Inorganic Arsenic and Respiratory Health: An Update of a Systematic Review

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Abstract

This systematic review updates a systematic review that synthesized inorganic arsenic exposure and respiratory health effects published in 2016. The final review added eight publications from six countries. It examined the relationship between inorganic arsenic exposure and five respiratory outcomes, including lung function, respiratory symptoms, acute respiratory infections, chronic respiratory disease, and non-malignant lung disease mortality. Emerging evidence showed a general association between InAs and non-malignant respiratory illnesses, including consistent evidence on lung function impairment, respiratory symptoms, acute respiratory tract infections, and non-malignant lung disease. Early life InAs exposure has lasting effects on the respiratory system throughout the lifespan. This review found some research gaps, including mixed evidence of sex differences, limited evidence at low-level exposure (water arsenic<100 μg/L), and uncertainty on pathogenic mechanisms in response to arsenic exposures. Limitations including potential publication bias, potential language bias, incomplete exposure histories, ecological fallacy, and non-comparability of outcome measures across publications. The public health significance of this systematic review is providing more robust epidemiologic evidence. It could be helpful and instructive for future research on the detrimental effects of arsenic on respiratory health.

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Preface

Acknowledgements:

Last summer, my advisor Dr. Aaron Barchowsky recommended me to Dr. George Leikauf's lab. I really appreciate that Dr. Leikauf gave me the opportunity to work as a student worker in his lab and instructed me everything in person and aroused my interest in research. I would like to acknowledge Dr. Kiflai Bein, who has helped me every step of the way with learning cell culture and electrophoretic mobility shift assay techniques. I want to acknowledge my advisor Dr. Barchowsky for welcoming me to EOH and always encouraging me and guiding me. Lastly, I would like to appreciate Dr. Mauricio Rojas for offering to be a part of my thesis committee.

1.0 Introduction

Inorganic arsenic (InAs) is listed as one of 10 chemicals of primary public health concern by the World Health Organization (WHO) (Organization, 2010b). Arsenic exposure threatens the health of millions of people around the world through the consumption of naturally contaminated groundwater or food (Organization, 2010a). Inorganic arsenic naturally occurs at high levels in the groundwater (wAs) of many countries, including Argentina, Chile, China, India (West Bengal), Mexico, the United States and particularly Bangladesh, which above the WHO provisional guideline value of 10 μg/L (Organization, 2010a). The International Agency for Research on Cancer lists arsenic in drinking water as a type 1 lung carcinogen, meaning there is sufficient evidence to conclude that arsenic in water causes lung cancer (Straif et al., 2009). Arsenic's non-malignant lung effects have been less well studied than its lung cancer effects, but results of several human epidemiologic studies suggest deleterious effects of arsenic on a variety of non-malignant pulmonary outcomes, including impaired pulmonary function, respiratory symptoms, airway epithelial damage, chronic obstructive pulmonary disease (COPD), and tuberculosis (D. N. Mazumder et al., 2000; D. N. Mazumder et al., 2005; Milton, Hasan, Rahman, & Rahman, 2003; Milton & Rahman, 2002; Parvez et al., 2008; Rahman, Vahter, Ekstrom, & Persson, 2011; Smith et al., 2006; Smith et al., 2011). There is also growing evidence linking arsenic to non-malignant respiratory diseases (Tiffany R Sanchez, Perzanowski, & Graziano, 2016).

However, only two review articles on InAs and non-malignant lung disease were published in 2007 (D. G. Mazumder, 2007) and 2016 (Tiffany R Sanchez et al., 2016). (Tiffany R Sanchez et al., 2016) identified twenty-nine articles that examined the relationship between inorganic arsenic exposure and respiratory outcomes. They found strong evidence of a correlation between

arsenic and non-malignant respiratory illness, including consistent evidence of lung function impairment, respiratory symptoms, acute respiratory tract infections, and non-malignant lung disease mortality. This review aims to synthesize the additional research on InAs and respiratory health effects that have been published since 2016, based on a systematic review of the literature from 1998 through 2015 (Tiffany R Sanchez et al., 2016).

