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A Review of Environmental Epidemiology Studies in Southwestern and Mountain West Rural Minority Populations

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Abstract

Purpose of Review.—This review summarizes the recent epidemiologic literature examining environmental exposures and health outcomes in rural, minority populations in the southwestern and mountain west region of the United States identifying areas requiring further data and research.

Recent Findings.—Recent studies (2012–2017) in this region have primarily focused on arsenic exposure (n=10 studies) with similar results reported across populations in this region. Associations between arsenic and cadmium were reported for cardiovascular and kidney disease, type II diabetes, cognitive function, hypothyroidism, and increased prevalence and mortality for lung and other cancers. Also in this review are studies of exposure to particulate matter, environmental tobacco smoke, pesticides and fungicides, heat and ozone.

Summary.—Although small, the current literature identified in this review report consistent adverse health outcomes associated with particulate matter, arsenic, cadmium, and other exposures among rural, minority populations in the southwest/mountain west region of the U.S. This literature provides important insight into the environmental exposures and health effects experienced by the rural populations in these regions. Additional studies that identify sources of environmental exposure are needed. Greater representation of the rural and minority populations from this region into large health studies also remains a need.

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Keywords

environmental epidemiology; environmental exposure; rural population; minority population; western United States; southwestern United States

Introduction

The southwestern/mountain west region of the United States, rich in minerals and other natural resources, played a significant role in the frontier history of the country. The population of this region includes a large proportion of Hispanics and Native Americans [1]. In fact, almost one-half of the US Native American population live in the western region [2]. Because the region is sparsely populated [3], it is the beneficiary of relatively few epidemiology studies assessing the association of environmental exposures and health outcomes. Our objective is to conduct a systemized review [4] of the environmental epidemiology studies conducted among rural, minority populations in southwestern/ mountain west region of the U.S. published between mid 2012 and mid 2017.

Methods

Database search and eligibility criteria

We developed an *a priori* protocol which guided our search and inclusion/exclusion criteria by which we judged eligibility of study inclusion. We performed searches in PubMed, EMBASE, CINAHL, PsychINFO, Cochrane Library, Web of Science, Scopus, and the Native Health Database during August 2017 using controlled and keyword terms for Environmental Exposure, Epidemiology, Rural, and Minority. We also performed hand searching of reference lists, the National Institute of Environmental Health Sciences website, and Google Scholar. Similar to the other reviews in this issue, we limited our searches in each database to those studies published in the five years between July 2012 and June 2017 in English. Full search strategies for each database are available in supplemental information.

Studies were eligible for inclusion if they were environmental epidemiological studies in rural populations; conducted in the Southwest and Mountain West geographical locations of the U.S., in an area including the states of Arizona (AZ), Colorado (CO), Nevada (NV), New Mexico (NM), Texas (TX), and Utah (UT), and reported a clinical health outcome related to an environmental exposure. Studies that were conducted in urban locations were excluded, as were studies of pre-clinical biomarkers. After a pilot round to calibrate agreement, two investigators independently screened titles and abstracts against the exclusion criteria. Three investigators then screened full-text articles against the inclusion criteria. We managed this process with the systematic review application Rayyan [5].

Data Abstraction, evaluation, and synthesis

Data were abstracted from the records to capture exposure, study design, location and population, health outcome(s), covariates and main results. The main results during the article evaluation and selection phase were defined as the measures of association between exposure and health outcome reported in the abstract and along with the confidence interval or significance level. Records were classified by exposure type and the data organized in tables.

Results

Search Results

Our search identified 1413 studies via database searching and hand-searching relevant publications. After removing duplicates, 977 records remained to be screened by review of the title and abstract. This resulted in exclusion of 910 that with closer review did not meet our inclusion criteria of including an environmental exposure *and* a health outcome *and* a rural population from our study region. After screening the remaining studies by reading the full text (N=67), we further excluded 46 that did not fully fit the above inclusion criteria, as they were either not epidemiological studies (n=27), not a rural population (n=7), not a minority population (n=9), and were outside of the geographical region of interest (n=3). Twenty one studies were included in our final narrative synthesis. Figure 1 is a flowchart of the search, screening, and inclusion/exclusion process. Tables 1a-1d describe the data organized by exposure category: air, water, biomarker, and all other exposures.

