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Supplemental Material

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

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PubMed and EMBASE database search strategies for arsenic metabolism and outcomes of interest

Medline/PubMed (Jan 25, 2016):

Strategy: We combined the results for three major concepts (#1 to #3 below using "AND") with restriction to human studies (#4 using "NOT").

#1. Arsenic [32,451 results]: "Arsenic"[Mesh] OR "Arsenic Poisoning"[Mesh] OR "Arsenicals"[Mesh] OR "Arsenic"[tw] OR "Arsenic Poisoning"[tw] OR "Arsenicals"[tw] OR arsenite OR arsenate OR arsenicals

#2. Metabolism [6,801,179 results]: "Metabolism"[Mesh] OR "metabolism" [Subheading] OR "Metabolic Networks and Pathways"[Mesh] OR "Carbohydrate Metabolism"[Mesh] OR "Lipid Metabolism"[Mesh] OR "Glucose Metabolism Disorders"[Mesh] OR "Secondary Metabolism"[Mesh] OR "Lipid Metabolism Disorders"[Mesh] OR "Pyruvate Metabolism, Inborn Errors"[Mesh] OR "Purine-Pyrimidine Metabolism, Inborn Errors"[Mesh] OR "Phosphorus Metabolism Disorders"[Mesh] OR "Metal Metabolism, Inborn Errors"[Mesh] OR "Amino Acid Metabolism, Inborn Errors"[Mesh] OR "Steroid Metabolism, Inborn Errors"[Mesh] OR "Iron Metabolism Disorders"[Mesh] OR "Metabolism, Inborn Errors"[Mesh] OR "Lipid Metabolism, Inborn Errors"[Mesh] OR "Energy Metabolism"[Mesh] OR "Carbohydrate Metabolism, Inborn Errors"[Mesh] OR "Calcium Metabolism Disorders"[Mesh] OR "Methylation"[Mesh] OR "DNA Methylation"[Mesh] OR "Arsenic metabolism" OR "Arsenic methylation"

#3. **Health outcome measures [8,091,941 results]: [Cancer]** cancer[sb] OR **[Cardiovascular diseases]** "Atherosclerosis"[Mesh] OR "Carotid Artery Diseases"[Mesh] OR "Coronary Artery Disease"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Stroke"[Mesh] OR "Cerebrovascular Disorders"[Mesh] OR "Peripheral Vascular Diseases"[Mesh] OR "Peripheral Arterial Disease"[Mesh] OR "Mortality"[Mesh] OR atherosclerosis OR arteriosclerosis OR "cardiovascular disease" OR "cardiovascular diseases" OR

"myocardial infarction" OR stroke OR “cerebrovascular disease” OR "peripheral vascular disease" OR "peripheral arterial disease" OR mortality OR “blackfoot disease” OR “infarct*” OR “ischemia” OR “ischemic heart disease” OR “heart diseases” OR **[Diabetes related outcome]** "obesity"[mh] OR "body mass index"[mh] OR "weight gain"[mh] OR "adipogenesis"[mh] OR "adipose tissue"[mh] OR "adipokines"[mh] OR "adiponectin"[mh] OR "leptin"[mh] OR resistin[mh]) OR ("diabetes mellitus"[mh] OR "glucose metabolism disorders"[mh] OR "insulin"[mh] OR "insulin resistance"[mh] OR "blood glucose"[mh] OR "islets of langerhans"[mh]) OR “body composition”

#4. Animal Study [4,188,771 results]: ["animals"[MeSH Terms] NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms])]

EMBASE (Jan 25, 2016):

Strategy: We combined the results for three major concepts (#1 to #3 below using “AND”) with restriction to human studies (#4 using “NOT”).

#1. Arsenic [27,218 results]: 'arsenic'/exp OR 'arsenic poisoning'/exp OR arsenic AND poisoning OR 'arsenicals'/exp OR arsenicals OR arsenite OR arsenate

#2. Metabolism [4,589,864 results]: 'metabolism'/exp OR metabolism OR 'methylation'/exp OR methylation OR 'arsenic methylatoin' OR 'arsenic metabolism'