2.0 Methods

2.1 Search Strategy

This review's search strategy followed the PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). Systematic searches were conducted in two bibliographic databases, including EMBASE and PUBMED. A Gray literature search was conducted with Google Scholar.

For bibliographic databases, searched were conducted combining comprehensive English terms representing non-malignant respiratory health effects with terms for InAs exposure with the Boolean operator AND (See supplementary material for a complete list of search terms, (Tiffany R Sanchez et al., 2016)). I used both keywords and MeSH terms/ emtree terms to search PubMed and EMBASE between January 2016 to April 2020 with English-language restrictions. To be included, articles had to meet the following a priori criteria: " (1) included original human-based research published in a peer-reviewed journal; (2) had a control or referent group; and (3) inclusion of an indicator of InAs exposure studied related to any one or more of the following outcome categories listed in Table 1" (Tiffany R Sanchez et al., 2016).

Search results were downloaded using Endnote and subsequently screened title and abstract. Articles that meet the initial screening stage were reviewed in full text by all authors.

During the full-text review, whether multiple publications from the same study population contained duplicate data were assessed. Various publications of the same study were identified by checking author affiliation, study design, cohort name, enrollment criteria, and enrollment dates. When multiple articles were reporting on the same study, the relevant literature and noted possible overlaps in the results section would be reviewed.

2.2 Data Abstraction

For publications that categorized exposure of outcome, evidence from the highest category vs. the lowest category was put forward. Additional subgroup analyses were performed on (1) critical exposure periods; (2) gender differences; and (3) low-level InAs exposure (wAs < 100 μg/L) (Tiffany R Sanchez et al., 2016). All subgroup analyses were specified a priori.

2.3 Quality Assessment

Quality appraisal criteria were based on existing systematic reviews on InAs exposure (Navas-Acien et al., 2005; Tiffany R Sanchez et al., 2016; Zheng et al., 2014). Quality assessment questions fall into five categories: exposure assessment, outcome assessment, statistical analysis, data collection, and specific questions for longitudinal studies. The exposure assessment for each study is also described in more detail in the results subsection. All authors independently evaluate the quality and risk of bias for each article. Together, the authors resolved all disagreements and discussed the potential risks of any biases that might be overlooked.

Table 1 Eligibility criteria objectives are pre-created using an adaptive PICOS format

Topic	Question	Exclude if
Participants	Are the study participants human?	Not human
Exposure	Does the article have a relevant exposure measurement?	No measure of exposure (or occupationally /ATO Chemotherapy exposed)
Comparisons	Does the article have a control or referent group?	No reference group (i.e., case study or case report)
Outcome	Does the article have a relevant outcome (i.e., lung function, respiratory symptoms, acute respiratory infections, chronic non-malignant lung disease, and non-malignant respiratory mortality)?	Not relevant
Study design	Does the article report primary data?	No primary data

Note. Reprinted from "Inorganic arsenic and respiratory health, from early life exposure to sex-specific effects: A systematic review," by Sanchez, T. R., Perzanowski, M., & Graziano, J. H. (2016), Environmental Research, 147, 537-555.

3.0 Results

3.1 Overview

The results from my systematic search are outlined in Fig. 1. A total of 1174 articles were identified from two databases, resulting in 1094 unduplicated articles. Following a screening of titles and abstracts, 36 articles were selected for full-text review. The final review included eight publications from six countries. Two publications were from the USA, two were from Bangladesh, two were from Chile, and one from Turkey and China. Articles were published in seven different journals between 2016 and 2020. Six publications were cross-sectional studies, and two were longitudinal studies.

Several publications reported multiple related endpoint categories: eight publications examined lung function, four examined respiratory symptoms, one examined acute respiratory infections, one examined acute respiratory infections, and two examined chronic respiratory disease.

3.1.1 Sub-analyses of interest

Three articles examined the effects of utero InAs exposure at different life stages, including endpoints during childhood (Ahmed et al., 2017a), and adulthood (Nardone et al., 2017; Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016). Two publications stratified their results by sex (Ahmed et al., 2017a; Shih, Argos, & Turyk, 2019). Two publications examined the effects of InAs<100μg/L (Powers et al., 2019; Shih et al., 2019).