Study Locations and Populations

The results included studies from eight states (AZ, CO, NM, TX, Oklahoma (OK), North Dakota (ND), and South Dakota (SD)). The study populations included 15 studies of Native Americans from AZ, OK, SD, and ND, and five studies of with large proportions of Hispanics from NM, CO, and TX (see Table 2). Five of these states were included among our original six target states, no studies in UT were found, and OK, ND and SD were included as these populations were aggregated with a large cohort from AZ and it was not possible to disaggregate the results. The population in that study cohort was Native American and rural, and shared many of the characteristics of our targets as well. Exposure and outcomes were evaluated with the same methods and the populations represented were all rural.

Seventeen studies represented the results of two population-based cohorts. Three of these 17 studies were included from the Facing Rural Obstacles Now Through Intervention, Education and Research (FRONTIER study), which was based in rural western TX and focused on Hispanics [6–8]. Fourteen of the 17 studies were included from the Strong Heart Study cohort of Native Americans living in AZ, OK, ND and SD.

Recent Findings

Particulate Matter and Environmental Tobacco Smoke—Mass concentration of ambient particulate matter (PM) less than or equal to 10 um in diameter (PM_{10}) and $PM_{10–2.5}$ (the mass difference between PM_{10} and $PM_{2.5}$) were associated with an increase emergency room visits for cardiovascular events among adults during the warm season in a southern NM community adjacent to the U.S.-Mexico border [9]. Similar effects were noted for respiratory emergency visits when high PM_{10} (>4150 μg/m3) concentrations were excluded. Participants exposed to environmental tobacco smoke in the Strong Heart Study (n

=1843 non-smoking Native Americans) were at increased risk for cardiovascular disease relative to unexposed participants as demonstrated in the hazard ratio of 1.22 (CI:1.03 – 1.44) [10]. Stronger effects were observed among participants who consumed low vitamin E diets compared to those consuming higher amounts, particularly on the additive scale.

Arsenic and Iodine

Cardiovascular Disease.: When analyzing urinary arsenic exposure markers among Strong Heart Study participants, Moon et al. [11] reported significant associations with cardiovascular disease incidence as well as mortality. Although long-term, low-to-moderate concentrations of urinary arsenic and increasing arsenic methylation did not impact atherosclerosis risk among Strong Heart Study participants [12], these species were associated with small increases in carotid intima media thickness and atherosclerotic plaque in the carotid [13]. In the FRONTIER study, arsenic exposure - quantified by interpolated residential groundwater concentrations - was associated with coronary heart disease and hypertension, while hyperlipidemia association was associated with an allelic variant of the AS3MT gene, but not water arsenic concentrations [7].

Kidney Disease and Metabolic Disorders.: Also in the Strong Heart Study, long-term, low-to-moderate urinary arsenic concentrations and increasing arsenic methylation significantly elevated the risk of diabetes and chronic kidney disease [12]. The sum of inorganic and methylated species combined also increased the risk for diabetes [14–16]. Higher relative levels of urinary dimethylated arsenic species (DMA) excretion and lower levels of monomethylated species (MMA) were associated with increased body mass index [17]. In the FRONTIER study, Gong et al. [8] investigated associations between arsenic and iodine groundwater concentrations and hypothyroidism among 726 participants. Arsenic in groundwater >8 μg/L and cumulative arsenic exposure were significant predictors for hypothyroidism among Hispanics.

Kidney Disease.: Independent findings of the inverse association of inorganic arsenic with the prevalence of chronic kidney disease as evidenced by elevated prevalence of albuminuria points toward the importance of the detoxication processes of accumulated body burden of arsenic [18]. In a follow up analysis, both MMA and DMA were associated with increased chronic kidney disease incidence [19].

Other Outcomes.: Comparing the 80^{th} versus 20^{th} percentiles of urinary arsenic concentrations in the Strong Heart Study cohort, concentrations of methylated and inorganic urinary arsenic were also shown to increase the risk for lung and prostate cancer mortality [20]. Edwards et al. [6] reported that exposure to low-level arsenic, based on estimated ground water concentrations in the FRONTIER study, was negatively associated with language ($p < 0.001$) and executive functioning ($p < 0.001$).

Cadmium—Urinary cadmium levels were associated with increased risk for cardiovascular and coronary heart disease mortality in the Strong Heart Study cohort when comparing the 80^{th} to the 20^{th} percentile of concentrations [21]. The associations were similar in most study subgroups, including never-smokers. Urinary cadmium concentrations were also associated with an increased risk for incident peripheral arterial disease in models adjusted for smoking [22], and elevated systolic blood pressure in models adjusted for kidney function [23]. Also in the Strong Heart Study, Garcia-Esquinas et al. [24] reported significant associations between urinary cadmium concentrations and total incidence of cancer, as well as increased mortality from lung cancer, pancreatic cancer, and all smoking-related cancers combined.

