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Short communication

Considerations when using longitudinal cohort studies to assess dietary exposure to inorganic arsenic and chronic health outcomes

Carolyn G. Scrafford [a,*], Leila M. Barraj [a], Joyce S. Tsuji [b]

[a] Center for Chemical Regulation and Food Safety, Exponent, Inc., 1150 Connecticut Avenue, NW, Washington DC, 20036, USA
[b] Toxicology and Mechanistic Biology, Exponent, Inc., 15375 SE 30th Place, Suite 250, Bellevue, WA, 98007, USA

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ABSTRACT

Dietary arsenic exposure and chronic health outcomes are of interest, due in part to increased awareness and data available on inorganic arsenic levels in some foods. Recent concerns regarding levels of inorganic arsenic, the primary form of arsenic of human health concern, in foods are based on extrapolation from adverse health effects observed at high levels of inorganic arsenic exposure; the potential for the occurrence of these health effects from lower levels of dietary inorganic arsenic exposure has not been established. In this review, longitudinal cohort studies are evaluated for their utility in estimating dietary inorganic arsenic exposure and quantifying statistically reliable associations with health outcomes. The primary limiting factor in longitudinal studies is incomplete data on inorganic arsenic levels in foods combined with the aggregation of consumption of foods with varying arsenic levels into a single category, resulting in exposure misclassification. Longitudinal cohort studies could provide some evidence to evaluate associations of dietary patterns related to inorganic arsenic exposure with risk of arsenic-related diseases. However, currently available data from longitudinal cohort studies limit causal analyses regarding the association between inorganic arsenic exposure and health outcomes. Any conclusions should therefore be viewed with knowledge of the analytical and methodological limitations.

1. Introduction

The level of arsenic in food and chronic health outcomes associated with dietary exposure is currently a topic of considerable interest for the public, U.S. and international regulatory agencies, scientific researchers, and public health professionals. Publication of arsenic monitoring results in apple juice and rice and rice-based products by the U.S. Food and Drug Administration (FDA) (U.S. FDA, 2011,2013) and fruit juices and rice-based products by the Consumer Reports Magazine (Consumers Union, 2012a,b) followed by a quantitative assessment of inorganic arsenic in apple juice conducted by the U.S. FDA (Carrington et al., 2013) has increased the consumers' awareness of the presence of arsenic in their food supply.

Inorganic arsenic is the primary form of arsenic that has been associated with human health effects. Recent concerns regarding background levels of inorganic arsenic in foods have been based on extrapolation from adverse health effects observed at much higher inorganic arsenic doses. Further, often only total arsenic levels are reported for foods and therefore, arsenic exposure estimated from such data will include inorganic arsenic along with organic forms, which are much less toxic (Cohen et al., 2013). These risk estimates are typically based on high exposures in populations drinking inorganic arsenic in groundwater from outside of the U.S. linked to cancers of the skin, lung, and bladder (IARC, 2012) as well as ischemic heart disease, hypertension and stroke (NRC, 2013). Health risks in populations have not been documented at considerably lower levels of inorganic arsenic from background dietary exposures (e.g., dose levels over 100 times lower than in the more highly exposed populations, Cohen et al., 2013; Xue et al., 2010), and some recent research has indicated that such low exposures would be associated with negligible risk of health effects (Cohen et al., 2013). A meta-analysis of observational epidemiological studies of nutritionally-sufficient populations indicates that low levels of exposure to inorganic arsenic, based on populations primarily exposed to lower levels of arsenic in water (e.g., <100 μg/L), does not increase risk of bladder cancer incidence (Tsuji et al., 2014). Cross-sectional evaluations to estimate dietary exposure to inorganic arsenic using national survey data have been conducted

* Corresponding author.
E-mail address: cscrafford@exponent.com (C.G. Scrafford).

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(Xue et al., 2010; Davis et al., 2012); however, association of such data with incidence of health outcomes are complicated by limitations in the available inorganic arsenic data in foods and accurate estimations of consumption of these foods along with the cross-sectional study design in which no information is available to assess whether the exposure preceded the disease in question. Databases from longitudinal studies could provide an improved basis to understand whether the dietary patterns may be associated with health outcomes.