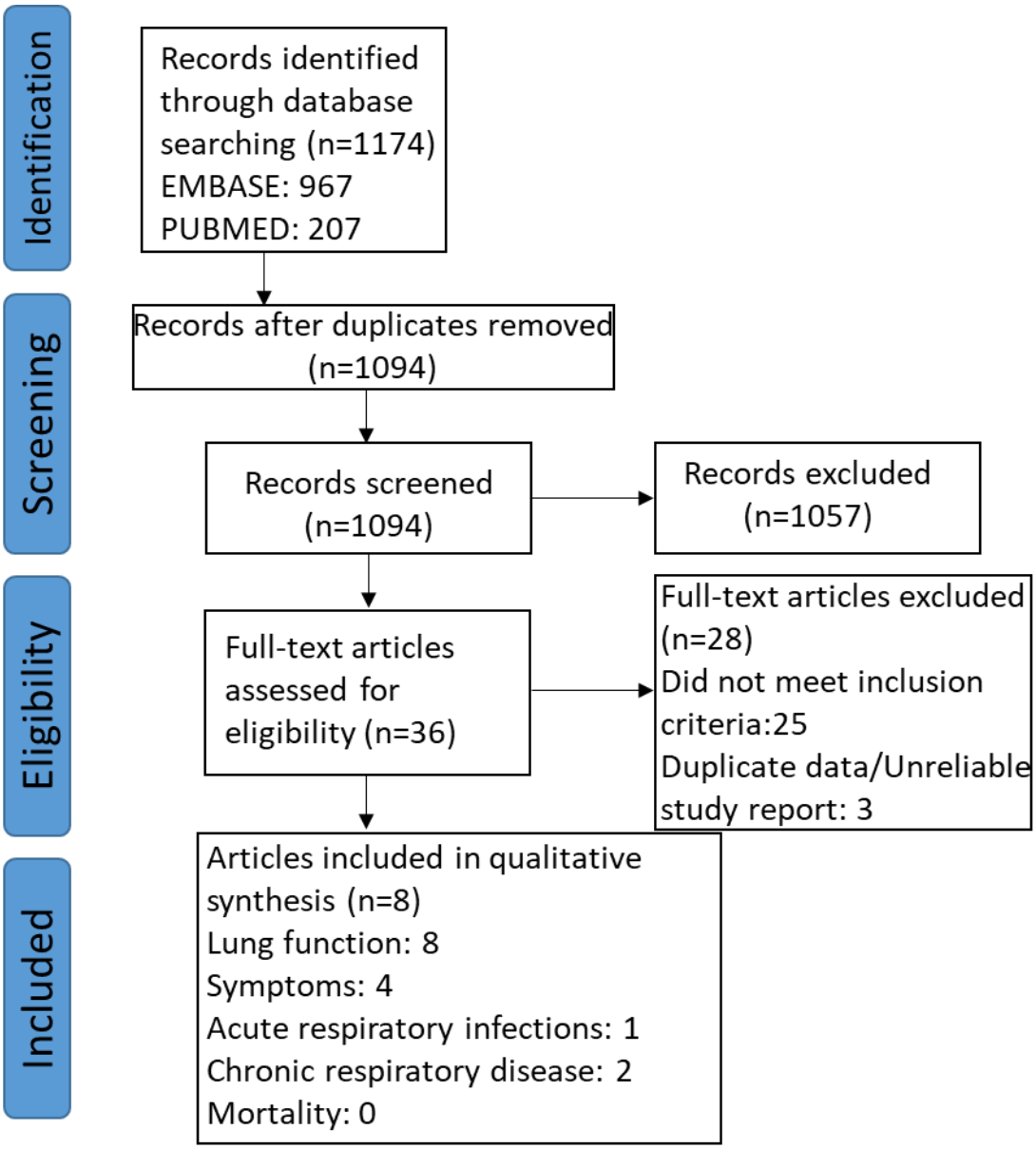

Figure 1 Publication selection process

3.1.2 Quality assessment

Fig.2 shows an overview of the quality assessment for each publication. Each result subsection for the selected publications applied a more rigorous quality evaluation.

