A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP577.

The Association of Arsenic Metabolism with Cancer, Cardiovascular Disease, and Diabetes: A Systematic Review of the Epidemiological Evidence

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Background: The available evidence on the role of arsenic metabolism in individual susceptibility to the development of cancer, cardiovascular disease, and diabetes has not been formally and comprehensively reviewed.

Objectives: Our goal was to systematically investigate the association of arsenic metabolism with cancer, cardiovascular disease, and diabetes-related outcomes in epidemiologic studies. As a secondary objective, we characterized the variation of arsenic metabolism in different populations worldwide.

Methods: We searched Medline/PubMed and EMBASE from inception to January 2016 and applied predetermined exclusion criteria. Compositional data analysis was used to describe the distribution of arsenic metabolism biomarkers and evaluate the association between arsenic exposure and metabolism.

Results: Twenty-eight studies met the inclusion criteria, 12 on cancer, nine on cardiovascular disease, and seven on diabetes-related outcomes. The median (interquartile range) for mean iAs%, MMA%, and DMA% was 11.2 (7.8–14.9)%, 13.0 (10.4–13.6)%, and 74.9 (69.8–80.0)%, respectively. Findings across studies suggested that higher arsenic exposure levels were associated with higher iAs% and lower DMA% and not associated with MMA%. For cancer, most studies found a pattern of higher MMA% and lower DMA% associated with higher risk of all-site, urothelial, lung, and skin cancers. For cardiovascular disease, higher MMA% was generally associated with higher risk of carotid atherosclerosis and clinical cardiovascular disease but not with hypertension. For diabetes-related outcomes, the pattern of lower MMA% and higher DMA% was associated with higher risk of metabolic syndrome and diabetes.

Conclusions: Population level of iAs% and DMA%, but not MMA%, were associated with arsenic exposure levels. Overall, study findings suggest that higher MMA% was associated with an increased risk of cancer and cardiovascular disease, while lower MMA% was associated with an increased risk of diabetes and metabolic syndrome. Additional population-based studies and experimental studies are needed to further evaluate and understand the role of arsenic exposure in arsenic metabolism and the role of arsenic metabolism in disease development. https://doi.org/10.1289/EHP577

Introduction

Inorganic arsenic in water and food is a top priority toxicant for risk assessment and exposure reduction/mitigation (ATSDR 2011; IPCS 2010) as chronic arsenic exposure affects multiple organ systems, resulting in various cancers and cardiovascular disease, and possibly also in respiratory disease, diabetes, neurocognitive outcomes, and kidney disease (Kuo et al. 2013; Moon et al. 2012; NRC 2001; Naujokas et al. 2013; Tyler and Allan 2014; Wu et al. 2014b). Understanding the health effects of arsenic requires assessing the role of interindividual variation in inorganic arsenic metabolism. After absorption, inorganic arsenic (iAs including arsenate and arsenite) is mainly methylated into monomethylated and dimethylated compounds (MMA, DMA) in the liver, which are then excreted through the kidney together with unmethylated inorganic arsenic (Vahter 2002). Whether the methylation process is to detoxify or potentiate arsenic toxicity, however, remains an ongoing debate and may depend on the study outcome (Rossman 2003; Styblo et al. 2000).

Arsenic metabolism in urine is generally reported as the percentage of each arsenic species divided by their sum (iAs%, MMA%, and DMA%) and/or as the primary and secondary methylation indices (PMI, the ratio of MMA over iAs; and SMI, the ratio of DMA over MMA) (Del Razo et al. 1997). The relative proportion of arsenic metabolites in urine has been reported to be around 10–30% inorganic arsenic, 10–20% MMA, and 60–80% DMA, with substantial interpopulation and intrapopulation variations (Hernandez and Marcos 2008; Huang et al. 2009; Steinmaus et al. 2005; Vahter 2000). Higher levels of MMA% and lower levels of DMA% have been related to cancer and cardiovascular outcomes in populations from Taiwan, Bangladesh, and Argentina (Chen et al. 2013b; Hsueh et al. 1997; Steinmaus et al. 2006; Tseng et al. 2005). Lower levels of MMA% and higher levels of DMA%, on the other hand, have been related to higher body mass index and diabetes-related outcomes in populations from Mexico, Taiwan, and the United States (Chen et al. 2012; Gomez-Rubio et al. 2011; Gribble et al. 2013).

The available evidence on the role of arsenic metabolism in individual susceptibility to the development of cancer, cardiovascular disease, and diabetes has not been formally and comprehensively reviewed. Our objective was to conduct a systematic review to examine the role of arsenic metabolism, as measured in urine, in the development of cancer, cardiovascular disease, and diabetes-related outcomes. We evaluated whether the methylation patterns associated with higher risk of disease are consistent across diseases and across populations with varying arsenic exposure levels. In a secondary analysis, we characterized the urine arsenic metabolism profile in populations around the world.

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Supplemental Material is available online (https://doi.org/10.1289/EHP577).

The authors declare they have no actual or potential competing financial interests.

Received 1 June 2016; Revised 26 February 2017; Accepted 27 February 2017; Published 1 August 2017.

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Methods

Search Strategy and Study Selection

The systematic search and review processes were conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al. 2000). We searched PubMed/Medline (https://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (https://www.embase.com/) for original epidemiologic studies investigating the role of arsenic metabolism in the risk of cancer, cardiovascular disease, and diabetes-related outcomes. For arsenic metabolism, we used the following MeSH terms and free text: "arsenic," "methylation," "metabolism," "arsenic metabolism," "arsenic methylation," combined with other specific text-word terms related to the key research concepts. The PubMed and EMBASE database search strategies in the supplementary material ["PubMed and EMBASE database search strategies for arsenic metabolism and outcomes of interest Medline/PubMed (Jan 25, 2016)" and "EMBASE (Jan 25, 2016)"] show the full search strategy, and Figure S1 shows the flow diagram of study identification, selection, and exclusion. The search period was January 1966 through January 2016. There were no language restrictions. We also manually reviewed the reference lists from relevant original research and the investigators' files.

Our primary exclusion criteria to screen records, after removing studies in nonhuman populations, were as follows: *a*) publications contained no original research (i.e., reviews, editorials, nonresearch letters); *b*) case reports and case series; *c*) studies did not measure cancer, cardiovascular outcomes (coronary heart disease, stroke, peripheral arterial disease, and hypertension), or diabetes and diabetes-related outcomes (including prediabetes and metabolic syndrome); and *d*) studies did not report information on arsenic metabolism, as measured by urine (percentage or ratios of urine arsenic species). After full text review, records were excluded if they met any of the following conditions: *a*) lacked report of the association between arsenic metabolism and the study outcome; *b*) focused only on arsenic-related skin lesions (premalignancy); *c*) were conducted among pregnant women (pregnancy may influence arsenic metabolism) (Hopenhayn et al. 2003), or *d*) were conducted among those less than 18 y of age (Su et al. 2012). Several studies that measured arsenic metabolism were excluded because they only reported the association for arsenic exposure with study outcomes stratified by arsenic metabolism levels, but not for arsenic metabolism per se (Engström et al. 2015; Leonardi et al. 2012; Tseng et al. 2005). For studies conducted in the same study population and with same outcome of interest [11 studies from the same population in Taipei (Chiang et al. 2014; Chung et al. 2008, 2010, 2011a, 2011b, 2013a, 2013b; Huang et al. 2016; Pu et al. 2007; Wu et al. 2013a; Wu et al. 2013b), 2 studies from the same population in Tainan (Chen et al. 2003a, 2005), and three studies in the endemic Blackfoot disease area (Hsu et al. 2015; Huang et al. 2008a, 2008b), all of above from Taiwan; four studies in Bangladesh (Chen et al. 2013a, 2013b; Wu et al. 2014a, 2015); two studies in Inner Mongolia (Li et al. 2013a, 2015)], we selected the publication with the largest sample size and with more complete information for the final statistical analysis (Chen et al. 2013b, 2003a; Huang et al. 2008a; Li et al. 2013a; Pu et al. 2007).

Data Abstraction

Two authors, C.-C.K. and K.A.M., independently abstracted data from articles that met the selection criteria. We used a standardized data extraction form to record the study characteristics (authors, journal, year of publication, country, study design, and study objectives); the participant characteristics [study population (general vs. hospital-based), number of participants, age, sex, and arsenic exposure levels as measured in urine or water]; measures of arsenic metabolism (iAs%, MMA%, DMA%, PMI, and SMI); outcome definitions; and the results of the association analysis, including the variables used for adjustment. To assess study quality, we adapted the criteria used by Longnecker et al. for observational studies (see Tables S1–S3) including the domains related to exposure assessment, outcome definition, and modeling approaches (Longecker et al. 1988). Disagreement between the two reviewers was resolved by consensus and discussion with a third reviewer if needed.

Statistical Methods

For mean age and sex distribution, mean arsenic concentrations in water or urine, and for each arsenic metabolism biomarker (iAs%, MMA%, DMA%, PMI, and SMI), we derived the numbers when not directly reported. For four studies included in the evaluation of metabolism distribution across populations that did not report arsenic concentrations in water or urine, the exposure level was imputed based on reported arsenic levels in water [50 μg/L in Argentina and in California/Nevada in the United States (Steinmaus et al. 2006), 100 μg/L in China (Li et al. 2013a), and 100 μg/L in Northern Chile (Melak et al. 2014)] assuming that arsenic levels in urine and water are positively associated (Murcott 2012). Throughout the study, the estimated arsenic exposure level (eAs, μg/L) was defined by derived arsenic concentrations in water (μg/L), urine (μg/L or μg/g creatinine), or previous biomonitoring data indicating arsenic concentrations in water (μg/L) relevant at the time of study recruitment. Most studies reported means of arsenic metabolism biomarkers in the population. For studies that did not, we calculated the means of each arsenic metabolism biomarker by dividing the mean concentrations of each arsenic species by the mean of total arsenic or the sum of inorganic and methylated arsenic. For three studies that provided medians of arsenic metabolism biomarkers among cases and noncases, we used the data from noncases to approximate the means of arsenic metabolism biomarkers (Gilbert-Diamond et al. 2013; Huang et al. 2008a; Lopez-Carrillo et al. 2014).