To evaluate the feasibility and appropriateness of quantifying the association between dietary inorganic arsenic exposure and associated chronic health outcomes, we reviewed 11 publically available epidemiological cohorts with underlying data that would allow for a longitudinal evaluation of consumption of foods known to contribute to dietary inorganic arsenic and select health outcomes. This article summarizes our findings based on reviews of existing study populations and cohorts that represent the data that are available in the U.S. with a focus on the methodological and analytical considerations. These considerations are particularly relevant to an assessment of health outcomes associated with dietary consumption patterns with higher potential inorganic arsenic exposure. Specifically, this review focuses on the dietary assessment methods available in longitudinal studies to quantify, or surrogate for, exposure; the correlation with, and availability of, inorganic arsenic levels in dietary sources; and the feasibility of quantifying statistically reliable associations with chronic health outcomes as it relates to dietary inorganic arsenic exposure.

2. Methods

We reviewed the National Health and Nutrition Examination Surveys (NHANES) 1988–1994 (NHANES III) to determine if the dietary information collected in the food frequency questionnaire (FFQ) can be used to identify dietary patterns for use in an evaluation of the association with mortality from long-term health outcomes in the U.S. population as collected in the NHANES III Mortality Follow-up survey. We also researched and evaluated a selection of longitudinal cohort studies conducted in the U.S. for assessment of health outcomes associated with consumption of foods assumed to have higher inorganic arsenic levels. Table 1 presents a summary of the criteria used to evaluate the components and characteristics of selected individual studies and cohorts. The health outcomes evaluated included incidence of, or mortality from cancer, cardiovascular disease, and diabetes based on previous scientific research in populations with higher inorganic arsenic exposures (IARC, 2012; USDHHS/ATSDR, 2011; NRC, 2013).

3. Results of review of longitudinal studies

The individual study/cohorts included in the review are summarized in Table 2. A summary of the methodological and analytical considerations in using these studies to evaluate the association between dietary inorganic arsenic exposure and health outcomes follows.

3.1. Dietary assessment

The primary method of dietary assessment in the studies included in this review was an FFQ aimed at estimating usual or longer-term consumption patterns. These questionnaires are primarily administered at baseline only (i.e., enrollment). For example, the NHANES III FFQ was collected once at enrollment and included 60 food categories. Study participants were asked to report their frequency of consumption of each category over the past month. The implementation of the FFQ in NHANES III was intended to collect qualitative dietary data that allows for the assessment of general trends in the subject's diet (NCHS, 1994). NHANES III also collected 24-dietary recalls from the participants; however, this represents short-term intake and would not necessarily be representative of the participant's typical diet. Use of the FFQ as the method of measuring usual, long-term dietary patterns and the association with mortality from chronic diseases such as cardiovascular disease, diabetes, and/or cancer is more appropriate than relying on short-term consumption patterns based on 24-h dietary recalls (Willett, 1998).

The FFQs included in the studies reviewed contained food categories ranging from approximately 60 to 131 items. Table 3 provides an example of the food categories collected in the NHANES III FFQ that may be of interest in an evaluation of dietary patterns associated with potentially higher dietary inorganic arsenic exposure based on previously published research (Xue et al., 2010; Schoof et al., 1999). Specifically, Xue et al. (2010) reported that the major food contributors to inorganic arsenic exposure were vegetables (24%), fruit juices and fruits (18%), rice (17%), beer and wine (12%), and flour, corn and wheat (11%).

Many of the categories of food included in the FFQ include a broad grouping of products. Some of the foods that are combined into one question within an FFQ may be high contributors to arsenic exposure while others were not. This aggregation of individual foods into broader categories would lead to potential exposure misclassification. For example, the NHANES III FFQ combines green beans, corn, peas, mushrooms, and zucchini under the “Other vegetables category”, while Schoof et al. (1999) sampled and analyzed green beans, corn, and peas, but not mushrooms and zucchini. Additionally, grapes, which have higher inorganic arsenic levels (Schoof et al., 1999), are often combined into a category with a number of other fruits, including those with low inorganic arsenic levels (e.g., bananas). Therefore, if an individual responds to the FFQ as a high consumer of “Other fruits” but is primarily a banana consumer, they may be incorrectly classified as having high exposure to inorganic arsenic-containing foods when in reality, they do not consume fruits known to have high levels.

Table 1
Criteria used to select and evaluate studies.

Component/characteristic	Criteria
Dietary assessment method	Food frequency questionnaire with appropriate grouping of foods and food groups with higher inorganic arsenic levels, including: a Rice b Beer/wine c Cereal products and breakfast cereal d Fruits and fruit juices e Fish/shellfish f Vegetables g Other grains including corn and flour
Sample size	Large population size to produce sufficient number of cases/deaths to allow for detection of statistically significant associations.
Population age	Study population ages 40 years and up to allow opportunity for incident cases to develop.