Five publications evaluated InAs exposure at the individual level. The other three assessed InAs exposure ecologically. Most publications had either incomplete exposure histories or did not include exposure from all major sources (water and diet). In general, publications with a history of incomplete exposure measured either current urinary arsenic (uAs) or wAs measurements (and/or recent exposure history) but had no record or a history of early life exposure. Alternatively, publications had prenatal/early life InAs exposure measurements but did not have later life exposure/ exposure measurement in conjunction with the outcome. Therefore, publications that use early exposure markers do not necessarily include all major sources of exposure throughout the life course. Besides, as a vital factor of exposure, the InAs exposure in the diet is getting more and more attention, especially in the case of a low level of InAs in drinking water. Thus, publications that used exposure biomarkers and reported previous InAs exposure levels (including lifetime exposure levels) had an assessment of higher quality exposure than publications that classified InAs exposure only on the basis of wAs levels or used isolated uAs measurements.

Most studies standardized respiratory symptom questionnaires and lung function measurements; however, most chronic lung disease outcomes were self-reported. Diagnostic criteria for several outcomes (including chronic bronchitis and pneumonia) were inconsistent in various publications, thus increasing uncertainty of the results of classification (respiratory symptoms versus acute respiratory infections and chronic respiratory diseases) and making comparisons between publications challenging.

Most publications showed the internal comparison between the study group. Most publications also fully controlled the important potential confounding factors, including age, sex, and smoking. Different publications reported differently on the selection criteria and participation rates of participants. The participant rates were generally adequate. The two cohort publications

both reported follow-up rates and described how those lost to follow-up. It was often unclear whether the interviewer was blinded to the exposure status of the person interviewed. Only two publications reported both adjusted and unadjusted results. The accumulation of strength of the evidence about InAs and non-malignant lung disease was attenuated by these methodological limitations. In summary, this systematic review includes articles of both high quality (reliable exposure assessment, adjusted potential confounders and standardized outcome measures) and low quality (incomplete exposure assessment/history, no adjustment for potential confounders, and non-standardized outcome indicators).

	Bangladsh			Chile		USA		China	Turkey
Quality assessment	Siddique et al., 2020	Ahmed et al., 2017b		Steinmaus et al., 2016	Nardone et al., 2017	Powers et al., 2019	Shih et al., 2019	(Wang et al., 2020)	(Gunduzoz et al., 2018
Was the exposure marker assesed using a biomarker or water arsenic at the individual-level?	☐	☑		☐	☐	☑	☑	☑	☑
Was an appropriate latency period considered?	☑	☑		☑	☑	☐	☐	☑	☑
Were all major exposure sources/time points included?	☐	☑		☐	☐	☐	☐	☐	☐
Was exposure assessment independent of disease status?	☐	☑		☑	☑	☑	☑	☑	☑
Were outcomes based on objective tests of standardized criteria in ⩾90% of study participants?	☑	☑		☑	☑	☑	☑	☐	☑
Did the authors present internal comparisons within study participants?	☐	☑		☑	☑	☑	☑	☑	☐
Did the authors control for potential confounding risk factors in addition to age?	☑	☑		☑	☐	☑	☑	☑	☑
Were other potential confounders (i.e.smoking) appropriatedly measured and accounted for?	☑	☑		☑	☑	☑	☑	☑	☑
Were appropriate statistical methods used?	☑	☑		☑	☑	☑	☑	☑	☑
Are both adjusted and unadjuste results given?	☐	☑		☑	☐	☐	☐	☐	☐
Did participation rates include those who declined, provided inadequated data or other exclusions?	..	☑		☑	☑	☑	☑	..	..
Were the participation rates adequate (e.g.>70%)?	..	☑		☑	☑	☑	☐	..	..
Were the data collected in a similar manner for all participants?	☑	☑		☑	☑	☑	☑	☑	☑
Where the same exclusion criteria applied to all participarts?	..	☑		☑	☑	☑	☑	..	..
Was the time period over which exposed/unexposed interviewed the same?	..	☑		☑	☑	☑	☑	..	..
Was the interviewer blinded with respect to the exposure status of the person interviewed?	☑	☐		☐	☐	☐	☐	☐	☐
Longitudinal Studies:									
Were follow-up rates adequate?	..	☑		..	..	☑	..	..	..
Were there nominal differences in follow-up rates based on disease and exposure status?	..	☑		..	..	☑	..	..	..
	legend: ☑ Yes ☐ No/unknown .. N/A								