To describe arsenic metabolism across populations, we reported the median (interquartile range) of means in each study for each arsenic metabolism biomarker (iAs%, MMA%, and DMA%). The interpretation of these biomarkers is complicated because they are interdependent and their sum equals 100%. Higher MMA%, for example, could indicate either lower iAs% or lower DMA%. We used a three-axis diagram (triplot, or ternary plot) to represent the means of iAs%, MMA%, and DMA% across study populations. This inherent non-normality of the data makes the conventional linear regression modeling not feasible. We described the relationship between mean arsenic concentrations in urine (among studies without reported urine arsenic levels, concurrent measurements of arsenic levels in drinking water, or published arsenic biomonitoring data were used) and arsenic metabolism biomarkers (iAs%, MMA%, and DMA%) using the isometric log-ratio approach to compositional data analysis (van den Boogaart and Tolosana-Delgado 2013a). Essentially, we used log-ratio transformations of the arsenic metabolism components in order to apply standard multivariate regression techniques, and we estimated predicted values of each arsenic metabolism component by estimated arsenic exposure. A key principal of this method is scale invariance, meaning that only the relative, not absolute, magnitude of the components is important. Applying the log-ratio methodology with zero or missing values requires additional assumptions (van den Boogaart et al. 2015). For further information on compositional data analysis, including model

diagnostics and variable selection, we refer the reader to the available textbooks and reviews (Aitchison 1986; Lovell et al. 2015; Pawlowsky-Glahn et al. 2007; Pawlowsky-Glahn and Buccianti 2011; van den Boogaart and Tolosana-Delgado 2013a). All statistical analyses and graphical displays for compositional data analysis were performed using packages ggtern (extension of ggplot2 for the creation of tertiary diagrams; Nicholas Hamilton) and compositions: Compositional Data Analysis (version 1.30-1; K. G. van den Boogaart, Raimon Tolosana, Matevz Bren) in R (version 3.0.0; R Development Core Team).

To evaluate the association between arsenic metabolism biomarkers and health effects (cancer, cardiovascular disease and diabetes-related outcomes), we retrieved the relative risk estimates from the model adjusted for the most covariates. There were no large differences between the fully adjusted and crude models. To identify patterns across studies, we assessed the magnitude and direction of the association across studies without taking into account statistical significance but describing whether the individual studies were statistically significant or not. We did not perform a meta-analysis due to the small number of studies for most health endpoints evaluated and inconsistencies in the reporting format across studies.

Results

Arsenic Metabolism across Study Populations

Twenty-six studies met the inclusion criteria, including 12 on cancer, 10 on cardiovascular diseases, and 5 on diabetes-related outcomes. Twelve studies were conducted in Taiwan (Chen et al. 2012, 2003a, 2003b; Chung et al. 2009; Hsueh et al. 1997; Huang et al. 2007, 2008a; YL Huang et al. 2009; Pu et al. 2007; Wang et al. 2011; Wu et al. 2006; Yu et al. 2000), four in the United States (Gilbert-Diamond et al. 2013; Kuo et al. 2015; Moon et al. 2013; Steinmaus et al. 2006), three in Bangladesh (Chen et al. 2013a, 2013b; Nizam et al. 2013), three in Mexico (Del Razo et al. 2011; Lopez-Carrillo et al. 2014; Mendez et al. 2016), 2 in China (Li et al. 2013a, 2013b), two in Argentina (Steinmaus et al. 2006, 2010), and one in Chile (Melak et al. 2014). The medians (interquartile range) for mean iAs%, MMA %, and DMA% of the 14 unique populations included were 9.4 (7.4–10.2)%, 12.9 (10.1–13.3)%, and 77.3 (71.3–80.1)%, respectively. The compositional means for iAs%, MMA%, and DMA% were 9.4%, 12.3%, and 78.4%, respectively. The distribution and variability of arsenic metabolism across study populations are summarized in Figure 1 and Figure 2, upper panel. Compared with iAs% and DMA%, MMA% showed lower interpopulation variance, with population means ranging from 9.4% in Faridpur, Bangladesh (Nizam et al. 2013) to 14.6% in Cordoba, Argentina (Steinmaus et al. 2006) (Figure 2, upper and middle panel). In an analysis of the relationship between arsenic exposure levels and arsenic metabolism biomarkers, a 2-fold increase in the estimated urine arsenic concentrations was associated with a 0.8% [95% confidence interval (CI): -0.2, 1.9] increase in iAs%, no association with MMA% (0.1% increase, 95% CI: -0.5, 0.8), and a 1.3% (95% CI: -3.0, 0.5) decrease in DMA%. In compositional data analysis, we confirmed a similar relationship between arsenic exposure levels and arsenic metabolism indicators at the population level (Figure 2, bottom panel). We conducted sensitivity analyses removing studies with urine arsenic concentrations estimated from imputed water arsenic levels (Li et al. 2013a; Melak et al. 2014; Steinmaus et al. 2006), with similar results: a 2-fold increase in the estimated urine arsenic concentrations was associated with a 0.9% (95% CI: -0.1, 1.9) increase in iAs%, no association with MMA% (0.1% increase, 95% CI: -0.6, 0.8), and a 1.2% (95% CI: -3.0, 0.6) decrease in DMA% (also see Figure S2).

Study Design and Quality Assessment

By study design, seven studies were cross-sectional, 12 were case–control, and seven were prospective cohorts. The studies showed marked heterogeneity in reporting and modeling biomarkers of arsenic metabolism (see Tables S2–S4). Among case–control studies, most of them did not describe the timing of interview, response rate among noncases, and case–control selection, criteria commonly used to address potential surveillance, selection, and recall bias. Prospective studies, on the other hand, generally met important quality criteria, although associations between arsenic metabolism and health outcomes were not adjusted for total arsenic exposure in three studies (Chung et al. 2009; Hsueh et al. 1997; Wang et al. 2011).

Arsenic Metabolism and Cancer

Of the 12 studies on arsenic metabolism and cancer, 2 were prospective cohort studies (Chung et al. 2009; Huang et al. 2008a) and 10 were case–control studies (Table 1). Seven studies were conducted in Taiwan, six in the Blackfoot disease endemic area (arsenic in drinking water $\geq 100\,\mu g/L$) (Chen et al. 2003a, 2003b; Chung et al. 2009; Hsueh et al. 1997; Huang et al. 2008a; Yu et al. 2000), and one in Taipei City/County (arsenic in drinking water $<100\,\mu g/L$) (Pu et al. 2007). Outside of Taiwan, the studies were conducted in populations from Argentina (Steinmaus et al. 2006, 2010), Chile (Melak et al. 2014), the United States (Gilbert-Diamond et al. 2013; Steinmaus et al. 2006), and Eastern Europe (Leonardi et al. 2012). Study populations from Argentina and Chile were exposed to arsenic levels in drinking water $\geq 100\,\mu g/L$ (Melak et al. 2014; Steinmaus et al. 2006). The U.S. study populations from California and Nevada were exposed to arsenic levels $>50\,\mu g/L$ (Steinmaus et al. 2006), and the study population from New Hampshire was exposed to arsenic levels in drinking water $<100\,\mu g/L$ (Gilbert-Diamond et al. 2013). Five studies evaluated urothelial cancers (Chen et al. 2003b; Huang et al. 2008a; Melak et al. 2014; Pu et al. 2007; Steinmaus et al. 2006), four evaluated skin cancer (Chen et al. 2003a; Gilbert-Diamond et al. 2013; Hsueh et al. 1997; Yu et al. 2000), two evaluated lung cancer (Melak et al. 2014; Steinmaus et al. 2010), one evaluated breast cancer (Lopez-Carrillo et al. 2014), and one evaluated all-cancer incidence (Chung et al. 2009) (Table 1). All studies confirmed incident cancer outcomes using pathological and medical information but did not provide analyses by histological subtypes (Table 1). Arsenic metabolism was defined based on the percentages of arsenic metabolites (iAs %, MMA%, and DMA%) in four studies (Hsueh et al. 1997; Melak et al. 2014; Steinmaus et al. 2006; Steinmaus et al. 2010), based on the methylation indices (PMI and SMI) in one study (Chen et al. 2003b), and based on both the arsenic species proportions and the methylation indices in seven studies (Chen et al. 2003a; Chung et al. 2009; Gilbert-Diamond et al. 2013; Huang et al. 2008a; Lopez-Carrillo et al. 2014; Pu et al. 2007; Yu et al. 2000) (Table 1).