Table 2
Summary of NHANES III Mortality Follow-up and longitudinal cohort studies in the U.S.

Study	Duration	Study population	Dietary assessment	Considerations
NHANES III Mortality Follow-up	1988–1994; follow-up for mortality through Dec 31, 2006 (12–18 years)	N = 20,024; large study population representative of the US population 17 + years of age	60-item FFQ including rice (all kinds), fish/shellfish, fruits/veg and juices; leafy greens (including spinach); separates citrus fruits/juices from other fruits/juices	CVD, cancer, and diabetes mortality; no incidence 24-h dietary recall records allows for adjustment for dietary/nutrient factors Linkage to NDI allows for a complete assessment of outcomes Small number of deaths for specific types of cancer (e.g., skin, bladder) FFQ does not differentiate between white and brown rice Dietary FFQ/risk factors assessment administered once so potential for measurement error due to dietary changes over time.
NIH-AARP Diet and Health Study	Enrolled in 1995–1996; 1996–1997 received a risk-factor questionnaire, 2004–2006 received a follow-up questionnaire	N = 566,399; current members of AARP, aged 50–71 years residing in California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana OR metropolitan areas of Atlanta, Georgia and Detroit, Michigan; largely non-Hispanic white population	124-item NCI SFFQ with usual portion size: beer, cereals, cornbread/muffins, flour or corn tortillas, fish/shellfish, fruits/veg and juices; separates citrus fruits/juices from other fruits/juices; cooked vs raw leafy greens	CVD, cancer, and diabetes outcomes (incidence and mortality) Semi-quantitative FFQ will allow for more refined estimate of high consumers Linkage to NDI and state cancer registries allows for a complete assessment of outcomes Large study population (N = 566,401) 15 year follow-up FFQ does not differentiate between white and brown rice; also includes rice with all other cooked grains. Dietary FFQ/risk factors assessment administered once so potential for measurement error due to dietary changes over time. A follow-up questionnaire in 2005–2006 assessed a limited number of potential risk factors (FFQ not included).
ARIC: Atherosclerosis Risk in Communities Study	1987-present; Baseline: 1987–89 Follow-up: 1990–92 1993–95 1996–98 2011-13	N = 15,792; 4 center study with participants 45–64 years	66-item FFQ: fruits/juices, fish, shellfish, cold/hot cereal, rice (all types), beer, wine, cornbread/biscuits Second, more detailed FFQ administered in a subsample of participants	Includes CVD, cancer, an diabetes outcomes (incidence and mortality) via surveillance, registries and NDI Provides biological measurements of CVD risk factors – platelets, lipids, arterial health FFQ does not differentiate between white and brown rice Smaller study population may limit statistical power in analysis of specific health outcomes
Cardiovascular Health Study (CHS)	Enrolled in 1989–1990; 1992–1993, Examination June 1989. Participants contacted every 6 months to ascertain health status for events follow-up since 1999.	N = 5201; adult men and women aged 65 + years from 4 US communities; Additional 687 African Americans recruited after initial baseline survey.	Five category picture-sort version of the NCI SFFQ; consumption in past year. Food categories include: fruits; vegetables; fried fish; fish; high-fiber cereals	Includes CVD and incidence of diabetes outcomes Usual dietary intake assessed at baseline and at sixth annual visit allowing for evaluation of changes in dietary patterns and minimizing misclassification Reassessment of risk factors/lifestyle every year Average follow-up of 13 years Small study population may limit statistical power in analysis of specific health outcomes
HPFS: Health Professionals Follow-up Study	Initiated in 1986 - Ongoing - Updates every 2 years; dietary questionnaires every 4 years.	N = 51,529; men in health professions	131-item FFQ; fruits /fruit juices, veggies /veggie juice, fish, shellfish; cold breakfast cereal, cooked oatmeal, other cooked breakfast cereal, brown rice, tortillas, white rice; beer, red wine, white wine	FFQ with a fairly detailed fruits/vegetables/cereal section Brown/white rice as separate questions Incidence of myocardial infarction, CV revascularization procedures, cancer, diabetes Cause-specific mortality Has been combined with Nurses' Health Study Re-assessment of measurements every two years – allow for changes in dietary behavior/risk factors

(*continued on next page*)

Table 2 (*continued*)