Figure 2 Quality assessment at the publication level

Table 2 Evidence table on InAs and lung function

Reference Study design	Location Size	Age(yrs) male	Exposure level	Outcome	Effect estimate	95% CI/ p-Value	Comments
Ecological-level water arsenic publications							
(Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016) Cross-sectional	Chile n=795	Exp: in utero Out: Adults Male: 51	wAs:<11 vs. wAs>200	FVC (mL) FEV1 (mL)	Mean Diff -224 Mean Diff -64	-351, -29 -174, 47	Among non-smokers with the highest single-year arsenic water concentrations. Adj: smoking (in smokers) and Aymara race
(Nardone et al., 2017) Cross-sectional	Chile n=751	Exp: in utero Out: Adults Male: 45	wAs<11 vs. wAs: 11-200	FVC (mL) FEV1 (mL) FEV1/FVC	Mean Diff -59 Mean Diff -27 Mean Diff 0.80	p=0.07 p=0.69 p<0.004	For lifetime highest single year exposure. Unadjusted.
(Siddique et al., 2020) Cross-sectional	Bangladesh n=842	Exp: Adults Out: Adults Male:51.1	wAs: 0.03-5.3 **vs.** wAs: 135-1800	FEV1 (mL) FEV6 (mL) FEV1/FEV6	Association -0.203 Association -0.169 Association -0.055	p<0.003 p<0.019 p<0.001	Adj: age, sex, BMI, smoking habits, income, education and occupation
Urinary arsenic publications							
(Ahmed et al., 2017b) Longitudinal	Bangladesh n=540	Exp: in utero Out: 9 Male:49	uAs>150 vs. uAs<50	FVC (mL) FEV_1 (mL)	Mean Diff -79 Mean Diff -76	-159, 0.5 -154, 2.1	Adj: age, HAZ, SES, sex, season, mothers' education, plasma concentrations of CRP, and maternal micronutrient supplementation groups.
(Gunduzoz et al., 2018) Cross-sectional	Turkey n=150	Exp: Adults Out: Adults Male: 100	uAs: 2.5-246 vs. uAs: 0.1-6	FVC (%) FEV1 (%) FEV1/FVC FEF_{25-75} (%)	(-) (-) (-) (-)	p<0.001 p<0.001 p<0.001 p<0.001	Adj: age, work years, gender, smoking and race.
(Powers et al., 2019) Longitudinal	USA n=2132	Exp: Adults Out: Adults Male: 40	uAs>16.7 vs. uAs<5.8	FEV1 (%pred) FVC (%pred)	Mean Diff -1.39 Mean Diff -1.13	-2.51, -0.25 -2.21, -0.05	Adj: age, sex, education, study site, smoking status, smoking pack-year, eGFR, tuberculosis, and BMI.

Table 2 (continued)

Reference Study design	Location Size	Age(yrs) male	Exposure level	Outcome	Effect estimate	95% CI/ p-Value	Comments
(Shih et al., 2019) Cross-sectional	USA n=3626	Exp: Adults Out: Adults Male: 50	uAs<5.61 vs. uAs: 6.0-6.4	FVC (mL) FEV1 (mL) FEF25-75 (mL/s)	Mean Diff -45.15 Mean Diff -69.40 Mean Diff -125.06	-126.76, 36.45 -133.73, -5.06 -229.30, -20.82	Among non-smokers with the highest single-year arsenic water concentrations. Adj: smoking (in smokers) and Aymara race
Hair arsenic publication							
(Wang, Wang, Zou, Zheng, & Zhang, 2020) Cross-sectional	China n=292	Exp: Adults Out: Adults Male: 61.3	hAs: 0.09-0.19 vs. hAs: 0.18-0.39	FVC (%) FEV1(%) FEF25 (%) FEF50 (%) FEF75 (%) FVC/FEV1	Mean Diff -3.26 Mean Diff -2.73 Mean Diff -8.43 Mean Diff -6.20 Mean Diff -6.19 Mean Diff -0.03	p<0.05 p<0.05 p<0.05 p<0.05 p<0.05 p>0.05	Among those without skin lesions. Adj: age, gender, BMI, smoking, and alcohol consumption.