Other Exposures—Associations between residential proximity to natural gas development and birth outcomes were examined using 124,842 birth records from Colorado Vital Birth Statistics [25]. Prevalence of congenital heart defects increased with exposure tertile. Neural tube defect was associated with the highest tertile of exposure (>125 natural gas wells per mile) compared with no natural gas wells within a 10-mile radius. Exposure was negatively associated with preterm birth and positively associated with fetal growth and no association was found between exposure and oral clefts.

Zhang et al. [26] evaluated the effects of daily temperature, humidity and ozone on clinic visits in a retrospective electronic medical records review that included 380 clinic visits from Hispanic migrant and seasonal farmworkers to a community clinic in CO. Heat effects were associated with increased average daily clinic visits among migrant farmworkers, with stronger associations among male seasonal farmworkers. Increased excess risk on patient clinic visits were 88.0% without adjustment for ozone, and 92.6% with adjustment.

Conclusions

Although small, the current body of literature suggests that rural populations in the southwest, mountain west, and adjacent regions of the US experience exposures to environmental pollutants sufficient to result in elevated risks for numerous health outcomes despite living in areas with lower levels of many anthropogenic pollutants characteristic of urban areas. Sources of these pollutants may differ from those in urban areas, but exposures are still identifiable as are associated adverse health outcomes. Rural populations in this region can experience exposures from anthropogenic sources such as resource extraction, smoking, and wood smoke, as well as from naturally occurring contaminants such as arsenic in drinking water and particulate matter from windblown dust.

There are many inherent challenges to conducting environmental population studies in rural areas. Due to sparse population density, and low environmental exposure levels, it is a challenge to obtain sufficient sample size to achieve statistical power. Therefore, the environmental epidemiology studies represented in this review provide important insight into the burden environmental exposures and health effects experienced by the rural populations in this region, often by inclusion of numerous similar populations across multiple regions with similar exposures.

The body of literature identified and summarized in this review consistently reported adverse health outcomes associated with environmental exposure to particulate matter, arsenic, cadmium, and other agents for rural, minority populations. These findings were also supported by a large US-wide cancer prevention study analysis that reported that arsenic and other metals had significant contribution to health risks through particulate matter exposure pathways [27].

It is important to emphasize that there is still an existing research gap in understanding the mechanisms through which arsenic and its methylated products influence cardiovascular risk, mortality, and type II diabetes development resulting in consistently adverse, severe health effects. There remains opportunity to build on this work to further address the environmental and health disparities observed among these populations. Resource and land use patterns among rural and minority populations often differ from those in urban areas, and extrapolation to exposure may require different modeling methods.