Study	Duration	Study population	Dietary assessment	Considerations
NHS: Nurses' Health Study I and II	I: Initiated in 1976 - Ongoing - updates every 2 years II: Initiated in 1989- Ongoing - updates every 2 years; dietary questionnaires every 4 years.	I: N = 122,000 married registered female nurses 30–55yrs in 1976 from CA,CT, FL,MD,MA, MI, NJ, NY,OH,PA, and TX II: N = 116,686 female nurses 25–42 years in 1989	131-item FFQ; fruits/fruit juices; veggies /veggie juice; fish, shellfish; cold breakfast cereal, cooked oatmeal, other cooked breakfast cereal, brown rice, white rice, tortillas - corn and flour; beer, red wine, white wine	FFQ with a fairly detailed fruits/ vegetables/cereal section Brown/white rice as separate questions Incidence of myocardial infarction, CV revascularization procedures, cancer, diabetes Cause-specific mortality Has been combined with Health Professionals Follow-up Study Re-assessment of measurements every two years – allow for changes in dietary behavior/risk factors
Iowa Women's Health Study	Ongoing - Initiated in 1986; follow-up survey years: 1987, 1989, 1992, 1997, 2004	41,836 post-menopausal women (aged 55–69 years at baseline)	126 –item FFQ; 15 fruits/29 veggies; fruits, fruit juices; veggies, veggie juice; fish, shellfish; cold breakfast cereal, cooked oatmeal, other cooked breakfast cereal, brown rice, white rice, other grains; beer, red wine, white wine	FFQ with a fairly detailed fruits (n = 15)/vegetables (n = 29)/cereal section Brown/white rice; beer/wine as separate questions Incidence as well as mortality; publications on cancer include bladder, colon, kidneys, lung, ovarian, uterine Large study population
Women's Health Initiative (WHI) - Observational Study (OS)	1993–2005: enrollment began in 1994/ended in 1998. Follow-up 3 years after enrollment.	93,676 postmenopausal women (50 –79 years), ethnically diverse women.	Dietary FFQ (last 3 months) - fruits, fruit juices (some foods are combined and some are separate); vegetables (some foods are combined and some are separate); fried fish/shellfish (combined), not fried fish/shellfish; cold cereal, cooked cereals and grits; beer, wine (not specific); Rice combined with grains and plain noodles; corn bread, "corn muffins, and cornmeal mush", "tortillas, corn", "tortillas, flour or wheat"	Large study population Detailed data on risk factors/ confounders Shorter average follow-up (i.e., 8 years) Limited FFQ; rice combined with grains and plain noodles.
Bogalusa Heart Study	1973–74, 1976–77, 1978–79, 1981–82, 1988–91, 1992, 1997 –2002	N = 12,000 children screened since 1973 in Bogalusa, LA; followed up through 45 years of age.	64-item FFQ – consumption over the week before the survey; 24-h diaries; conducted from 1988 to 91 on all the 1963, 66, and 68 birth cohorts in the Post High School Study.	Atherosclerosis, coronary artery disease, hypertension, CVD risk factors Measured blood lipid and lipoprotein levels Individuals through age of 45 only; may limit follow-up for chronic disease outcomes
Framingham Heart Study/ Offspring Study[a]	1948-present; examination every two years Offspring: 1971-present; follow-up every 4–6 years	Men/women living in Framingham, MA (28–62 years) Offspring: N = 5124 men/women offspring of original FHS participants (5–70 years)	126- item SFFQ	Measured blood lipids, blood pressure, insulin Incidence and prevalence of CVD, stroke, hypertension, arterial disease, congestive heart failure In offspring study, participants have completed six exams Small study population may limit statistical power in analysis of specific health outcomes
CARDIA: Coronary Artery Risk Development in Young Adults	1986, 1987–1988 (Year 2), 1990 –1991 (Year 5), 1992–1993 (Year 7), 1995–1996 (Year 10), and 2000 –2001 (Year 15), 2005–2006 (Year 20), 2010–2011 (Year 25)	N = 5115 black and white men and women aged 18–30 years in Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA.	FFQ, diet and nutrition history questionnaires. CARDIA diet history last taken in 1992; FFQ taken once in 1987. FFQ: white rice, brown rice, rice mixes, fried rice, Mexican rice; hot cereals (broken down into regular and instant – oatmeal, farina, corn grits), cold cereals (broken down into unsweetened and sweetened and some brands), cornbread or hushpuppies; fruits and fruit juices (broken down into different types and some sweetened/ unsweetened), vegetables (broken down into individual types and raw/ fresh vs. canned) and vegetable juices, fish, shellfish (broken down into specific types) Alcohol questionnaire (separate from diet): beer, wine	Incidence and mortality endpoints Rice included in separate question. Small study population may limit statistical power in analysis of specific health outcomes Younger ages (18–30); may not allow enough follow-up for chronic disease endpoints. Limited FFQ – no wine, but includes 15 fruits and juices, 21 vegetables Dietary FFQ assessment administered once so potential for measurement error due to dietary changes over time.