#3. Health outcome measures [8,997,148 results]: [Cancer]'cancer'/exp OR cancer OR 'neoplasm'/exp OR neoplasm OR 'malignancy' OR 'malignant' OR **[Cardiovascular diseases]** 'carotid artery diseases'/exp OR 'carotid artery diseases' OR 'coronary artery disease'/exp OR 'coronary artery disease' OR 'cardiovascular diseases'/exp OR 'cardiovascular diseases' OR 'myocardial infarction' OR 'myocardial infarction'/exp OR stroke OR 'stroke'/exp OR 'stroke' OR 'cerebrovascular disorders' OR 'cerebrovascular disorders'/exp OR 'peripheral vascular diseases' OR 'peripheral vascular diseases'/exp OR 'peripheral arterial diseases' OR 'peripheral arterial

diseases'/exp OR 'mortality' OR 'mortality'/exp OR 'atherosclerosis'/exp OR 'atherosclerosis' OR atherosclerosis OR 'arteriosclerosis'/exp OR 'arteriosclerosis' OR arteriosclerosis OR 'blackfoot disease'/exp OR 'blackfoot disease' OR 'infarct'/exp OR 'infarct' OR infarct OR 'ischemia'/exp OR 'ischemia' OR ischemia OR 'ischemic heart disease'/exp OR 'ischemic heart disease' OR 'heart disease'/exp OR 'heart disease' OR **[Diabetes related outcome]** 'diabetes' OR 'diabetes'/exp OR diabetes OR 'obesity' OR 'obesity'/exp OR obesity OR 'body mass index'/exp OR 'body mass index' OR 'weight gain'/exp OR 'weight gain' OR 'adipogenesis' OR 'adipogenesis'/exp OR adipogenesis OR 'adipose tissue'/exp OR 'adipose tissue' OR 'adipokines' OR 'adipokines'/exp OR adipokines OR 'adiponectin' OR 'adiponectin'/exp OR adiponectin OR 'leptin' OR 'leptin'/exp OR leptin OR 'resistin' OR 'resistin'/exp OR resistin OR 'glucose metabolism disorders'/exp OR 'glucose metabolism disorders' OR 'insulin' OR 'insulin'/exp OR insulin OR 'insulin resistance'/exp OR 'insulin resistance' OR 'blood glucose'/exp OR 'blood glucose' OR 'islets of langerhans'/exp OR 'islets of langerhans' OR 'body composition'/exp OR 'body composition'

#4. Animal Study [4,588,327 results]: 'animal'/exp NOT ('animal'/exp AND 'human'/exp)

Figure S1. Flow diagram of study selection process.