Additional studies that more explicitly identify sources of contaminant exposure and provide multiple and consistent methods to identify exposures, including spatial analytical methodologies, are urgently needed. Large-scale land-use information that can integrate with community settings, outdoor recreational activities and potential toxicant patterns would aid future intervention efforts to reduce exposures. Additionally, more inclusion of rural and minority populations in larger health studies would further illustrate existing disparities among populations with the ultimate goal to find solutions decreasing such health inequities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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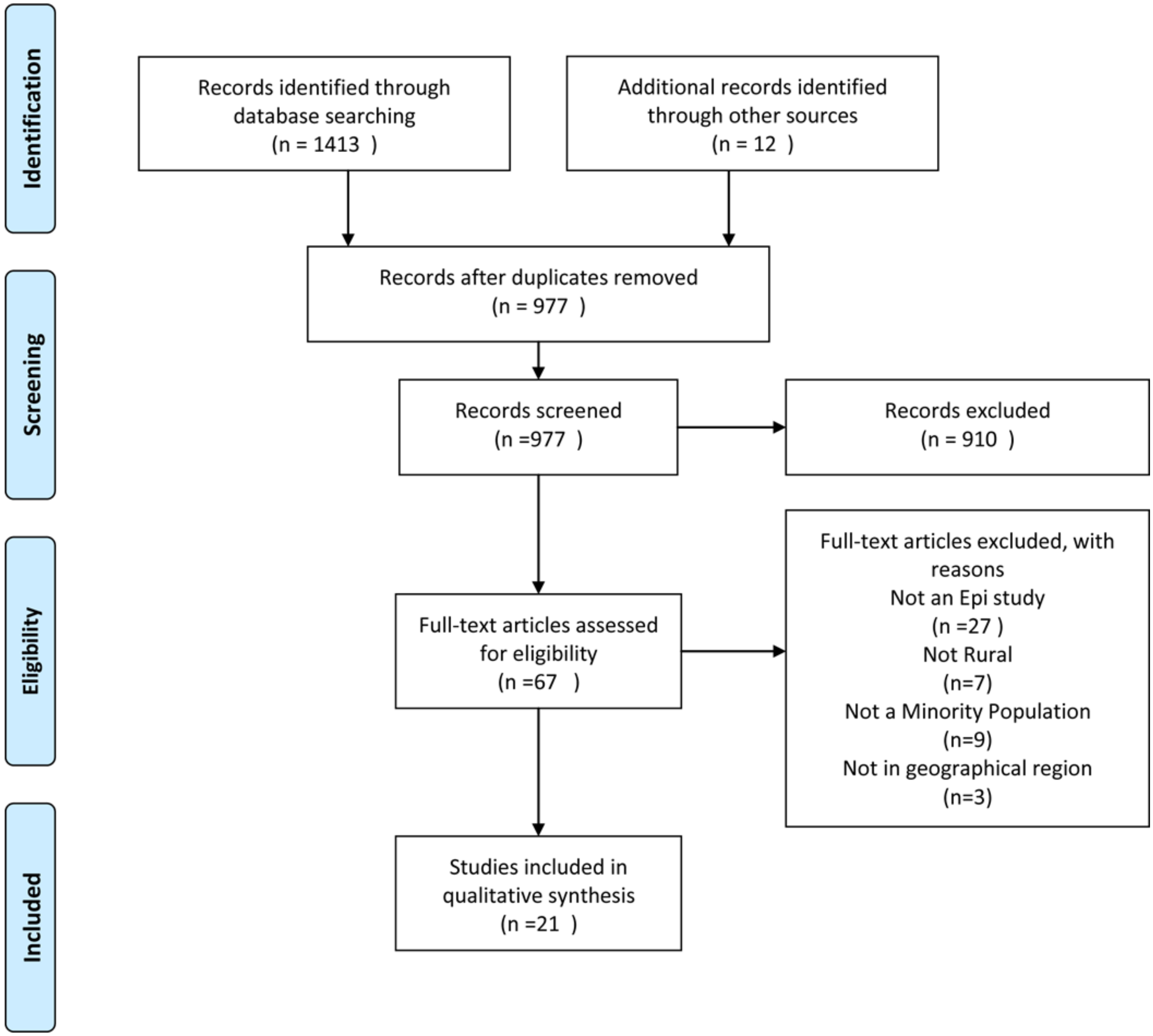

Figure 1.
Flowchart of the search, screening, and inclusion/exclusion process. From [6]. For more information, visit www.prisma-statement.org

Table 1.

Summary of environmental epidemiology studies among rural, minority populations in the southwest/mountain west region of the United States published between 2012 and 2017 by environmental or biological media used to assess exposure.

Table 1.a. Air.

Reference	Study Location	Sample size (source)	Sample Characteristics	Exposure	Health Outcome	Covariates	Results
Rajkumar, et al. 2017[10]	Arizona (AZ), Oklahoma (OK), South Dakota (SD), North Dakota (ND)	n=1843 (Strong Heart Study)	1254 smokers, 1843 non-smokers, Adult Native Americans, age: 45– 74 years, 62.8% women non-smokers	Environmental tobacco smoke (ETS), dietary factors (vitamin E, vitamin C, fiber, β-carotene, total polyunsaturated fatty acids)	Cardiovascular disease (CVD)	Age, sex, smoking history, albuminuria, total calorie intake.	Elevated hazard ratio for CVD among ETS exposed versus unexposed (HR 1.22; 95% Ci, 1.03 to 1.44). Stronger effects of ETS on CVD among those consuming diets low in vitamin E.
Rodopoulou, et al. 2014[9]	Las Cruces and Dona Ana Counties, New Mexico (NM)	n= 4739 Emergency room visits; n=2381 hospital admissions (Memorial Medical Center 2007–2010)	Adults > 18 years, 46.7% Hispanic	PM10; PM10–2.5; PM2.5; Ozone (with and without lag, by season and regional source of air pollution)	Respiratory and cardiovascular emergency room (ER) visits and hospital admissions	Season, long-term pollutant trends, daily temperature, influenza outbreaks	Significant increase in cardiovascular ER visits for PM10 (3.1%) and PM10-(2.5%) in warm season (April–Sept). When high PM10 (4150 μg/m3) was excluded, significant increased incidence of respiratory ER visits reported for PM10 (3.2%) and PM2.5 (5.2%)