Abbreviations: CVD – cardiovascular disease; FFQ – Food Frequency Questionnaire; NCI SFFQ–National Cancer Institute Semi-quantitative Food Frequency Questionnaire; NDI – National Death Index.

[a] FFQ was not publically available for review.

This aggregation is not universally problematic. For example, many of the FFQs differentiate between citrus fruits and non-citrus fruits; since citrus juice and fruits have been reported to be lower in inorganic arsenic compared to other fruits and juices (Schoof et al., 1999) this is one example of an FFQ design that would help to reduce exposure misclassification. Further, if one was looking to evaluate the association between just citrus fruits and a health outcome this dietary assessment method may prove to be sufficient and appropriate. However, for identifying overall dietary patterns associated with high inorganic arsenic exposure, the aggregation is an important limitation of any analysis that needs to be considered.

Of particular importance to inorganic arsenic is the method used to assess rice consumption, a food with considerable inorganic and organic arsenic data (Schoof et al., 1999; U.S. FDA, 2013; U.S. FDA, 2016). The frequency of rice consumption is often included with other cooked grains in the same question making it difficult to isolate the independent effects of rice on health outcomes. For example, the NIH-AARP Diet and Health Study includes rice with all other cooked grains while the Women's Health Initiative Observational Study (WHI-OS) includes rice with other grains and plain noodles. Alternatively, there are other studies, including NHANES III, the Atherosclerosis Risk in Communities Study (ARIC), and the Cardiovascular Health Study (CHS), with an FFQ designed to ask about rice consumption alone while other studies differentiate between white and brown rice (e.g., Iowa Women's Health Study, the Health Professionals Follow-up Study (HPFS), and Nurses' Health Study (NHS)). This isolation allows researchers to focus on high rice consumers and quantify the association with adverse health outcomes. For example, two recent pooled analyses of the HPFS and the NHS I and II quantified the association between white and brown rice consumption and health outcomes and concluded there was no statistically significant association with increased risk for the incidence of any cancer, site-specific cancers including prostate, breast, colon and rectum, melanoma, bladder, kidney, and lung, as well as CVD risk (Muraki et al., 2015; Zhang et al., 2016). A similar prospective cohort study in over 91,000 men and women in Japan found that higher rice consumption did not increase the risk of developing or dying from cardiovascular disease (Eshak et al., 2014).

3.2. Inorganic arsenic levels in food

Data on the level of inorganic arsenic in the foods reported consumed or typically consumed by participants in these various studies are lacking. The magnitude of inorganic levels in food varies greatly, even within a food category such as vegetables or rice. For example, in one study the mean concentration of inorganic arsenic in vegetables ranged from <0.8 ppb (potatoes) to 6.1 ppb (spinach) (Schoof et al., 1999). The U.S. FDA recently released their risk assessment on arsenic in rice and rice products where the average concentration of inorganic arsenic in brown rice was over 1.5 times higher the average concentration in white rice (92 ppb in white rice versus 154 ppb in brown rice) and the levels ranged from 23 ppb to 196 ppb and 34 ppb to 249 ppb, respectively (U.S. FDA, 2016). As a result, depending on the magnitude and variability of inorganic arsenic in the particular foods, conclusions regarding associations between a dietary pattern and inorganic arsenic exposure may not be an indication of a causative link between inorganic arsenic exposure and the health outcome.