Urothelial cancer. Of five studies on urothelial cancer (Chen et al. 2003b; Huang et al. 2008a; Melak et al. 2014; Pu et al. 2007; Steinmaus et al. 2006), four reported a positive association with MMA% (Huang et al. 2008a; Melak et al. 2014; Pu et al. 2007; Steinmaus et al. 2006), three with iAs% and DMA% (Huang et al. 2008a; Melak et al. 2014; Pu et al. 2007), and three with PMI and SMI (Chen et al. 2003b; Huang et al. 2008a; Pu et al. 2007). For MMA%, the direction of the estimated relative risks for urothelial cancer comparing the highest to lowest

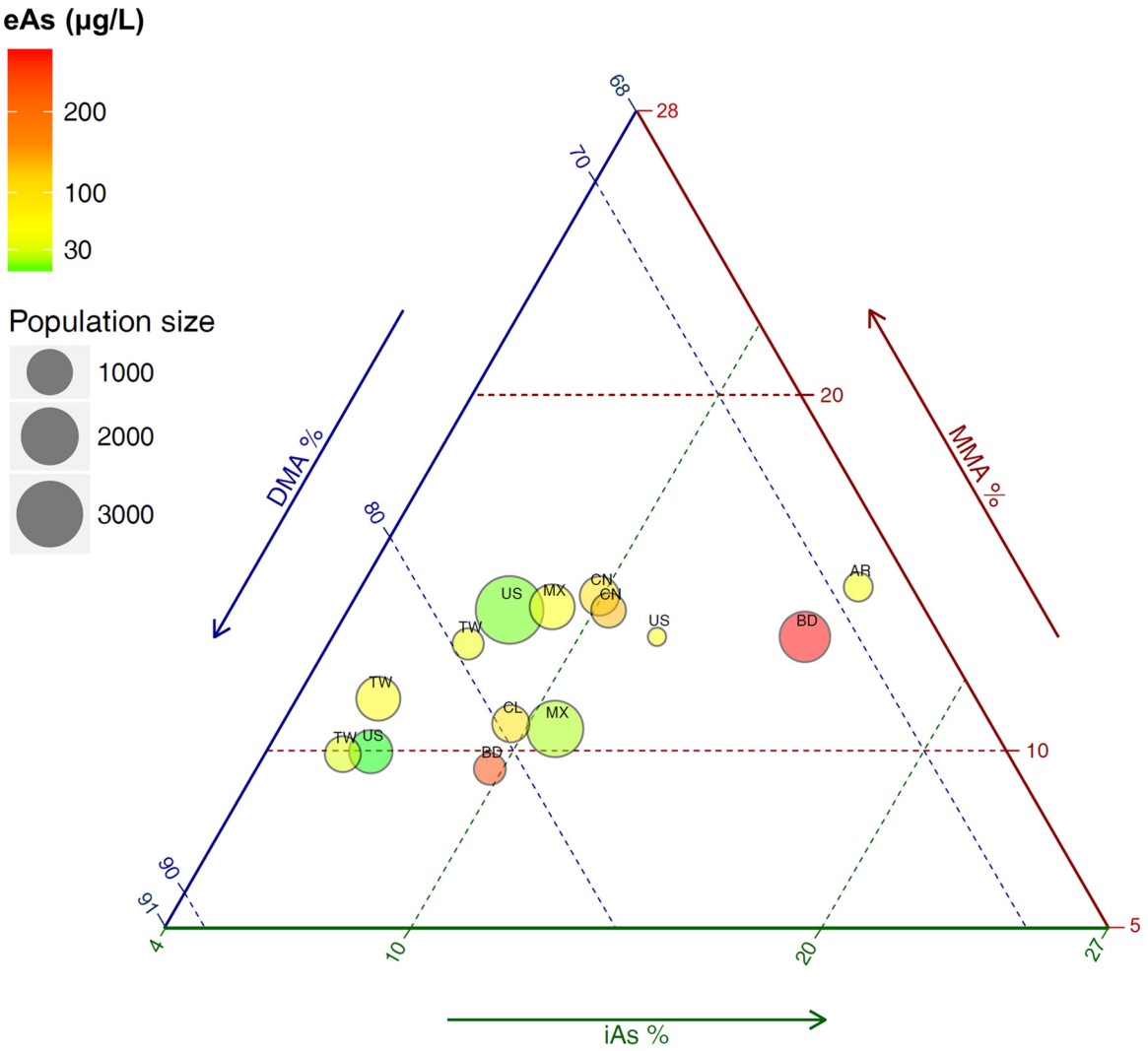

Figure 1. The distribution of urine arsenic metabolism profile across enrolled populations worldwide on ternery plot diagram. Three-axis graph (triplot) representing the compositional mean of arsenic metabolism biomarkers (iAs%, MMA%, and DMA%) in different study populations. The circles represent each study population and the country of the study is indicated with an acronym (AR, Argentina; BD, Bangladesh; CL, Chile; CN, China; MX, Mexico; TW, Taiwan; US, USA). The size of the circle corresponds to the study population size. The color of the circles reflects the estimated urine arsenic concentrations (eAs, µg/L) as indicated in the top left legend (the highest two countries: BD and CN; while the lowest two: US and MX. For exact ranking of eAs, please refer to the top panel of Figure 2). The bottom side of the triplot represents iAs%, the right side represents MMA%, and the left side represents DMA%. For each population, the mean iAs%, MMA%, and DMA% can be estimated along parallel lines to the dashed green lines for iAs%, dashed red lines for MMA% and dashed blue lines for DMA%. For instance for the study from Chile (CL), the arsenic metabolism profile was 9.6% for iAs%, 10.8% for MMA% and 79.6% for DMA%. In this graph, we can observe that population means ranged between 5.9% and 16.1% for iAs%, between 9.4 and 14.6% for MMA%, and between 69.3% and 84.2% for DMA%.

category of MMA% was consistent for all studies (relative risks (RR) range from 1.2 to 2.8), although only one study association was statistically significant (Table 1 and Figure 3) (Pu et al. 2007). For SMI, the corresponding estimated relative risks were also consistent across studies (RR from 0.3 to 0.6), although only one study association was statistically significant (Pu et al. 2007). The corresponding estimated relative risks for iAs%, DMA% and PMI were inconsistent across studies and ranged from 0.3 to 1.4 for iAs%, from 0.3 to 1.7 for DMA%, and from 0.5 to 3.1 for PMI (Table 1).

Lung cancer. Of the two studies on lung cancer (Melak et al. 2014; Steinmaus et al. 2010), both reported an association with MMA% (Melak et al. 2014; Steinmaus et al. 2010), and one also reported associations with iAs% and DMA% (Melak et al. 2014). No studies of lung cancer reported associations with PMI and SMI. For MMA%, the estimated relative risks comparing the highest to lowest category of MMA% were 2.3 and 3.1, both of them statistically significant (Table 1).

Skin cancer. Of the four studies on skin cancer [three nonmelanoma skin cancer (Chen et al. 2003a; Hsueh et al. 1997; Yu et al. 2000), one squamous cell carcinoma (Gilbert-Diamond et al. 2013)], four reported on the association with MMA% (Chen et al. 2003a; Gilbert-Diamond et al. 2013; Hsueh et al. 1997; Yu et al. 2000), two with iAs% (Gilbert-Diamond et al. 2013; Yu et al. 2000), three with DMA% (Chen et al. 2003a; Gilbert-Diamond et al. 2013; Yu et al. 2000), two with PMI (Chen et al. 2003a; Gilbert-Diamond et al. 2013), and three with SMI (Chen et al. 2003a; Gilbert-Diamond et al. 2013; Yu et al. 2000). For MMA%, the estimated relative risks for skin cancer comparing the highest to lowest category of MMA% were consistent for all studies (RR range from 1.4 to 5.5), although only one study association was statistically significant (Yu

