Use of Large Language Models, AI and Machine Learning Tools: Not applicable.

Conflict of interest: The authors have no conflict of interest to declare.

Research funding: KRvD received funding from the Gates Cambridge Trust (OP114) for her PhD studies, and received funding for publication of this article from the Gates Foundation. KRvD is funded by the BHF Cambridge Centre for Research Excellence RE/24/130011. This work was supported by core funding from the British Heart Foundation (RG/18/13/33946: RG/F/23/110103), NIHR Cambridge Biomedical Research Centre (NIHR203312) [*], BHF Chair Award (CH/12/2/29428), and by Health Data Research UK, which is funded by the UK Medical Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Department of Health and Social Care (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation and the Wellcome Trust. *The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Data availability: All data is available in the publication and its supplement materials.

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- Supplementary Material:** This article contains supplementary material (<https://doi.org/10.1515/reveh-2025-0041>).