Inorganic arsenic in crops is affected by arsenic in soil and water, growing conditions (e.g., anaerobic or aerobic conditions, bacteria action affecting transformation to organic forms) and the rate of uptake and accumulation of particular plant species, strains, and plant parts (Schoof et al., 1999; Zhao et al., 2009). Arsenic in livestock or fish would originate from their local environmental and dietary sources, although a large majority of arsenic is in the organic form (Schoof et al., 1999), which is associated with less health concern. Therefore, arsenic levels and forms in foods would be associated with types of foods, possibly strains, and the region/location of production. While the regional location of study participants is largely known by design in the selected longitudinal studies and the NHANES III database contains information on the respondent's region and county of residence, this does not necessarily correlate with where the food was grown and/or produced. Further, participants may have moved over the course of the follow-up and therefore if this data was available and incorporated, any associations, or lack thereof, may still reflect an inaccurate measurement of exposure. Inaccuracies in exposure from such variability may be less problematic for studies focusing on specific foods (e.g., rice; U.S. FDA, 2013) with relatively higher levels of inorganic arsenic for which regional variability may be relatively minor compared to whether people consume more or less amounts of the foods. When estimating total dietary exposure to inorganic arsenic, as is the focus of the current study, it is important to recognize the potential sources of variability and the effect this variability will have on the assessment. Regional differences in arsenic water concentrations (as considered by Muraki et al., 2015; Zhang et al., 2016) should be considered because inorganic arsenic exposure at the drinking water standard greatly exceeds dietary exposure (Tsuji et al., 2007), and may therefore confound dietary exposure. Differences in arsenic water concentrations also affect dietary arsenic exposure from use of water in food preparation, although direct consumption of drinking water results in much greater exposure to arsenic.

3.3. Use and limitations of biomarkers for exposure assessment

Arsenic biomarkers such as urinary arsenic levels can be used to represent total inorganic arsenic exposure in individuals from diet and water together. If such measures include total arsenic forms, however, they are confounded by potentially large amounts of the organic compounds in foods. Some studies have therefore speciated arsenic in urine for inorganic arsenic and its methylated metabolites (monomethylarsonic acid [MMA] and dimethylarsinic acid [DMA]) (e.g., Moon et al., 2013), which eliminates common essentially non-toxic organic arsenic compounds such arsenobetaine. Enzymatic oxidative metabolism of ingested inorganic arsenic produces MMA^{V} which is reduced to MMA^{III} and further methylated to DMA^{V}, the predominant form excreted in urine in humans (Cohen et al., 2013). Nevertheless, even such speciated measures of inorganic arsenic and its metabolites are confounded by contribution of additional methylated forms, particularly DMA or its organic precursors (e.g., arsenosugars), from the diet (Aylward et al., 2014; Tsuji et al., 2015). Such DMA in urine arising from dietary organic arsenic sources is not associated with health risks that result from exposure to the more reactive arsenic forms, i.e., inorganic arsenic and its trivalent metabolite MMA^{III}.

The higher speciated arsenic levels in urine of the U.S. population arise largely from DMA, which was correlated with the seafood compound arsenobetaine, and therefore are likely confounded by exposure to DMA and DMA precursors from seafood and is therefore not representative of inorganic arsenic exposure (Aylward et al., 2014). As a result, Aylward et al. (2014) suggest a speciated urinary arsenic measure limited to inorganic arsenic and MMA. With the exception of the NHANES database, the longitudinal cohorts included in this review do not collect data on biomarkers for inorganic arsenic exposure. Unfortunately, the detection limits for inorganic arsenic and MMA in the NHANES database are relatively high and these measures are mostly nondetectable.

Table 3
Example of selected food categories included in the NHANES III Food Frequency Questionnaire.

Food group	Question on NHANES III FFQ
Main dishes, meat, fish, chicken, and eggs	
Fish[a]	Fish including fillets, fish sticks, fish sandwiches, and tuna fish?
Shellfish	Shrimp, clams, oysters, crab, and lobster?
Fruit and fruit juices (include all forms – fresh, frozen, canned, and dried)	
Citrus fruits	Citrus fruits including oranges, grapefruits, and tangerines?
Other fruit juices	Other fruit juices such as grape juice, apple juice, cranberry juice, and fruit nectars?
Melons	Melons including cantaloupe, honeydew, and watermelon?
Stone fruits	Peaches, nectarines, apricots, guava, mango, and papaya?
Other fruits	Any other fruits such as apples, bananas, pears, berries, cherries, grapes, plums, strawberries? (Include plantains)
Vegetables (includes all forms – fresh, raw, frozen, canned, and cooked vegetables)	
Carrots	Carrots and vegetable mixtures containing carrots?
Broccoli	Broccoli
Brussels sprouts and cauliflower	Brussels sprouts and cauliflower
Squash	Sweet potatoes, yams, and orange squash including acorn, butternut, hubbard, and pumpkin?
Leafy greens	Spinach, greens, collards, and kale?
Salad	Tossed salad?
Cabbage	Cabbage, cole slaw, and sauerkraut?
Hot peppers	Hot red chili peppers. Do not count ground red chili peppers?
Peppers	Peppers including green, red, and yellow peppers?
Other vegetables	Any other vegetables such as green beans, corns, peas, mushrooms, and zucchini?
Nuts/legumes	
Peanut butter	Peanuts, peanut butter, other types of nuts, and seeds?
Cereals and grains	
Cereal	How about Bran Cereals?
	All other cold cereals and presweetened cereals?
	Cooked, hot cereals like oatmeal, cream of wheat, cream of rice, and grits?
Grains	Corn bread, corn muffins, and corn tortillas?
	Flour tortillas?
	Rice?
Alcoholic beverages	
Beer and wine	Beer and lite beer?
	Wine, wine coolers, sangria, and champagne?