3.2 Lung Function

Eight publications evaluated the relationship between InAs and lung function. (Ahmed et al., 2017a; Gunduzoz et al., 2018; Nardone et al., 2017; Powers et al., 2019; Shih et al., 2019; Siddique et al., 2020; Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016; Wang, Wang, Zou, Zheng, & Zhang, 2020). Table 2 shows the relationship between InAs and three spirometric outcomes used to measure lung function commonly: forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and the ratio of FEV1 to FVC (FEV1/FVC), and other spirometric outcomes including forced expiratory volume in 6 second (FEV6), the ratio of FEV1 to FEV6 and The mid-expiratory flow rate (FEF25–75%).

3.2.1 Strength of the evidence

Spirometry is a common and effective pulmonary function test (PFT). Seven of eight publications used American Thoracic Society (ATS) criteria (Miller et al., 2005) to evaluate spirometry acceptability (Ahmed et al., 2017a; Gunduzoz et al., 2018; Nardone et al., 2017; Powers et al., 2019; Shih et al., 2019; Siddique et al., 2020; Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016). The direction of the correlation between InAs and lung function was consistent. Eight reported point estimates had four found in the publications of FVC in statistically significant decline, and five found a statistically significant decrease in FEV1.

In the four articles using ATS criteria and reporting raw values, the trend between the increase of InAs concentration and the decrease of FEV1 and FVC is consistent. (Steinmaus,

Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphiné, et al., 2016), a cross-sectional PFT study analysis among 795 northern Chilean adults, found that among never-smokers with highest single-year arsenic water concentrations of >200μg/L, had adjusted FVC residuals of -224mL and adjusted FEV1 residuals of -64mL respectively, compared to those exposed to wAs<11 μg/L. Although the exposure assessment was based on wAs levels measured at enrollment time, participants were all born and lived at least 80% of their lives in their respective cities. (Nardone et al., 2017), a cross-sectional PFT study analysis among 751 northern Chilean adults, found that among participants with a single year lifetime highest arsenic exposure of 11-200 μg/L were associated with a 59 ml (p=0.07) decrease in FVC and a 27 ml (p=0.69) decrease in FEV1, respectively, compared to those never exposed to arsenic concentrations ≥11 μg/L. However, the results did not reach statistical significance. (Siddique et al., 2020), a cross-sectional PFT study analysis among 842 Bangladesh adults, found that adjusted for age, sex, BMI, smoking habits, income, education and occupation, participants with a high concentration of wAs exposure of 135-1800 μg/L showed a significant negative association with FEV1 (p<0.003) compared to the low group of wAs (water As range=0.03-5.3). Results for hair As and nail As were similar. (Ahmed et al., 2017a), a longitudinal PFT analysis among a sample size of 540 Bangladeshi children at nine years of age, found that adjusted for age, HAZ, SES, sex, season, mothers' education, plasma concentrations of CRP, and maternal micronutrient supplementation groups, high exposed group (>150 μg/L at all three-time points) had a 79 mL and 76 mL reduction of FVC and FEV1, respectively, compared to low exposed group (<50 μg/L at all three-time points), although the 95% confidence intervals included the null value.