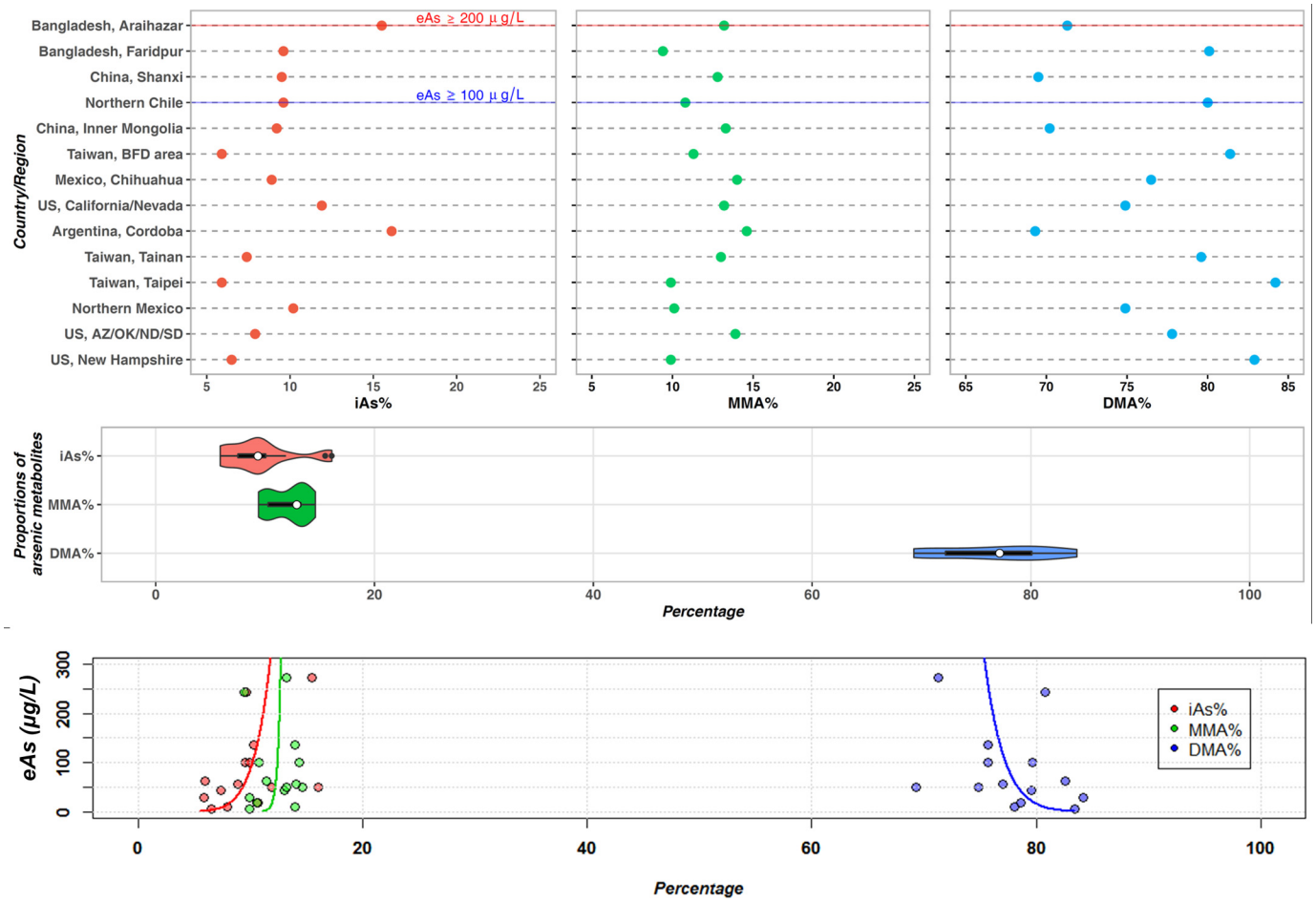

Figure 2. Variability of arsenic metabolism biomarkers in the study populations. Top panel: The distribution of each arsenic metabolism biomarker (iAs%, MMA%, DMA%) is plotted for each study listed in increasing order (from bottom to top) of the estimated urine arsenic levels in (eAs, μg/L) in the study area. Middle panel, violin plot showing the median (open circle) with interquartile range (horizontal bar) and the kernel probability density for each arsenic metabolism biomarker (iAs%, MMA%, DMA%) across all studies. Bottom panel, the prediction curve (line) (right for iAs%, central for MMA%, and left for DMA%) derived from the compositional regression of each arsenic metabolism biomarker based on estimated urine arsenic levels (eAs, μg/L). The right increasing curve supports that iAs% increases as eAs increases and the left decreasing curve supports that DMA% decreases as eAs increases. The central curve supports that MMA% does not change with changes in eAs concentrations as the line is vertical.

et al. 2000). For iAs%, one study reported a null association and another showed a positive nonsignificant association (Table 1). For DMA%, one study found a positive significant association (RR of 3.25 (Yu et al. 2000)) and the others found inverse but nonstatistically significant associations (Chen et al. 2003a; Gilbert-Diamond et al. 2013). For PMI, both studies showed positive but nonsignificant associations (Chen et al. 2003a; Gilbert-Diamond et al. 2013). For SMI, one study was nonsignificantly positive (Yu et al. 2000), one study was inverse but nonsignificant (Chen et al. 2003a), and the other was null (Gilbert-Diamond et al. 2013).

Arsenic Metabolism and Cardiovascular Disease

From 10 studies reporting cardiovascular outcomes, five were conducted in Taiwan (Huang et al. 2007; YL Huang et al. 2009; Wang et al. 2011; Wu et al. 2006), 2 in Bangladesh (Chen et al. 2013a, 2013b), two in China (Li et al. 2013a, 2013b), one in the United States (Moon et al. 2013), and 1 in Mexico (Mendez et al. 2016). All study populations were characterized by high arsenic exposure (>100 μg/L in drinking water), except the study from the United States (Moon et al. 2013). Three were prospective cohort studies (Chen et al. 2013b; Moon et al. 2013; Wang et al. 2011), one was a nested case–control study (Wu et al. 2006), and six were cross-sectional studies (Chen et al. 2013a; Huang et al. 2007; YL Huang et al. 2009; Li et al. 2013a, 2013b; Mendez et al. 2016). Study outcomes included hypertension ($n=5$) (Huang et al. 2007; Li et al. 2013a, 2013b; Mendez et al. 2016; Wang et al. 2011), carotid atherosclerosis ($n=3$) (Chen et al. 2013a; YL Huang et al. 2009; Wu et al. 2006), and overall cardiovascular disease ($n=2$) (Chen et al. 2013b; Moon et al. 2013). Five studies reported results for percentages of each metabolite (iAs%, MMA%, and DMA%) (Li et al. 2013a, 2013b; Moon et al. 2013; Wang et al. 2011; Wu et al. 2006), whereas the other five studies reported both percentages of each metabolite and methylation indices (PMI and SMI) (Table 2) (Chen et al. 2013a, 2013b; Huang et al. 2007; YL Huang et al. 2009; Mendez et al. 2016).

Cardiovascular disease incidence and mortality. Clinical cardiovascular disease was defined as the occurrence of fatal and nonfatal stroke, coronary heart disease, heart failure, or other heart disease during the follow-up (Chen et al. 2013b; Moon et al. 2013). Two prospective cohort studies, one from Bangladesh and one from the United States, investigated the association between arsenic metabolism and incident cardiovascular disease based on MMA% (Table 2) (Chen et al. 2013b; Moon et al. 2013). The U.S. cohort (Moon et al. 2013) also investigated the association of arsenic metabolism with cardiovascular

Table 1. Studies of arsenic metabolism and cancer.

Reference	Study design (case/noncase)	Men (%) Age range Source	Outcome (Ascertainment method)	Arsenic exposure						Adjustment factors
				Sample (level)	iAs%	MMA%	DMA%	PMI	SMI	
Chung et al. 2009	CO 17/191	Putai, Taiwan 36% Mean 46 y General	All cancer (registry)	Urine (mean total arsenic 78 μg/L)	7.5 ± 7.5 ≥5.9 vs. <5.9 0.6 (0.2, 1.7)	13.0 ± 8.9 ≥10.8 vs. <10.8 2.4 (0.8, 9.1)	79.5 ± 12.7 ≥82.4 vs <82.4 0.9 (0.3, 2.7)	NR	9.4 ± 8.4 ≥7.4 vs. <7.4 0.4 (0.1, 1.4)	Age, sex, education
Chen et al. 2003b	CC 49/224	Tainan, Taiwan 63% >40 y Hospital	Urothelial (pathology)	Water (mean CAE 8.5 mg/L-y)	NR	NR	NR	4.8 >2.7 vs. ≤0.9 0.5 (0.2, 1.4)	10.9 >9.4 vs. ≤4.8 0.6 (0.3, 1.5)	Age, sex, education, smoking, BMI, hair dye, CAE
Steinmaus et al. 2006	CC 114/114	Córdoba, Argentina 82% 20-80 yrs General	Urothelial (pathology)	Water (low-moderate)	16.1 ± 10.0 NR	14.6 ± 9.7 ≥16.7 vs. <16.7 1.3 (0.7, 2.4)	69.3 ± 16.3 NR	NR	NR	Age, sex, smoking, bombilla use
	23/49	California and Nevada, USA 80% 40-85 y General	Urothelial carcinoma (registry)	Water (low-moderate)	11.9 ± 4.9 NR	13.2 ± 4.1 ≥14.9 vs. <14.9 1.2 (0.4-3.7)	74.9 ± 6.9 NR			Age, sex, smoking
Pu et al. 2007	CC 177/313	Taipei, Taiwan 66% 24-93 y Hospital	Urothelial (pathology)	Urine (mean sum iAs, MMA, and DMA 30 μg/g creatinine)	5.9 ± 6.9 >5.2 vs. ≤2.4 1.2 (0.7, 2.0) *p*-trend = 0.7	9.9 ± 10.1 >9.2 vs. ≤3.0 2.8 (1.6, 4.8) *p*-trend <0.0001	84.2 ± 12.6 >92.5 vs. ≤85.0 0.4 (0.2, 0.7) *p*-trend = 0.004	3.3 ± 11.3 >2.0 vs. ≤0.3 3.1 (1.7, 5.6) *p*-trend <0.001	12.9 ± 29.7 >12.7 vs. ≤4.8 0.3 (0.2, 0.6) *p*-trend = 0.001	Age, sex, education, alcohol, paternal and maternal ethnicity, pesticide usage
Huang et al. 2008a	CO 37/928	Putai, Taiwan 43% >30 y General	Urothelial (registry and pathology)	Urine (median sum iAs, MMA, and DMA 64 μg/L)	5.9 ± median ≥8.0 vs. <4.3 1.4 (0.5, 3.6) *p*-trend >0.05	11.3 ± median ≥15.6 vs. <8.4 1.7 (0.7, 4.0) *p*-trend >0.05	81.4 ± median ≥85.7 vs. <76.0 0.3 (0.1, 0.9) *p*-trend <0.05	1.9 ± median ≥2.8 vs. <1.3 0.8 (0.4, 2.0) *p*-trend >0.05	7.0 ± median ≥9.8 vs. <4.8 0.5 (0.2, 1.3) *p*-trend >0.05	Age, sex, education, smoking, CAE
Melak et al. 2014	CC Lung: 94/347; uro-thelial: 117/347	Northern Chile 69% >25 y Hospital	Urothelial (medical records) Lung (medical records)	Water (lifetime average arsenic 109 μg/L)	9.6 ± 6.3 ≥10.8 vs. <10.8 Urothelial 0.3 (0.2, 0.5) Lung 1.1 (0.7, 1.8)	10.8 ± 4.8 ≥12.5 vs. <12.5 Urothelial 1.4 (0.9, 2.2) Lung 2.3 (1.4, 3.8)	80.0 ± 8.3 ≥83.9 vs. <83.9 Urothelial 1.7 (1.1, 2.6) Lung 0.6 (0.4, 1.1)	NR	NR	Age, sex, smoking
Steinmaus et al. 2010	CC 45/75	Córdoba, Argentina 88% 20-80 y Hospital	Lung (medical records)	Water (low-moderate)	15.7 ± 5.5 NR	15.5 ± 6.7 ≥17.2 vs. <11.8 3.1 (1.1, 8.1) *p*-trend = 0.04	68.7 ± 9.6 NR	NR	NR	Age, sex, smoking, drinking-water arsenic exposure
Hsueh et al. 1997	CC 16/61	Putai, Taiwan 42% >30 y General	Non-melanoma skin (pathology)	Water (artesian well 700–930 μg/L)	10.7 ± 6.2 NR	24.6 ± 11.2 Among CAE ≤20 mg/L-y, ≤26.7 vs. >26.7%:3.0 (0.3-27.8)	64.7 ± 13.3 NR	3.3 ± 2.3 NR	3.6 ± 4.6 NR	Age, sex, β-carotene
Yu et al. 2000	CC 26/26	Putai, Taiwan 54% Mean 63 y Hospital	Non-melanoma skin[a] (dermatologist diagnosis)	Urine (mean sum iAs, MMA, and DMA 56 μg/L)	12.3 >2.3 vs ≤2.3 3.5 (0.7, 16.9)	15.5 >15.5 vs ≤15.5 5.5 (1.224.8)	72.2 <72.2 vs ≥72.2[b] 3.25 (1.1, 10.0)	NR	4.6 <4.5 vs. ≥4.5 3.3 (0.9, 12.1)[c]	Age, sex
Chen et al. 2003a	CC 76/224	Tainan, Taiwan 60% >30 y Hospital	Non-melanoma skin (pathology)	Urine (mean sum iAs, MMA, and DMA 44 μg/L)	7.4 ± 6.6 NR	13.0 ± 10.9 Highest vs. lowest tertile 1.4 (0.6, 3.4) *p*-trend >0.05	79.6 ± 16.3 Highest vs. lowest tertile 0.8 (0.3, 1.9) *p*-trend >0.05	4.3 ± 8.8 >3 vs. ≤1 1.3 (0.6, 2.9) *p*-trend >0.05	10.7 ± 11.5 >9.4 vs. ≤5 0.9 (0.4, 2.1) *p*-trend >0.05	Age, sex, education, smoking, alcohol, body mass index, sun exposure, CAE
Gilbert-Diamond et al. 2013	CC 323/319	New Hampshire, USA 59% 25–74 y General	Squamous cell (pathology and medical records)	Urine (median sum iAs, MMA, and DMA 5.3 μg/L)	~6.3 ± median per 1% increase 1.00 (0.97, 1.04)	~9.5 ± median per 1% increase 1.01 (0.97, 1.05)	~78.4 ± median per 1% increase- 0.99 (0.97, 1.02)	~1.5 ± median per 1% increase 1.08 (0.95, 1.23)	~8.3 ± median per 1% increase 1.00 (0.97, 1.03)	Age, sex, education, smoking, BMI, urine creatinine, skin reaction to sun exposure, water arsenic