[a] Fish and shellfish have a considerable amount of arsenic in the organic form, although a fraction is in the inorganic form.

3.4. Health outcomes

Health outcomes suggested to be associated with inorganic arsenic exposure cover a range of incidence, prevalence, and mortality rates. This is a consideration when designing a statistically reliable analysis. For health outcomes with a high incidence rate such as cardiovascular disease or total cancers, most longitudinal cohort studies included in this review will have followed-up a sufficient number of individuals to allow for a large sample size for analysis of both incidence and mortality. The NHANES III mortality follow-up data is limited to mortality outcomes only; therefore, incidence of cardiovascular disease, diabetes, or cancer is not available in this database. An analysis of bladder or skin cancer mortality will be difficult in any study population regardless of the duration of follow-up since these diseases have a high survival rate. Definitions for mortality outcomes as defined based on the International Classification of Diseases, Tenth Revision (ICD-10) used in NHANES III (NCHS, 2013) with the number of deaths reported in the current Mortality Follow-up database are summarized in Table 4. Note that the number of skin and bladder deaths is only 13 and 15, respectively, after 12–18 years of follow-up in a large study population ($N = 20{,}024$ people eligible to be matched to the National Death Index (NDI)). For this reason, bladder cancer mortality, while directly relevant to the question of the risks associated with inorganic arsenic exposure, will be more difficult to evaluate in most epidemiological analyses of prospective cohorts regardless of other methodological considerations due to less statistical power to detect associations. Cohort studies that collect data on incidence of cancer or cardiovascular cases (e.g., Muraki et al., 2015; Zhang et al., 2016) would provide a more robust database for analysis compared to those limited to mortality outcomes only.

4. Discussion and conclusions

Ideal studies for examining whether dietary arsenic results in increased risk of disease would be large prospective cohort studies that have 1. followed individuals long enough to observe a sufficient number of cases of and/or deaths from chronic health outcomes such as cancer and heart disease and 2. collected detailed dietary information that distinguishes among foods and their inorganic arsenic content. The key component of these studies that is largely missing in the current research is the data to understand and measure the magnitude and variability of inorganic arsenic in the foods consumed by the individuals within these cohorts to accurately assess exposure and associated health outcomes. The key factors that have been discussed in this review are summarized in Table 5.

A review of NHANES III along with longitudinal cohort studies in the U.S. was conducted to determine if the dietary information collected could be used to identify patterns associated with consumption of foods with higher inorganic arsenic exposure for use in an evaluation of the association with mortality from or incidence of long-term health outcomes in the U.S. population. The NHANES III database has many strengths, including a large population representative of the U.S., complete ascertainment of cause of death using the NDI, and long follow-up time with further updates planned for this year. Limitations include the small number of deaths due to some cancers of particular interest for arsenic exposure, such as bladder and skin cancer, as well as the limitations of FFQ where larger categories of foods are grouped together to assess usual intake. However, many of the food categories of interest such as rice, breakfast cereals, and beer are in stand-alone categories within the NHANES FFQ and therefore, would allow for

Table 4
Summary of ICD-10 classification of underlying cause of death among NHANES III participants eligible for mortality follow-up.

Cause of death	ICD-10 codes	Number of deaths
CHD	I20–I25	1392
Stroke	I60–I69	414
Any cancer	C00–C97	
Trachea, bronchus, lung	C33–C34	321
Skin	C43	13
Bladder	C67	15
Diabetes	E10-E14	175
Diabetes flagged as a contributing or multiple cause of death[a]	N/A	606

ICD = International Statistical Classification of Diseases and Related Health Problems; N/A = not applicable.
[a] This entry was asked as a separate question coded under variable 'DIABETES' which refers to '1' if ICD-9 code '250' or ICD-10 codes 'E10 thru E14' was coded in entity-axis or record-axis multiple cause of death codes.

Table 5
Summary of key factors and considerations when using cohort studies to assess dietary exposure to inorganic arsenic and chronic health outcomes.