Table 1.b. Water

Reference	Study Location	Sample size (source)	Sample Characteristics	Exposure	Health Outcome	Covariates	Results
Edwards et al. 2014[6]	3 rural counties in west Texas (TX)	n=527 participants in the Facing Rural Obstacles Now Through Intervention, Education and Research (FRONTIER) cohort	Adults age 40–96 years, 42% Hispanic	Arsenic (As) and selenium (Se) in residential groundwater (used for drinking and cooking) estimated by inverse distance weighted interpolation	Cognitive function (language, delayed memory, executive functioning)	Age, ethnicity, gender, education, smoking status, AS3MT (rs10748835) polymorphism	Low-level As exposure was negatively associated with cognitive functioning including language ($p < 0.001$) and executive functioning ($p < 0.001$). AS3MT gene modified the risk
Gong et al. 2012[7]	3 rural counties in west Texas (TX)	N=499 participants (FRONTIER)	Adults from FRONTIER cohort (mean 61 years),	Interpolated residential	Coronary heart disease (CHD),	Age, ethnicity, gender, education,	Higher As associated with CHD ($p<0.05$) and AS3MT genotype GG

Table 1.b. Water

Reference	Study Location	Sample size (source)	Sample Characteristics	Exposure	Health Outcome	Covariates	Results
			68% women, 41% Hispanic	groundwater As	hypertension, or hyperlipidemia	smoking, alcohol, anti-hyperlipidemia medication, AS3MT (rs10748835)	vs. AA ($p<0.05$). Hypertension associated with higher As. Hyperlipidemia associated with AS3MT genotype AG vs. AA ($p<0.05$).
Gong, G. 2015[8]	3 rural counties in west Texas (TX)	n=726 participants in Facing rural obstacles now through intervention, education and research (FRONTIER)	Adults from FRONTIER cohort, 53% Hispanic, 69% female	Interpolated As and iodine levels in residential groundwater	Hypothyroidism	Age, gender, annual household income, and health insurance coverage	As concentrations >8 mg/L and cumulative As exposure significant predictors for hypothyroidism among Hispanics. Ethnic difference may be due to higher percentage of Hispanics ($p=0.0622$) living in areas with arsenic >8 mg/L compared to non-Hispanic Whites. Prevalence of hypothyroidism was significantly higher in this rural cohort than the US population

Table 1.c. Biomonitoring

Author (date)	Study Location	Sample size (source)	Sample Characteristics	Exposure	Health Outcome	Covariates	Results
Franceschini, et al. 2017[23]	Arizona (AZ), Oklahoma (OK), South Dakota (SD), North Dakota (ND)	N= 3714 (Strong Heart Study)	Adult Native Americans; age: 45–74 years; enrolled from 1989 to 1991; mean age 56 years, 59% female	Urinary cadmium (Cd)	Hypertension	Age, sex, geographic area, body mass index, smoking, and kidney function	Urinary Cd significantly associated with higher systolic blood pressure ($p=0.002$). Significant association present among light- and never-smokers $P=0.002$), but not among never-smokers ($p=0.18$). Cd was also associated with diastolic blood pressure among light- and never-smokers ($p=0.004$).
Garcia-Esquinas, et al. 2013[20]	AZ, OK, SD, ND	n= 3932; 386 overall cancer deaths (Strong Heart Study)	Adult Native Americans; age: 45–74 years; followed through 2008; 58.5% female	Urinary inorganic arsenic (iAs) and total As (iAs and methylated As)	Cancer mortality	Sex, age, education, smoking, alcohol use, BMI, Breast was adjusted for menopausal status and parity, Kidney was adjusted for glomerular filtration rate	Comparing the 80th versus 20th percentiles of As, hazard ratio (HR, 95% CI) for overall cancer 1.14 (0.92–1.41), lung cancer HR 1.56 (1.02–2.39), liver cancer HR 1.34 (0.66, 2.72), prostate cancer HR 3.30 (1.28–8.48), kidney cancer HR 0.44 (0.14, 1.14), pancreatic cancer HR 2.46