(Continued)

Table 1. Continued

Reference	Study design (case/noncase)	Men (%)	Age range	Source	Outcome (Ascertainment method)	Arsenic exposure: Sample (level)	iAs%	MMA%	DMA%	PMI	SMI	Adjustment factors
López-Carrillo et al. 2014	CC 1,016/1,028	Northern Mexico		Breast cancer (pathology)		Urine (geometric mean iAs conc. 18.4 μg/g creatinine)	10.2 ± median	9.8 ± median	79.7 ± median	1.00 ± median	8.00 ± median	Total inorganic arsenic, age, BMI, total breastfeeding, alcohol, smoking, age at first pregnancy, creatinine
		0%	Mean 54 y				>14.90 vs. ≤6.55 0.90 (0.65, 1.24)	>13.3 vs. ≤7.01 2.63 (1.89, 3.66)	>84.96 vs. ≤72.37 0.63 (0.45, 0.87)	>1.48 vs. ≤0.65 1.90 (1.39, 2.59)	>11.73 vs. ≤5.55 0.42 (0.31, 0.59)	

Note: Values shown as mean±SD, highest vs. lowest category, and eRR (95% CI), unless otherwise specified. BMI, body mass index, Ca, cancer; CAE, cumulative arsenic exposure; CC, case–control study; CI, confidence interval; CO, prospective cohort study; DMA, dimethylarsinate; eRR, estimated relative risk; iAs, inorganic arsenic; MMA, monomethylarsonate; NR, not reported; NS, not significant; PMI, primary methylation index (MMA/iAs); SD, standard deviation; SMI, secondary methylation index (DMA/MMA).

[a]Skin cancer refers to non-melanoma skin cancer.

[b]Lowest vs. highest categories.

[c]Association for the DMA/MMA, rather than MMA/DMA.

disease mortality. The Bangladesh cohort also reported iAs%, DMA%, PMI, and SMI. Higher MMA% and lower SMI were associated with higher risk of incident cardiovascular disease in Bangladesh, whereas the association for iAs%, DMA%, and PMI were around the null and nonsignificant (Chen et al. 2013b). In the U.S. cohort, lower iAs% was associated with increased risk of clinical cardiovascular incidence and mortality (Moon et al. 2013).

Carotid atherosclerosis. The evaluation of carotid atherosclerosis was based on extracranial carotid Doppler ultrasound (Chen et al. 2013a; YL Huang et al. 2009; Wu et al. 2006). Of the three studies on carotid atherosclerosis, one was prospective (Wu et al. 2006) and two were cross-sectional. All reported the association with MMA% (Chen et al. 2013a; YL Huang et al. 2009; Wu et al. 2006), two with iAs% and DMA% (Chen et al. 2013a; YL Huang et al. 2009), and two with PMI and SMI (Chen et al. 2013a; YL Huang et al. 2009) (Table 2). Two studies found higher levels of carotid intima-media with higher MMA%, although only one was statistically significant (Chen et al. 2013a; YL Huang et al. 2009). For iAs%, the two studies showed inconsistent results (Chen et al. 2013a; YL Huang et al. 2009). For DMA%, the results were consistently but nonsignificantly inverse for higher DMA% and reduced risk of carotid atherosclerosis (Chen et al. 2013a; YL Huang et al. 2009). For PMI and SMI, the findings were consistently null for both studies.

Hypertension. All studies on hypertension followed the World Health Organization standard protocol to measure blood pressure and define hypertension (Huang et al. 2007; Li et al. 2013a, 2013b; Mendez et al. 2016; Wang et al. 2011). Four studies were cross-sectional and one was a prospective cohort study (Wang et al. 2011). All reported the association with iAs%, MMA%, and DMA%, and two also reported on the association with PMI and SMI (Huang et al. 2007; Mendez et al. 2016). The association between MMA% and hypertension was inconsistent across studies, with studies finding positive (Li et al. 2013a), inverse (Mendez et al. 2016; Wang et al. 2011) and null associations (Huang et al. 2007; Li et al. 2013b), none of them statistically significant. The associations with iAs% and DMA% were also inconsistent (Table 2 and Figure 3).

Arsenic Metabolism and Diabetes-Related Outcomes

Five studies evaluated the associations of arsenic metabolism with diabetes-related outcomes (Chen et al. 2012; Del Razo et al. 2011; Kuo et al. 2015; Mendez et al. 2016; Nizam et al. 2013). All studies were published after 2011. Three studies were cross-sectional (Chen et al. 2012; Del Razo et al. 2011; Mendez et al. 2016), one was case–control (Nizam et al. 2013), and one was a prospective cohort (Kuo et al. 2015). The studies were conducted in populations from Taiwan (Chen et al. 2012), Bangladesh (Nizam et al. 2013), Mexico (Del Razo et al. 2011; Mendez et al. 2016), and the United States (Kuo et al. 2015). Most populations were exposed to high arsenic levels (>100 μg/L in drinking water) except in a study from the United States (Kuo et al. 2015). The study outcomes included diabetes ($n=4$) (Del Razo et al. 2011; Kuo et al. 2015; Mendez et al. 2016; Nizam et al. 2013) and metabolic syndrome ($n=1$) (Chen et al. 2012). The definitions of diabetes were consistent across studies using information on glycemia together with self-reported physician diagnosis or medication history (Del Razo et al. 2011; Kuo et al. 2015; Mendez et al. 2016; Nizam et al. 2013). Of the five studies, four reported the association with MMA%, iAs%, DMA% (Chen et al. 2012; Kuo et al. 2015; Mendez et al. 2016; Nizam et al. 2013), and four on the PMI and SMI (Chen et al. 2012; Del Razo et al. 2011; Mendez et al. 2016; Nizam et al. 2013). Four studies found that lower levels of MMA% and higher levels of DMA% were