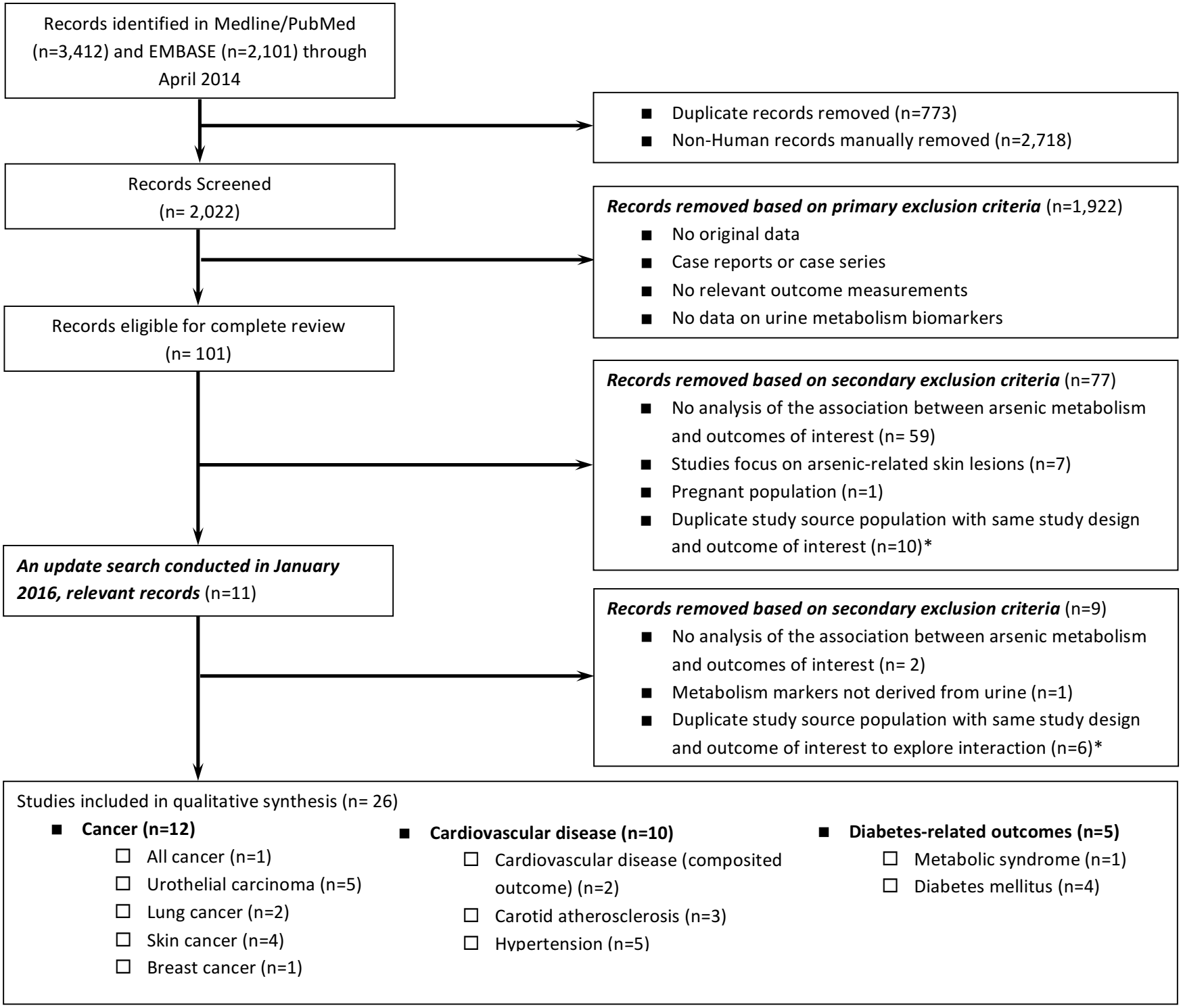


Table S1. Quality criteria applied and evaluation of the design and data analysis issued in selected studies on the relation between arsenic metabolism and cancers.

Note: Y: Yes; N: No; —: No relevant to the study design.

Quality Criteria	*Chung et al. 2009*	*Chen et al. 2003b*	*Steinmaus et al. 2006*	*Pu et al. 2007*	*Huang et al. 2008*	*Melak et al. 2014*	*Steinmaus et al. 2010*	*Hsueh et al. 1997*	*Yu et al. 2000*	*Chen et al. 2003a*	*Gilbert-Diamond et al. 2013*	*Lopez-Carrillo et al. 2014*
All studies												
Did the authors report all proportions of arsenic metabolism?	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did the authors report both primary and secondary arsenic methylation indices ?	N	Y	N	Y	Y	N	N	Y	N	Y	Y	Y
Were outcomes based on objective tests or standard criteria in ≥ 90% of study participants?	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Did the authors present internal comparisons within study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did the authors control for potential confounding risk factors at least including age, sex, and smoking?	N	Y	Y	N	Y	Y	Y	N	N	Y	Y	Y
Did the authors control for total arsenic exposure?	N	Y	N	N	Y	N	Y	N	N	Y	Y	Y
Follow-up studies												
Was loss to follow up independent of exposure?	N	—	—	—	N	—	—	Y	—	—	—	—
Was the intensity of search of disease independent of exposure status?	Y	—	—	—	Y	—	—	Y	—	—	—	—
Case-control and cross-sectional studies?												
Were the data collected in a similar manner for all participants?	—	Y	Y	Y	—	Y	Y	—	Y	Y	Y	Y
Were the same exclusion criteria applied to all participants?	—	Y	Y	Y	—	Y	Y	—	Y	Y	Y	Y
Was the time period over which cases and noncases or exposed and nonexposed participants were interviewed the same?	—	Y	N	N	—	N	N	—	N	Y	Y	Y
Was the interviewer blinded with respect to the case status of the person interviewed?	—	N	N	N	—	N	N	—	N	N	Y	N
Was the response rate among non-cases at least 70%?	—	Y	N	N	—	N	N	—	N	Y	Y	Y
Were all cases interviewed within 6 months of diagnosis?	—	N	N	N	—	N	N	—	N	N	N	Y
Was the study based on incident cases of diseases?	—	Y	Y	N	—	N	Y	—	N	Y	Y	Y
Were noncases people who, had they developed the disease, would have been cases?	—	N	Y	N	—	Y	Y	—	N	N	Y	Y