Table 1.c. Biomonitoring

Author (date)	Study Location	Sample size (source)	Sample Characteristics	Exposure	Health Outcome	Covariates	Results
							(1.09–5.58), lymphatic and hematopoietic cancers HR 0.46 (0.22–0.96). No association between As and cancers of the esophagus and stomach, colon and rectum or breast.
Garcia-Esquinas, et al. 2014[24]	AZ, OK, SD, ND	n= 3792; (Strong Heart Study)	Adult Native Americans; age: 45–74 years; 59.4% female	Urinary cadmium (Cd)	Cancer mortality	Sex, age, smoking status, cigarette pack-years, and body mass index	Comparing the 80th versus 20th percentiles of Cd, Hazard ratios (HR, 95% CI) for total cancer HR 1.30 (1.09, 1.55), lung cancer HR 2.27 (1.58, 3.27), pancreatic cancer HR 2.40 (1.39, 4.17), and for all smoking-related cancers combined, HR was 1.56 (95% CI: 1.24, 1.96). in mediation analysis, estimated % lung cancer deaths among smokers attributed to Cd was 9.0% (2.8%, 21.8%).
Gribble, et al. 2013[17]	AZ, OK, SD, ND	n= 3925 total; n= 1939 diabetics and n=1986 non-diabetics (Strong Heart Study)	Adult Native Americans; age: 45–74 years; 58.9% female	Percentages of urinary inorganic (iAs), methylarsonate (MMA) and dimethylarsinate (DMA) As species	Body mass index (BMI), percent body fat and fat free mass	Age, sex; education, alcohol use; smoking; BMI, geographical regions and urine creatinine	Higher mean %DMA and lower mean %MMA were associated with elevated BMI. %DMA was 2.4% (2.1, 2.6) higher per increase in BMI category, and %MMA was 1.6% (1.4, 1.7) lower. Similar patterns were observed for % body fat, fat free mass, and waist circumference, However these associations were attenuated or disappeared when adjusted for BMI.
Gribble, et al. 2012[16]	AZ, OK, SD, ND	n= 3925 total; n= 1939 diabetics and n=1,986 non-diabetics (Strong Heart Study)	Adult Native Americans; age: 45–74 years; Diabetic n= 1939, 62.8% female; Non-diabetic n=1986, 55.7% female	Urinary total As	Type II diabetes	Age, sex; education, alcohol use, smoking; BMI, geographic region, urinary creatinine	Comparing the 75th versus 25th percentiles of total As excretion, the prevalence ratio for diabetes was 1.14 (95% CI 1.08, 1.21).
Kim, et al. 2013[14]	AZ	n= 300; Type II Diabetes n= 150 (Strong Heart Study, AZ only)	Adult Native Americans; cases diagnosed between 1982–2007: mean age 33.0 (SD ± 6.9) years; controls mean age 31.6 (SD ± 8.0) years	Urinary total arsenic (As) and inorganic As (iAs)	Type II diabetes	Age, sex, urine creatinine, BMI	Two-fold increase in total and iAs, elevated risk for incident diabetes OR 1.11 (95% CI 0.79 −1.57) and 1.16 (0.89 – 1.53) respectively. Positive relationship between quartiles of iAs and incident diabetes (p = 0.056); post-hoc comparison of quartiles

Table 1.c. Biomonitoring

Author (date)	Study Location	Sample size (source)	Sample Characteristics	Exposure	Health Outcome	Covariates	Results
							2–4 with quartile 1 revealed 2-fold higher odds of diabetes in the upper quartiles (OR = 2.14 (95% CI 1.19 to 3.85)).
Kuo, et al., 2015[15]	AZ, OK, SD, ND	n=1694 (Strong Heart Study)	Adult Native Americans; age: 45–74 years; diabetes-free participants recruited in 1989–1991 and followed through 1998–1999, 53.0% female	Total and speciated urinary As; and percent inorganic arsenic (iAs), monomethylarsonate (MMA), and dimethylarsinate (DMA)	Type II diabetes, metabolic problem	Study center, age, sum of iAS and methylated arsenic concentrations, sex, education, smoking, alcohol consumption, BMI, and waist-to-hip ratio	Per 5% increase in MMA% the hazard ratio (95% CI) for diabetes incidence was 0.77(0.63–0.93) and 0.82 (0.73–0.92) when iAs% and DMA%, respectively, were not included. DMA% was associated with higher diabetes incidence only when MMA% decreased, but not when iAs% decreased. iAs% was associated with higher diabetes incidence when MMA% decreased.
Mateen, et al., 2017[13]	AZ, OK, SD, ND	n= 2402 baseline 1989–1991 cohort (Strong Heart Study)	Adult Native Americans; age: 45–74 years; 63.1% female	Total urinary arsenic (As)	Carotid intima media thickness (CIMT), atherosclerotic plaque in the carotid, and plaque score	Age, sex, education, smoking, body mass index, hypertension, diabetes, LDL cholesterol, and eGFR.	Comparing 80th vs. 20th percentile urinary As, the mean difference in CIMT was 0.01 mm (95%CI: 0.00, 0.02 mm), the relative risk of plaque presence was 1.04 (95%CI: 0.99, 1.09), and the geometric mean ratio of plaque score was 1.05 (95%CI: 1.01, 1.09).
Moon, et al. 2013[11]	AZ, OK, SD, ND	N=3575; CVD cases n=1184, fatal CVD n=439 (Strong Heart Study)	Adult Native Americans; age: 45–74 years; 60.2% female	Urinary arsenic as a sum of inorganic arsenic (iAs), and methylated arsenic species at baseline enrollment	Incident CVD	Socio-demographic factors, smoking, body mass index, and lipids	Comparing the highest to lowest quartile As concentrations, the hazard ratios (95% CI) for cardiovascular disease, coronary heart disease, and stroke mortality after adjustment were 1.65 (1.20, 2.27; p trend< 0.001), 1.71 (1.19, 2.44; p-trend<0.001) and 3.03 (1.08, 8.50; p-trend=0.061). Hazard ratios for incident cardiovascular disease, coronary heart disease, and stroke were 1.32 (1.09, 1.59; p-trend=0.002), 1.30 (1.04, 1.62; p-trend=0.006), and 1.47 (0.97, 2.21; p-trend=0.032).