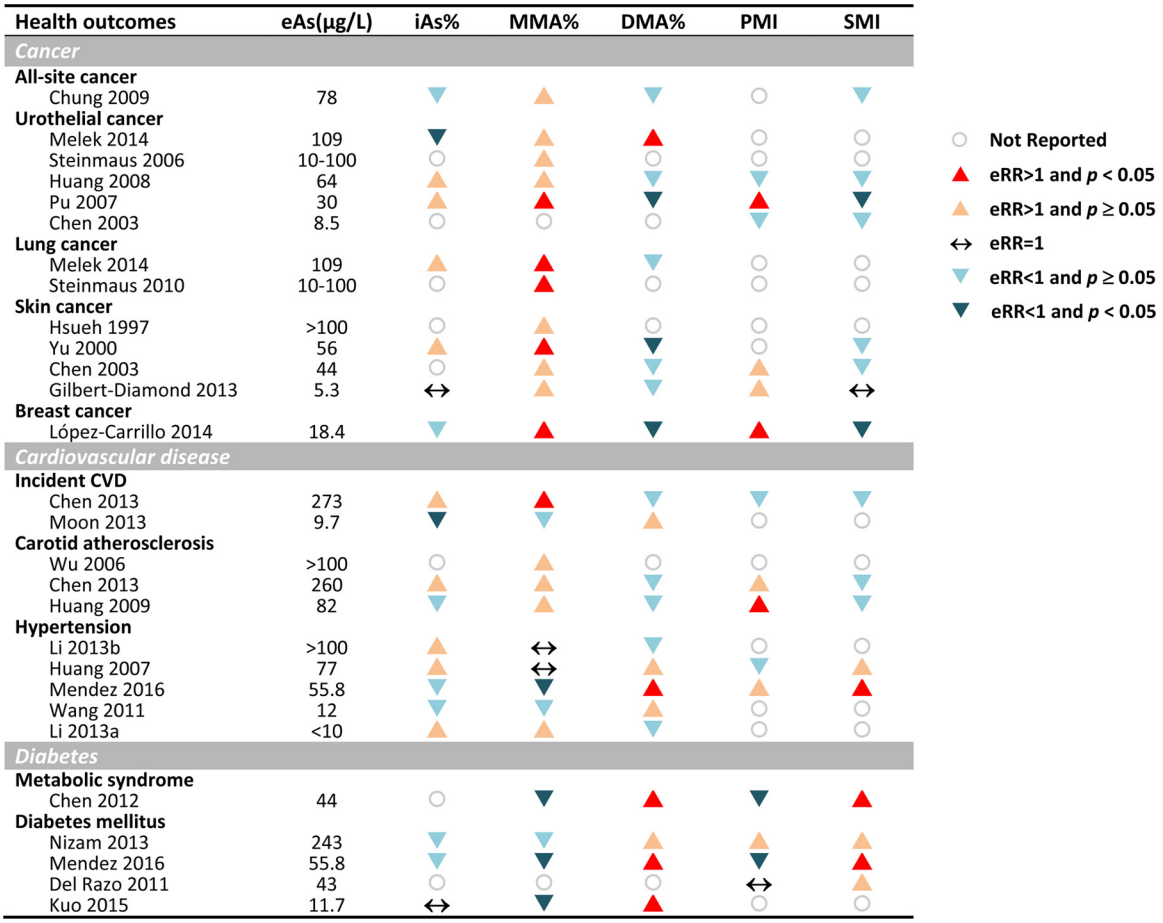

Figure 3. Summary of the associations of arsenic methylation patterns with cancer, cardiovascular disease, and diabetes-related outcomes based on the estimated relative risk (eRR) and 95% confidence interval (CI) shown in Tables 1–3. Studies are sorted by estimated arsenic exposure (eAs) within each health outcome. The triangles indicate the direction of the association. An upward-pointing triangle stands for positive association while a downward-pointing triangle stands for a negative association. An upward-pointing triangle indicates a positive and statistically significant association (eRR above 1 and 95% CI not overlapping 1) and a lighter upward-pointing triangle indicates a positive but not statistically significant increase (eRR above 1 but 95% CI overlapping 1). A downward-pointing triangle indicates a negative and statistically significant association (eRR below 1 and 95% CI not overlapping 1) and a lighter downward-pointing triangle indicates a negative but not statistically significant association (eRR below 1 but 95% CI not overlapping 1). A horizontal arrow (↔) indicates a null association (eRR equal to 1). Gray open circles with no arrows indicate the data were not reported in the study. All the associations represented in this figure are also shown in Tables 1–3 as eRR and 95% CI.

associated with higher risk of diabetes or metabolic syndrome (Chen et al. 2012; Kuo et al. 2015; Mendez et al. 2016; Nizam et al. 2013). The SMI was positively associated with higher risk of diabetes (Chen et al. 2012; Del Razo et al. 2011; Mendez et al. 2016; Nizam et al. 2013), although the association was significant only in two studies (Chen et al. 2012; Mendez et al. 2016). For PMI, the association with diabetes or metabolic syndrome was nonsignificantly positive in one study (Nizam et al. 2013), significantly inverse in two studies (Chen et al. 2012; Mendez et al. 2016), and null in one study (Del Razo et al. 2011).

Discussion

Main Findings

This systematic review of arsenic metabolism and disease found that the association with arsenic metabolism patterns was different across different chronic disease outcomes (Figure 3). For cancer, most studies found an association between cancer outcomes with higher MMA% and lower DMA%. For cardiovascular disease, most studies found that higher MMA% was associated with incident cardiovascular diseases and prevalent carotid atherosclerosis, although most of them were not statistically significant. For hypertension, no studies found any association with arsenic metabolism. For diabetes, lower MMA% and higher DMA% was associated with higher risk of diabetes or the metabolic syndrome in all studies. A major limitation in this area of research is the heterogeneity in the methods used for modeling arsenic metabolism and the selective reporting, which makes the comparison and interpretation of the results challenging. The research community should reach consensus on the appropriate methods for evaluating arsenic metabolism in epidemiologic studies.

In the evaluation of arsenic metabolism across populations, we found substantial interpopulation variability in the distribution of the arsenic metabolism measures. Interpopulation variability of arsenic metabolism has been recognized in previous studies (Loffredo et al. 2003; Vahter 2000). In the current review, we found that arsenic exposure (measured in drinking water or urine) was related to iAs% and DMA% (high arsenic in water being associated with higher iAs% and lower DMA%); however, there was a less pronounced association with MMA%. By comparing all the data on MMA% from multiple countries side by side, we also observed that the variability for MMA% across diverse populations was lower than variability of iAs% and DMA%. To our knowledge, few studies have directly investigated the association between arsenic exposure levels and arsenic metabolism. A

Table 2. Studies of arsenic metabolism and cardiovascular diseases.

Reference	Study design (case/noncase)	Men (%) Age range Source	Outcome (Ascertainment method)	Arsenic exposure: Sample (level)	iAs%	MMA%	DMA%	PMI	SMI	Adjustment factors
Moon et al. 2013	CO Total $n=3{,}381$	Arizona, Oklahoma, North/South Dakota, USA	CVD incidence and mortality (CHD, stroke and CHF; adjudicated by outcome assessment committee)	Urine (median sum iAs, MMA, and DMA 9.7 μg/g creatinine)	8.9 ± 5.0	14.5 ± 5.3	76.6 ± 8.6	NR	NR	Age, sex, education, smoking, BMI, LDL cholesterol, study site, total inorganic arsenic
		45.0%			0.91 (0.84, 0.99) for incident CVD	0.98 (0.90, 1.07) for incident CVD	1.04 (0.96, 1.12) for incident CVD			
		45–74 y General			0.83 (0.73, 0.94) for fatal CVD	1.01 (0.87, 1.16) for fatal CVD	1.03 (0.91, 1.17) for fatal CVD			
Chen et al. 2013b	CCO 369/1,109 (subcohort)	Araihazar, Bangladesh	Fatal and nonfatal CVD (CHD and stroke; medical records, death certificate, outcome assessment committee)	Urine (mean sum iAs, MMA, and DMA 273 μg/g creatinine)	15.5 ± 6.9	13.2 ± 5.2	71.3 ± 8.7	1.0 ± 0.8	6.0 ± 3.1	Age, sex, education, smoking, hypertension, diabetes
		51%			(17.4, 69.3) vs. (0.3, 12.4)	(14.4, 33.8) vs. (0.2, 10.3)	(75.6, 99.2) vs. (27.9, 68.6)	(1.06, 19.57) vs (0.01, 0.66)	(7.2, 32.3) vs. (1.4, 4.8)	
		≥18 y General			1.1 (0.7, 1.6)	1.6 (1.1, 2.2)	0.8 (0.5, 1.1)	0.9 (0.6, 1.3)	0.5 (0.3, 0.9)	
Wu et al. 2006	NCC 163/163	Ilan, Taiwan	Carotid atherosclerosis (IMT ≥1.0 mm or the presence of ECCA plaque)	Water (<0.15 ~ 3,590 μg/L)	NR	NR	NR	NR	NR	Age, sex, smoking, total cholesterol, hypertension, CAE
		47% ≥40 y General				≥13.4 vs. <13.4 0.5 (0.1, 2.0)				
Huang et al. 2009	CS 121/183	Putai, Taiwan	Carotid atherosclerosis (IMT ≥1.0mm or the presence of ECCA plaque)	Urine (mean sum iAs, MMA, and DMA 82 μg/L)	7.2 ±7.2	13.9 ± 8.9	78.9 ± 11.9	3.3 ± 5.3	13.3 ± 47.9	Age, sex, smoking, hypertension, diabetes, total cholesterol, total urine arsenic
		52%			Case (6.9) vs. control (7.4) $p=0.19$	Case (15.1) vs. control (13.1) $p=0.11$	Case (78.1) vs. control (79.5) $p=0.08$	Case (3.9) vs. control (2.9) $p=0.78$	Case (9.1) vs. control (16.0) $p=0.10$	
		≥30 y General								
Chen et al. 2013a	CS Total $n=959$	Araihazar, Bangladesh	Carotid IMT	Urine (mean sum iAs, MMA, and DMA 260 μg/g creatinine)	15.5	13.0	71.6	0.98	6.7	Age, sex, education, smoking, body mass index, systolic blood pressure, diabetes
		40%			Per 10% change:	Per 10% change	Per 10% change	Per 1-unit change	Per 1-unit change	
		≥18 y General			4.1 (−4.1, 12.3)	12.1 (0.4-23.8)	−6.3 (−12.8, 0.2)	1.5 (−5.2, 8.1)	−1.2 (−2.8, 0.4)	
Huang et al. 2007	CS 372/499	Putai, Taiwan	HTN	Urine (mean sum iAs, MMA, and DMA 77 μg/L)	8.2 ± 7.6	13.6 ± 8.7	78.1 ± 12.2	3.1 ± 8.0	11.6 ± 31.0	Age, sex, smoking, alcohol, body mass index, triglyceride, CAE
		44% ≥30 y General	(History and/or a SBP ≥160 mmHg or a DBP ≥90 mmHg)		≥8.0 vs. <4.5 −1.2 (0.8-1.9)	≥15.5 vs. <8.1 1.0 (0.7, 1.6)	≥85.3 vs. <75.8 1.1 (0.7, 1.6)	≥2.7 vs. <1.2 0.9 (0.6, 1.3)	≥9.8 vs. <4.9 1.1 (0.7, 1.7)	
Wang et al. 2011	CO 110/242	Putai, Taiwan	HTN	Water (mean CAE 12 mg/L-y)	NR	NR	NR	NR	NR	Age, sex, body mass index, glucose
		46% ≥30 y General	(SBP ≥140 mmHg, a DBP ≥90 mmHg, or anti-HTN medication)		>17 vs. <10 0.7 (0.3, 1.6)	>12 vs. <6 0.6 (0.3, 1.3)	>0.81 vs. <0.71 1.4 (0.6, 3.2)			
Li et al. 2013a	CS 182/487	Inner Mongolia, China	HTN (SBP ≥140 mmHg or DBP ≥90 mmHg or anti-HTN medication)	Water (geometric mean CAE 0.02–2.9 mg/L-y)	9.2	13.3	70.2	NR	NR	Age, sex, smoking, alcohol, body mass index, diabetes
		43% Mean 50 y General			Per % change within water arsenic (μg/L) categories <10 : 0.8 (0.3, 2.3) 10–50: 1.5 (0.6, 3.9) >50: 2.0 (1.0, 4.1)	Per % change within water arsenic (μg/L) categories <10 or anti-HTN medication): 0.5 (0.05, 4.5) 10–50: 0.8 (0.1, 7.1) >50: 1.8 (0.4, 7.9)	Per % change within water arsenic (μg/L) categories <10 : 0.8 (0.1, 6.9) 10–50: 0.1 (0.002, 4.4) >50: 0.04 (0.002, 0.8)			
Li et al. 2013b	CS 168/436	Shanxi, China	HTN (SBP ≥140 mmHg or DBP ≥90 mmHg or anti-HTN medication)	Urine (geometric mean sum iAs, MMA, and DMA 136–179 μg/g creatinine)	9.5	12.9	69.5	NR	NR	Age, sex, smoking, alcohol, body mass index
		42% -Mean 49 y General			>15.8 vs. <7.3 1.5 (0.9, 2.5)	>16.4 vs. <11.9 1.00 (0.6, 1.7)	>79.1 vs. <68.7 0.7 (0.4, 1.2)			