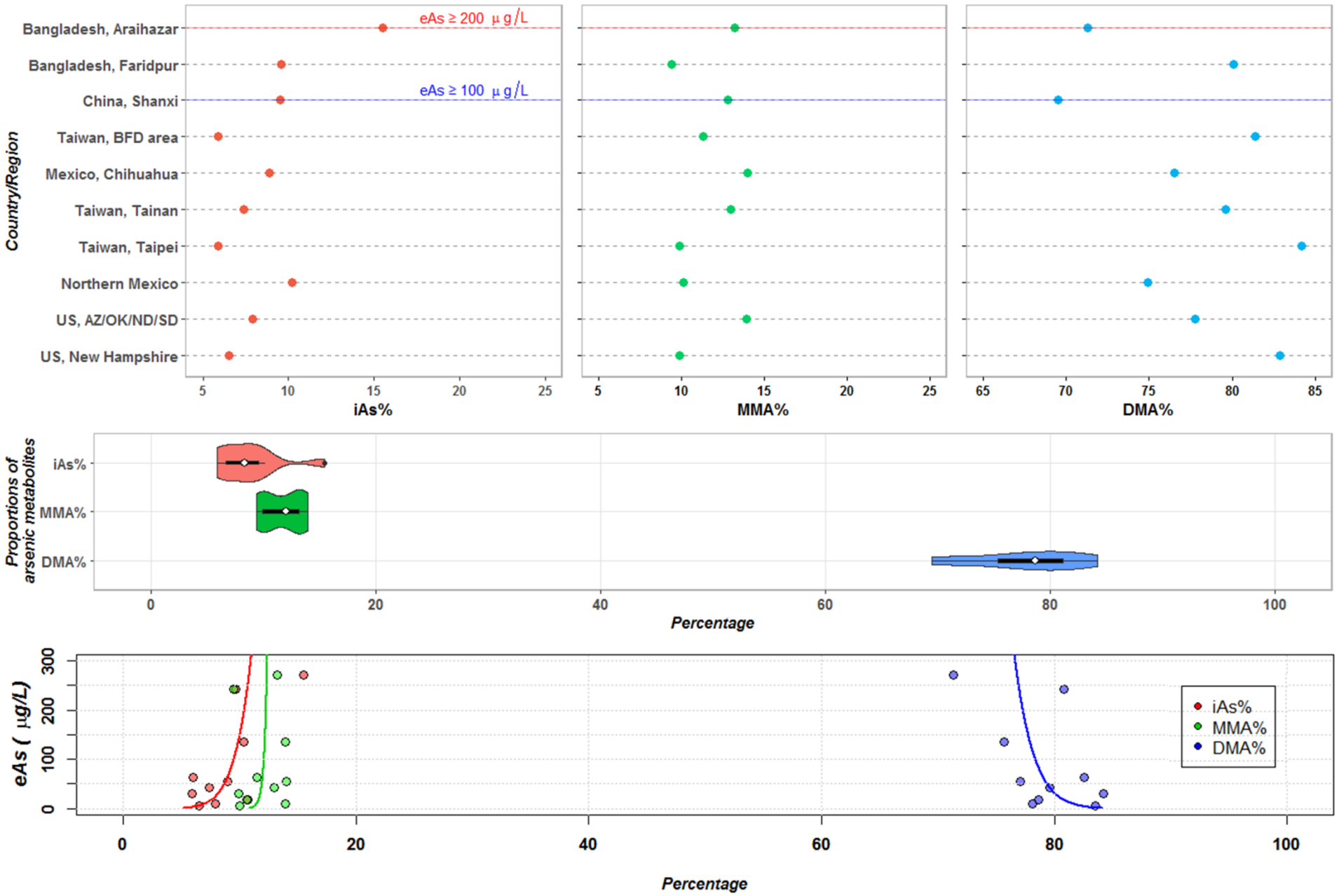
Table S2. Quality criteria applied and evaluation of the design and data analysis issued in selected studies on the relation between arsenic metabolism and cardiovascular diseases. Note: Y: Yes; N: No; —: No relevant to the study design.