Table 1.c. Biomonitoring

Author (date)	Study Location	Sample size (source)	Sample Characteristics	Exposure	Health Outcome	Covariates	Results
Newman, et al. 2016[12]	AZ, OK, SD, ND	N=2875 (Strong Heart Study)	Adult Native Americans; age: 45–74 years; 48.6% female	Sum of inorganic and methylated urinary arsenic (As) species at baseline enrollment	Peripheral arterial disease (PAD) measured by ankle brachial index (ABI)	Sex, age, education, smoking, body mass index, low-density lipoprotein cholesterol, diabetes, hypertension, and estimated glomerular filtration rate & study center	Comparing the highest to lowest tertiles of urinary As, hazard ratios (95% CI): were 0.57 (0.32, 1.01) for ABI <0.9 and 2.24 (1.01, 4.32) for ABI >1.4. Increased As methylation associated with 2-fold increased risk of ABI >1.4 (HR 2.04 (1.02, 3.41)). Long-term low-to-moderate total As and increased As methylation associated with ABI >1.4 but not ABI <0.9; where ABI< 0.9 indicative of atherosclerosis, and >1.4 associated with diabetes and chronic kidney disease
Tellez-Plaza, et al. 2013[23]	AZ, OK, SD, ND	n= 3348; CVD n=1084, and deaths n=400 (Strong Heart Study)	Adult Native Americans; age: 45–74 years; 60% female	Urinary cadmium (Cd)	Incident cardiovascular diseases and coronary heart disease (CHD) mortality	Sex, postmenopausal status for women, education, body mass index (BMI), total cholesterol, estimated LDL cholesterol, hypertension, diabetes, and estimated GFR, smoking status	Comparing 80th to 20th percentile of Cd, Hazard Ratio (HR, 95% CI) was 1.43 (1.21–1.70) for cardiovascular mortality, 1.34 (1.10–1.63) for CHD mortality; 1.24 (1.11–1.38) for incident CVD, 1.22 (1.08–1.38) for coronary heart disease, 1.75 (1.17–2.59) for stroke and 1.39 (1.01–1.94) for heart failure. The associations were similar across subgroups, including never-smokers.
Tellez-Plaza, et al. 2013[22]	AZ, OK, SD, ND	n=2864; PAD Cases n=470 (Strong Heart Study)	Adult Native Americans; age: 45–74 years; followed until 1999; 61.1% female	Urinary cadmium (Cd)	Incident peripheral arterial disease (PAD) measured by ankle brachial index (ABI)	Smoking status and pack-year	Hazard ratio (95% CI) comparing 80th to 20th percentile of Cd was 1.41 (1.05, 1.81) for PAD. Comparing the highest to lowest tertiles was HR1.96 (1.32, 2.81).
Zheng, et al. 2013[18]	AZ, OK, SD, ND	n=3821 (Strong Heart Study)	Adult Native Americans; age: 45–74 years; 59.1% female	Total urinary arsenic (As)	Albuminuria defined as urinary albumin-creatinine ratio (ACR)	Sex, age, location, education, BMI, smoking, alcohol use, diabetes, systolic blood pressure, hypertension medication, eGFR	Comparing the three highest to lowest quartiles of As, Adjusted prevalence ratios for ACR were 1.16 (1.00–1.34), 1.24 (1.07–1.43), and 1.55 (1.35–1.78), respectively (p-value for trend <0.001).
Zheng, et al. 2015[19]	AZ, OK, SD, ND	N= 3119 (Strong Heart Study)	Adult Native Americans; age: 45–74 years;	Total urinary arsenic (As) including inorganic (iAs),	Chronic kidney disease (CDK)	Sex, age, location, education, smoking, BMI,	The adjusted odds ratio (OR; 95% CI) of prevalent CKD for an interquartile