(Continued)

Table 2. Continued

Reference	Study design (case/noncase)	Men (%) Age range Source	Outcome (Ascertainment method)	Arsenic exposure: Sample (level)	iAs%	MMA%	DMA%	PMI	SMI	Adjustment factors
Mendez et al. 2016	CS Total $n=1{,}038$	Chihuahua, Mexico 31.4% Mean 46 y General	HTN (SBP ≥140 mmHg or DBP ≥90 mmHg or anti-HTN medication)	Urine (median total inorganic As 55.8 (μg/L))	8.9 ± Median ≥12.3 vs. <6.4 ~0.8 (*p*-value >0.05)	14.0 ± Median ≥17.7 vs. <10.9 ~0.5 (*p*-value <0.05)	76.8 ± Median ≥81.5 vs. <70.7 ~1.8 (*p*-value <0.05)	1.6 ± Median ≥2.1 vs. <1.2 ~1.2 (*p*-value >0.05)	5.5 ± Median ≥7.4 vs. <4.1 ~1.9 (*p*-value <0.05)	Total inorganic arsenic, age, sex, education, ethnicity, weight, waist circumference, smoking, alcohol, seafood intake, water source

Note: Values shown as mean±SD, highest vs. lowest category, and eRR (95% CI), unless otherwise specified. CAE, cumulative arsenic exposure; CCO, case-cohort study; CHF, congestive heart failure; CI, confidence interval; CO, prospective cohort study; CS, cross-sectional study; CVD, cardiovascular disease; DBP, diastolic blood pressure; DMA, dimethylarsinate; ECCA, extra-cranial carotid artery; eRR, estimated r4elative risk; HTN, hypertension; iAs, inorganic arsenic; IMT, intimal-medial thickness; MMA, monomethylarsonate; NCC, nested case–control study; NR, not reported; PMI, primary methylation index (MMA/iAs); SBP, systolic blood pressure; SD, standard deviation; SMI, secondary methylation index (DMA/MMA).

similar pattern was also observed in the region of Lagunera in Mexico, although the sample size was small (Del Razo et al. 1997). Lower variability in MMA% in human populations is also consistent with an animal study in mice showing that an increase in sodium arsenate from 0.5 to 5,000 μg/kg increased iAs% by 14.4% and decreased DMA% by 16.1% but only increased MMA% by 1.3% (Hughes et al. 1994). In Southwestern Taiwan, a 17.8-μg/L reduction in mean sum of inorganic arsenic exposure (baseline 74.9 μg/L to 57.1 μg/L) over 15 y of follow-up was associated with a 4.9% decrease in iAs%, a 6.8% decrease in MMA%, and an 11.7% increase in DMA%, although this observation did not account for survival bias (YK Huang et al. 2009). Future research is needed to understand how arsenic metabolism capacity responds to environmental arsenic exposure.

Beyond arsenic exposure levels, genetic polymorphisms, particularly in the arsenic (III) methyltransferase (AS3MT) gene, have been considered major determinants in interindividual variability of the arsenic methylation patterns (Agusa et al. 2011; Eichstaedt et al. 2015). Age, sex, and body mass index may be other major determinants of arsenic metabolism (Jansen et al. 2015). Epidemiological studies of arsenic metabolism and disease need to carefully consider for which factors to adjust. At a minimum, all studies of arsenic metabolism should adjust for arsenic exposure levels, in order to assess the health effects beyond what could be related to differences in arsenic exposure. Adjustment for age and sex should also be required. In addition to age and sex, body mass index, nutritional status, and genetic variants are other major determinants of arsenic metabolism. For instance, the large variation in arsenic metabolism profile observed in the two study populations with comparable age and arsenic exposure level in Bangladesh could potentially be explained by differences in nutritional status as reflected in urine creatinine level (178.5 mg/dL in Faridpur vs. 59.7 mg/dL in Araihazar). If possible, epidemiologic studies should also evaluate potential effect modification between arsenic exposure levels and arsenic metabolism. In the current systematic review, due to the limited number of studies for each endpoint, unfortunately we could not evaluate the joint effect between arsenic exposure and metabolism in disease development. As the number of studies evaluating arsenic exposure and metabolism in disease development increases, meta-regression techniques could contribute to that understanding.

Implications for Public Health

The importance of evaluating the role of arsenic metabolism in explaining interindividual differences in arsenic-related disease was recognized in the late 1990s, with the first study on the higher risk of nonmelanoma skin cancer with higher MMA% in Southwestern Taiwan being published in 1997 (Hsueh et al. 1997). With advances in analytical technology, including sensitive methods to detect the relevant arsenic species in the urine, and the recognition of the importance of understanding the role of arsenic metabolism for the evaluation of susceptibility in risk assessment, the number of epidemiologic studies evaluating the association between arsenic metabolism and health effects has grown. Initially, the studies pointed at a higher risk of disease being associated with higher MMA%. This finding was consistent with the detoxification interpretation of methylation and the need to fully methylate inorganic arsenic to DMA to minimize arsenic health effects. A slower second methylation could result in higher concentrations of trivalent MMA (MMA^{III}) in human tissues. In cytotoxicity studies, MMA^{III} has shown to be as toxic or more than arsenite (Petrick et al. 2000). Most epidemiologic studies cannot measure MMA^{III} in urine, as it is a very unstable compound that quickly revert to pentavalent MMA. In a small study

Table 3. Studies of arsenic metabolism and metabolic syndrome and diabetes.

Reference	Study design (case/noncase)	Men (%) Age range Source	Outcome (Ascertainment method)	Arsenic exposure						Adjustment factors
				Sample (level)	iAs%	MMA%	DMA%	PMI	SMI	
Chen et al. 2012	CS 111/136	Putai, Taiwan	Metabolic Syndrome (≥3 Adult Treatment Panel III Criteria)	Urine (mean sum iAs, MMA, and DMA 44 μg/g creatinine)	17.0 ± 15.4	10.1 ± 9.0	72.8 ± 19.1	0.8 ± 0.7	17.9 ± 32.0	Age, betel nut chewing
		43% ≥40 y General			NR	>11.3 vs. <5.8 0.4 (0.2, 0.7)	>81.9 vs. <72.4 2.0 (1.1, 3.9)	>0.9 vs. <0.4 0.4 (0.2, 0.8)	>12.0 vs. <6.1 2.6 (1.4, 5.1)	
Del Razo et al. 2011	CS 25/233	Zimapán and Lagunera, Mexico	Diabetes (FBG ≥126 mg/dL, OGTT ≥200 mg/dL, self-reported diagnosis, or medication)	Urine (mean sum iAs, MMA, and DMA 43 μg/L)	NR	NR	NR	1.3	5.6	Age, sex, obesity, hypertension
		33% Mean 34 y General						per IQR change 1.0 (0.9, 1.1)	per IQR change 1.4 (0.9, 2.1)	
Nizam et al. 2013	CC 140/180	Faridpur, Bangladesh	Diabetes (self-reported diagnosis and HbA1c ≥ 7%, confirmed by medical records)	Urine (mean sum iAs, MMA, and DMA 243 μg/L)	9.6	9.4	80.1	1.3	10.0	Age, sex, location, smoking, body mass index, family history of diabetes, income, duration of drinking water, water arsenic
		43% ≥20 y General			DM (8.6) vs. non-DM (10.4) $p = 0.35$	DM (8.8) vs. non-DM (9.7) $p = 0.08$	DM (82.6) vs. non-DM (79.9) $p = 0.14$	DM (1.4) vs. non-DM (1.2) $p = 0.37$	DM (11.6) vs. non-DM (10.0) $p = 0.09$	
Kuo et al. 2015	CO 396/1,298	Arizona, Oklahoma, North/South Dakota, USA	Diabetes (FBG ≥126 mg/dL, 2HPG ≥200 mg/dL, self-reported diagnosis, or medication)	Urine (mean sum iAs, MMA, and DMA 11.7 μg/g creatinine)	9.2	15.6	75.2	NR	NR	Age, sex, education, smoking, alcohol, BMI, waist-to-hip ratio, study sites, total inorganic arsenic
		45.0% 45–74 y General			per 5% change 1.0 (0.89, 1.12)	per 5% change 0.84 (0.76, 0.94)	per 5% change 1.07 (1.00, 1.15)			
Mendez 2016	CS Total $n = 1{,}038$	Chihuahua, Mexico	Diabetes (FBG ≥126 mg/dL, 2HPG ≥200 mg/dL, self-reported diagnosis, or medication)	Urine (median total inorganic As 55.8 (μg/L))	8.9 ± Median	14.0 ± Median	76.8 ± Median	1.6 ± Median	5.5 ± Median	Total inorganic arsenic, age, sex, education, ethnicity, weight, waist circumference, smoking, alcohol, seafood intake, water source
		31.4% Mean 46 y General			≥12.3 vs. <6.4 ∼0.6 (p-value >0.05)	≥17.7 vs. <10.9 ∼0.3 (p-value <0.05)	≥81.5 vs. <70.7 ∼3.1 (p-value <0.05)	≥2.1 vs. <1.2 ∼0.4 (p-value <0.05)	≥7.4 vs. <4.1 ∼4.9 (p-value <0.05)	