Key factor	Considerations
Quantifiable level of inorganic arsenic in foods consumed by cohort over time	Large range of magnitude and variability of inorganic arsenic concentration in foods makes achieving this with any degree of precision or accuracy a difficult task. Further, inorganic arsenic concentrations in foods have been shown to vary by region/water source/soil types/growing conditions, and uptake and accumulation differences in crops.
Sample size sufficient to evaluate association with rare outcomes (e.g., bladder cancer)	Outcomes such as bladder and skin cancer mortality are rare due to high survival rate so difficult to assess with sufficient statistical power using a prospective cohort design. Large prospective studies that collect data on incidence of cancer and cardiovascular cases provide a more robust database for analysis.
Dietary assessment tools that allow for differentiation between consumption of foods with varying magnitudes of inorganic arsenic	Requires lengthy and detailed FFQ that is time- and effort-intensive for individuals to accurately complete.
Data on changes in dietary patterns and location of individuals/food sources	Multiple dietary assessments throughout the follow-up period are required.

an analysis isolating the association of these foods with health outcomes.

Among the longitudinal cohort studies conducted within academic institutions as well as the U.S. government and selected for review, many have similar strengths as NHANES III, with the further benefit of collecting data on disease incidence in addition to mortality. Regardless of dietary assessment limitations, population size and representativeness, and number of health outcomes, the lack of data on the level of inorganic arsenic in the foods reported consumed or typically consumed by participants and their exposure to arsenic through drinking water in any of these studies will be critical limiting factors. As mentioned above, arsenic levels in foods can be associated with the region of production and therefore, inorganic arsenic levels in foods consumed in populations could be variable. However, regional differences in levels of inorganic arsenic likely have less of an effect on inorganic arsenic exposure than dietary patterns that favor foods with relatively higher (e.g., green vegetables, rice, grapes) or lower inorganic arsenic levels (e.g., beef, potatoes) (U.S. FDA, 2013; Xue et al., 2010).

To improve upon the analysis of dietary patterns associated with higher inorganic arsenic exposure and chronic health outcomes, it may be possible and advisable to incorporate data on levels of inorganic arsenic in representative food products. Data from the U.S. FDA's Total Diet Study (U.S. FDA TDS) could be used, however; the levels in the TDS are limited to total arsenic. Xue et al. (2010) used the U.S. FDA TDS (2001–2004) database to model dietary exposure to inorganic arsenic by assuming the same percent of total arsenic in representative foods as reported in Schoof et al. (1999). This modeling was based on a single day of the 24-h dietary recall records (i.e., cross-sectional) in NHANES 2003–2006 but this approach could be modified to model longitudinal dietary exposure. Alternatively, data from published studies on inorganic arsenic levels could be utilized as well as recently released data on the levels in rice and rice products and apple juice. The limitations to this analysis include the small number of foods with robust data for assessing inorganic arsenic exposures and lack of data on inorganic arsenic content of specific foods and drinking water consumed by individuals.

In conclusion, the epidemiological cohorts included in this review provide a resource for assessing the association between dietary patterns and health outcomes suggested to be related to dietary inorganic arsenic exposure. However, adequate sample sizes for health outcomes specific to inorganic arsenic effects, consideration of the dietary assessment methods and associated food categories within each study design as well as the limitations in surrogating dietary patterns for inorganic arsenic exposure are important to consider when conducting and interpreting these specific analyses. Further, the lack of data on the levels of inorganic arsenic in foods (and water) actually consumed with sufficient follow-up for health outcomes within an individual significantly limits the validity of any conclusions that could be drawn from such an analysis. Therefore, any association between a dietary pattern and inorganic arsenic exposure would be ecological and may not reflect causation between inorganic arsenic exposure and the health outcome.

Conflict of interest

The authors disclose the receipt of financial support for work on this manuscript from ILSI North America Technical Committee on Food and Chemical Safety. ILSI North America is a public, nonprofit foundation that provides a forum to advance understanding of scientific issues related to the nutritional quality and safety of the food supply by sponsoring research programs, educational seminars and workshops, and publications. ILSI North America receives support primarily from its industry membership. The views expressed in this study are those of the authors. The authors are employed with Exponent, a scientific and engineering research and consulting firm, and have provided these services for private and government clients, including on projects involving arsenic. JST has presented on arsenic risk assessment issues in public comments to EPA and NAS on behalf of industry and trade associations with interests in arsenic. JST has been retained in defense and plaintiff litigation cases related to arsenic.

Transparency document

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