Table 1.c. Biomonitoring

Author (date)	Study Location	Sample size (source)	Sample Characteristics	Exposure	Health Outcome	Covariates	Results
			no disease group - 57% female; prevalent CKD group - 77% female; incident CKD group - 68% female	Monomethylarsonate (MMA) and dimethylarsinate (DMA)	defined as glomerular filtration rate ≤ 60, kidney transplant or on dialysis.	hypertension medication, systolic blood pressure (SBP), diabetes status, and fasting glucose	range in total arsenic was 0.7 (0.6, 0.8), mostly due to an inverse association with iAs (OR: 0.4 [0.3, 0.4]) and MMA and DMA positively associated with prevalent CKD after adjustment for iAs (OR: 3.8 and 1.8). The adjusted hazard ratio (HR) of incident CKD for an IQR in total As was 1.2 (1.03, 1.41). The HR for iAs, MMA and DME were 1.0 (0.9, 1.2), 1.2 (1.00, 1.3), and 1.2 (1.0, 1.4) respectively.

Table 1.d. Other

Author (date)	Study Locaiton	Sample size (source)	Sample Characteristics	Exposure	Health Outcome	Covariates	Results
McKenzie, et al. 2014[25]	Rural Colorado (CO)	n=124842 birth records from Colorado Vital Birth Statistics	73% Non-Hispanic White mothers, 49% female babies	Inverse distance weighting of natural gas wells found within a 10 mile buffer around maternal residence	Congenital heart defects (CHDs), neural tube defects (NTDs), oral clefts, preterm birth, and term low birth weight.	Adjusted for maternal ethnicity, infant sex, maternal smoking, maternal alcohol, parity, residential elevation, and maternal education	Compared with the absence of any gas wells within a 10-mile radius, exposure tertile associated with increased risk of CHD (OR=1.3 (1.2, 1.5)) and NTD (OR = 2.0 (1.0, 3.9)). Exposure was negatively associated with preterm birth and positively associated with fetal growth, although the magnitude of association was small. No association was found between exposure and oral clefts.
Zhang, et al. 2016[26]	Colorado (CO) Community and Migrant Health Centre (C/MHC)	n=14481 patient records including 150 migrant and 231 seasonal farm workers	62% Hispanic for all patients, 87.7% and 86.6% Hispanic for migrant and seasonal farmworkers respectively	Daily mean apparent temperature (temperature and humidity), average daily ozone O3	Daily heat versus all-cause or cardiovascular-specific clinic visits	Time trends and weekly patterns	Estimates of heat effects on average daily clinic visits among migrant farmworkers were positive (88.0%, 95% CI: 26.2% to 180.0%). For migrant farmworkers, heat had a stronger association for males, and their risk of going to a clinic increased by 118.1% on hot days compared to normal days. estimated per cent increases of excess risk on patient clinic visits were 88.0% without adjustment for O3 and 92.6% with adjustment for O3, respectively.

Table 2:

Summary of reviewed studies by gender, race/ethnicity, exposure, and health outcomes for adults and children

Variable	Adults (18 years and older)	Children
Gender	Male and female[6–26]	Male and female[25]
Race/Ethnicity of Study Population	Native American[10–24] Mixed[6–9,25,26]	Mixed[25]
Exposure Media	Water[6–8,11] Air[9,10] Other[22,27]	Air[26] Other[25]
Exposure Measurement	Ambient Ozone[26] Ambient PM[9] Body composition[17] Diet[10] Drinking water[7] GIS interpolation[6,8] Daily Temperature[26] Proximity to emission sources[25] Environmental Tobacco Smoke[10] Urinary metabolites[11–16,18–26]	Proximity to emission sources[25]
Health Outcomes	Arsenic metabolism[17] Blood pressure[23] Cancer mortality[20,24] Cardiovascular Disease[7,9–13,21,22] Clinic visits[26] Cognitive function[6] Diabetes (Type II)[14–16] Hypothyroidism[8] Kidney disease[19,26] Respiratory conditions[9]	Birth defects[25]