Note: Values shown as mean±SD, highest vs. lowest category, and eRR (95% CI), unless otherwise specified. ATPIII, National Cholesterol Education Program's Adult Treatment Panel III report; BMI, Body mass index (kg/m^2); CC, case–control study; CI, confidence interval; CS, cross-sectional study; DM, diabetes mellitus; DMA, dimethylarsinate; eRR, estimated relative risk; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; 2HPG, 2-h postprandial glucose; iAs, inorganic arsenic; IMT, intimal-medial thickness; MMA, monomethylarsonate; NR, not reported; OGTT, oral glucose tolerance test; PMI, primary methylation index (MMA/iAs); SD, standard deviation; SMI, secondary methylation index (DMA/MMA).

in central Mexico, participants with skin lesions had higher levels of MMA^{III}, despite similar total urine arsenic (Valenzuela et al. 2005). Recent studies on diabetes-related outcomes, however, have shown that the association of arsenic metabolism patterns with health outcomes can be more complex than originally thought and suggest that faster methylation or more complete methylation could also increase the risk of diabetes. A similar association has also been found between higher DMA% and obesity and increased body mass index (Gomez-Rubio et al. 2011; Gribble et al. 2013; Su et al. 2012). From a mechanistic perspective, experimental evidence from animal studies has shown that methylation could be a bioactive process with DMA (III) being a highly toxic dimethylated arsenic species targeting murine pancreatic islet cells (Douillet et al. 2013; Lu et al. 2011; Mass et al. 2001). Other indirect lines of evidence suggest that the synthesis and regulation of the main methyl donor for arsenic methylation, *S*-adenosylmethionine (SAM) generated through the one-carbon metabolism, may be critical for glucose and lipid homeostasis (Jackson et al. 2012; Locasale 2013; Ngo et al. 2014; Vahter 2007; Walker et al. 2011). These complex findings imply that manipulating individuals' arsenic metabolism profile toward complete methylation via nutritional modification, for instance, through supplementation with folate (George et al. 2012; Hoque et al. 2000), may be more challenging than anticipated if increasing DMA% is related to a higher risk of diabetes-related metabolic complications. Additional long-term prospective epidemiological research and experimental research is needed to confirm and understand the role of arsenic metabolism and its connections with arsenic exposure, relevant exposure windows, genetics, nutrition, co-infections, and the microbiome (Chen 2014; Lu et al. 2014).

Limitations of Current Research

A major limitation in comparing studies, however, is the heterogeneity in the description and analysis of arsenic metabolism. For instance, when percentages of the species relative to their sum are presented, many studies only show the results for one of the species (Hsueh et al. 1997; Steinmaus et al. 2010; Wu et al. 2006). Similarly, only one of the two methylation indices are often presented. In addition to the selective reporting, the modeling methods used have generally failed to recognize that the three species (inorganic arsenic, MMA, and DMA) are interrelated and sum to 100%. Using conventional statistical methods designed for inherently compositional data may lead to inappropriate inferences (Aitchison 1986; Pawlowsky-Glahn and Egozcue 2006). In the 1980s, John Aitchison introduced compositional data analysis to address this common issue in geoscience (Aitchison 1981, 1986). However, this technique is not widely recognized even in the area of geochemical research (Buccianti and Grunsky 2014). Only recently, methods such as the leave-one-out approach or the use of triplots to represent the simultaneous distribution of arsenic metabolism have been used by environmental scientists (Gribble et al. 2013; Kuo et al. 2015).

The present findings should be interpreted cautiously. First, the possibility of publication bias cannot be ignored as null associations may be less likely to be published. Publication bias may overestimate the consistency of the relationship between arsenic metabolism and the selected health outcomes. Second, as most studies were cross-sectional or case–control designs, the possibility of reverse causation cannot be excluded. Also, adjustment for confounding was limited in some studies and overall we cannot exclude the possibility of residual confounding. However, the consistency of the findings adds support to conducting additional research to further assess the causality of these associations and a more comprehensive risk assessment targeting arsenic metabolism. Third, for the association between arsenic metabolism biomarkers and arsenic exposure we combined data across studies at different time periods, in different laboratories, and with different genetic background and nutritional status. Fourth, to obtain a fully comprehensive picture of the interplay between arsenic exposure and arsenic metabolism biomarkers, future reviews should expand to include all studies evaluating both arsenic exposure and metabolism. Fifth, in this review, we focused on the role of current arsenic exposure in arsenic metabolism rather than past exposure. Future research efforts should also be aimed to identify an appropriate population with both past and current arsenic exposure data to evaluate the effect of past arsenic exposure on the evolution of arsenic metabolism. Lastly, in this review, we focused on the role of current arsenic exposure in arsenic metabolism rather than past exposure. Future research efforts should identify a population with both past and current arsenic exposure data and longitudinal follow-up to evaluate the effect of past arsenic exposure on changes in arsenic metabolism.

Opportunities and Challenges for Future Studies

Future studies with large sample size, appropriate baseline and prospective arsenic metabolism estimation, and sufficient long-term follow-up will help verify the independent association between arsenic metabolism and various health effects, and the interaction between arsenic exposure and metabolism on the development of chronic diseases. Developing a simple and interpretable modeling approach for arsenic metabolism is a research priority, although it might be difficult due to population specific complexities and the contribution of unmeasured covariates such as diet and genetic determinants. For example, interpretation of ratio measures of methylation (both PMI and SMI) is challenging, despite their previous popularity in epidemiological studies (Del Razo et al. 1997). It is difficult to predict whether changes in the numerator or the denominator will have a dominant effect, and thus associations with a methylation index obscures whether the association lies with the numerator or the denominator.

The biological meaning of arsenic metabolism may extend beyond increasing risks of arsenic toxicity. Arsenic metabolism may be an integrated marker reflecting genetic variations on arsenic sensitivity and long-term environmental arsenic exposure on genetic modification (Eichstaedt et al. 2015). Arsenic metabolism may also reflect differential microbiome distribution across humans and human populations, as it has been shown that gut microorganisms can methylate inorganic arsenic (Dietert and Silbergeld 2015). Arsenic metabolism is also related to one-carbon nutrients as demonstrated in clinical trials from Bangladesh (Gamble et al. 2007; Peters et al. 2015). The interplay between one-carbon metabolism, arsenic metabolism, and DNA methylation provides an opportunity to explore the genomic coding, metabolism regulation, and phenotype expression from a mechanistic perspective (Baccarelli et al. 2010). One-carbon metabolism is composed of three key cycles including the methionine cycle, the folate cycle, and the cysteine-cystathionine cycle (Locasale 2013; Stipanuk 2004). The major methyl donor in humans, *S*-adenosylmethionine, is generated through the methionine cycle and facilitates more than 50 methylation reactions, including DNA methylation and arsenic methylation (Agusa et al. 2011; Stead et al. 2006). The methionine cycle is completed by the re-methylation of homocysteine back to methionine, through the folate cycle (Stover 2004), or by irreversibly degrading homocysteine into cysteine (Wijekoon et al. 2006). Dysfunction of the methionine cycle has been linked to chronic diseases including cancer and cardiovascular disease (Baccarelli et al. 2010; Locasale 2013). The cysteine–cystathionine cycle involves glutathione-transsulfuration and generates antioxidant

thio buffers, which are critical to maintaining intracellular reduction–oxidation status (Deplancke and Gaskins 2002). The imbalance of redox status has also been linked to cancer metabolism (Cairns et al. 2011; Moore et al. 2007), cardiovascular disease (Zimmet and Hare 2006), and diabetes (Dugan et al. 2013). Indeed, increasing epidemiological evidence supports the association between arsenic exposure and global DNA methylation status (Niedzwiecki et al. 2013; Ren et al. 2011). Moreover, mathematical modeling to approach the complexity of one-carbon metabolism and the interaction between the one-carbon and arsenic metabolism has been initiated (Lawley et al. 2011; Nijhout et al. 2008).

Conclusions

This is the first systematic review evaluating the association between arsenic metabolism and several chronic disease outcomes. Specific methylation patterns were associated with increased disease risk, in different directions for different diseases. Cancer and cardiovascular disease outcomes were related to higher MMA%, whereas diabetes and the metabolic syndrome were in general related to lower MMA% and higher DMA%. Our analysis scope and conclusions were constrained due to small sample size, limited prospective evidence, and inconsistent arsenic metabolism reporting and statistical approach across studies. These findings call for a consensus on reporting standards for the evaluation of the health effects of arsenic metabolism. Conducting large prospective cohort studies in populations exposed to a wide range of arsenic exposure levels is critical to better characterize the interplay of arsenic metabolism with factors that influence the individual metabolism patterns, including arsenic exposure levels and genetic determinants of arsenic metabolism. Understanding the biological and epidemiological meaning of arsenic metabolism could improve the risk assessment of arsenic toxicity and provide a potential tool for disease prediction, prevention, and control.

Acknowledgments

This work was supported by the National Institutes of Health (grants R01ES021367, 1R01ES025216, P42ES010349, and P30 ES009089), and by the Ministry of Science and Technology of Taiwan (grant 105-2314-B-039-040).

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