Quality Criteria	***Moon et al. 2013***	***Chen et al. 2013b***	***Wu et al. 2006***	***Huang et al. 2009***	***Chen et al. 2013a***	***Huang et al. 2007***	***Wang et al. 2011***	***Li et al. 2013a***	***Li et al. 2013b***	***Mendez et al. 2016***
All studies										
Did the authors report all proportions of arsenic metabolism?	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**
Did the authors report both primary and secondary arsenic methylation indices?	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**N**	**N**	**N**	**N**
Were outcomes based on objective tests or standard criteria in ≥ 90% of study participants?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Did the authors present internal comparisons within study participants?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Did the authors control for potential confounding risk factors at least including age, sex, and smoking?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**
Did the authors control for total arsenic exposure?	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**N**	**N**	**N**	**Y**
Follow-up studies	**Y**	**Y**	**Y**							
Was loss to follow up independent of exposure?	**Y**	**Y**	**Y**	—	—	—	**N**	—	—	—
Was the intensity of search of disease independent of exposure status?	**Y**	**Y**	**Y**	—	—	—	**Y**	—	—	—
Case-control and cross-sectional studies			**Y**							
Were the data collected in a similar manner for all participants?	—	—	**Y**	**Y**	**Y**	**Y**	—	**Y**	**Y**	**Y**
Were the same exclusion criteria applied to all participants?	—	—	**Y**	**Y**	**Y**	**Y**	—	**Y**	**Y**	**Y**
Was the time period over which cases and noncases or exposed and nonexposed participants were interviewed the same?	—	—	**Y**	**Y**	**Y**	**Y**	—	**Y**	**Y**	**Y**
Was the interviewer blinded with respect to the case status of the person interviewed?	—	—	**N**	—	—	—	—	—	—	—
Was the response rate among eligible participants or non-cases at least 70%?	—	—	**Y**	**N**	**Y**	**N**	—	**Y**	**Y**	**N**
Were all cases interviewed within 6 months of diagnosis?	—	—	**N**	—	—	—	—	—	—	—
Was the study based on incident cases of diseases?	—	—	**N**	—	—	—	—	—	—	—
Were noncases people who, had they developed the disease, would have been cases?	—	—	**Y**	—	—	—	—	—	—	—

Table S3. Quality criteria applied and evaluation of the design and data analysis issued in selected studies on the relation between arsenic metabolism and metabolic syndrome and diabetes. Note: Y: Yes; N: No; —: No relevant to the study design.

Quality Criteria	***Chen et al. 2012***	***Del Razo et al. 2011***	***Nizam et al. 2013***	***Kuo et al. 2015***	***Mendez et al. 2016***
All studies					
Did the authors report all proportions of arsenic metabolism?	**Y**	**N**	**Y**	**Y**	**Y**
Did the authors report both primary and secondary arsenic methylation indices ?	**Y**	**Y**	**Y**	**Y**	**N**
Were outcomes based on objective tests or standard criteria in ≥ 90% of study participants?	**Y**	**Y**	**Y**	**Y**	**Y**
Did the authors present internal comparisons within study participants?	**Y**	**Y**	**Y**	**Y**	**Y**
Did the authors control for potential confounding risk factors at least including Age and sex?	**N**	**Y**	**Y**	**Y**	**Y**
Did the authors control for total arsenic exposure?	**N**	**N**	**Y**	**Y**	**Y**
Follow-up studies				**Y**	
Was loss to follow up independent of exposure?	—	—	—	**Y**	—
Was the intensity of search of disease independent of exposure status?	—	—	—	**Y**	—
Case-control and cross-sectional studies					
Were the data collected in a similar manner for all participants?	**Y**	**Y**	**Y**	—	**Y**
Were the same exclusion criteria applied to all participants?	**Y**	**Y**	**Y**	—	**Y**
Was the time period over which cases and noncases or exposed and nonexposed participants were interviewed the same?	**Y**	**Y**	**Y**	—	**Y**
Was the interviewer blinded with respect to the case status of the person interviewed?	—	—	**N**	—	—
Was the response rate among eligible participants or non-cases at least 70%?	—	**N**	**N**	—	**N**
Were all cases interviewed within 6 months of diagnosis?	—	—	**N**	—	—
Was the study based on incident cases of diseases?	—	—	**N**	—	—
Were noncases people who, had they developed the disease, would have been cases?	**Y**	—	**Y**	—	—

Figure S2. Variability of arsenic metabolism biomarkers in the study populations after excluding studies without direct measurement of arsenic exposure(Li et al. 2013a; Melak et al. 2014; Steinmaus et al. 2006) 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 (hollow 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.


eAs ≥ 200 μg/L
eAs ≥ 100 μg/L
Bangladesh, Araihazar
Bangladesh, Faridpur
China, Shanxi
Taiwan, BFD area
Mexico, Chihuahua
Taiwan, Tainan
Taiwan, Taipei
Northern Mexico
US, AZ/OK/ND/SD
US, New Hampshire
Country/Region
iAs%
MMA%
DMA%
Proportions of arsenic metabolites
Percentage
eAs (μg/L)
Percentage

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