Whereas FVC and FEV1 values are known to differ by ethnicity, the FEV1/FVC ratio is independent of the ethnic group (Quanjer et al., 2012). Four publications reported on InAs and

FEV1/FVC (Ahmed et al., 2017a; Gunduzoz et al., 2018; Nardone et al., 2017; Wang et al., 2020). (Gunduzoz et al., 2018)A longitudinal analysis among 150 Turkey males found the FEV1/FVC ratio was significantly lower in firefighters compared to non-exposed male office workers ($p<0.001$). (Wang et al., 2020), a cross-sectional PFT study analysis among 292 Chinese adults, found that adjusted for age, gender, BMI, smoking, and alcohol consumption, there were no statistical differences in the FVC/FEV1(%) values ($Z=-0.03$, $p>0.05$) of the As-exposed and reference groups. (Ahmed et al., 2017a) described an inverse association between maternal U-As and FEV1/FVC ratio, although the association did not reach statistical significance. (Nardone et al., 2017) explained that participants with a single year lifetime highest arsenic exposure below 11 μg/L and a single year lifetime highest arsenic exposure of 11-200 μg/L had corresponding FEV1/FVC ratios of 0.78 and 0.80. The p-value for the difference in the mean FEV1/FVC ratio between arsenic exposure<11 μg/L and arsenic exposure of 11-200 μg/L was 0.004.

3.2.2 Early life exposure

Few studies have been able to capture all the main sources of exposure from pregnancy to adulthood. Although this for any epidemiologic study is an extremely challenging aspect, there were three publications had evidence of exposure from early life (Ahmed et al., 2017a; Nardone et al., 2017; Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphiné, et al., 2016). (Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016) and (Nardone et al., 2017) both had convincing historical evidence of early life exposure. Here, exposure history was based on participants' long-term residence in either Arica, Iquique, or Antofagasta, Chile. Arsenic water concentrations in Iquique and Arica have always remained 8-10 and 60 μg/L, respectively. In contrast, Antofagasta has a distinct period of very high arsenic water

concentrations of about 860 μg/L but dropped about 100 μg/L later. All study participants were born between 1958 and 1970, a period of high exposure for Antofagasta. (Ahmed et al., 2017a) examined a population of Bangladeshi children aged nine years old, arsenic exposure was assessed through urine collected from early pregnant mothers and their children aged 4.5 and 9 years. Maternal uAs was inversely associated with FVC and FEV1 in all children. In sum, these three publications suggest that early life exposure to InAs was particularly harmful to lung function.

3.2.3 Sex difference

Two articles presented sex-stratified results (Ahmed et al., 2017a; Shih et al., 2019). In (Shih et al., 2019), the expected changes of FVC and percent predicted values of FVC were lower among women than among men, and the expected changes of FEV1 and percent predicted values of FEV1 were lower among men than among women; however, evidence was not consistent, which may be explained by the low arsenic exposure levels. In (Ahmed et al., 2017a), early life InAs exposure was significantly associated with lower FVC and FEV1 among boys. Among girls, the direction of association was consistent but not significant.

3.2.4 Dosimetry

Two articles evaluated the trend of exposure-response of InAs and lung function (Ahmed et al., 2017a; Wang et al., 2020). In (Ahmed et al., 2017a), an exposure-response relationship was found between the increasing level of maternal uAs at gestational week eight and decreasing levels of FVC and FEV1. (Wang et al., 2020) also found an inverse exposure-response trend between H–As and FEV1(%), FEV1/FVC (%) and FEF75 (%) (all $P < 0.05$).

3.3 Respiratory Symptoms

Four articles evaluated the relationship between InAs and respiratory symptoms. Articles evaluated symptoms separately or in combination and reported from one to five different symptom-related endpoints. Three of the four articles on InAs and respiratory symptoms reported a statistically significant positive correlation between InAs and at least one respiratory symptom (Nardone et al., 2017; Siddique et al., 2020; Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016). A publication, however, did not find any significant relationship between InAs and respiratory symptoms assessed (Powers et al., 2019). Table 3 showed the associations between the most commonly reported endpoints, chronic cough, shortness of breath, and "any respiratory symptom."

Table 3 Evidence table on arsenic and respiratory symptoms

Reference Study design	Location Size	Age (yrs) Male (%)	Exposure level	Outcome	Sex	Effect estimate	95%CI	Comments
Ecological- level water arsenic publications								
(Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphiné, et al., 2016) Cross-sectional	Chile n=795	Exp: in utero Out: Adults Male: 51	wAs>200 vs. wAs<11	Dyspnea Chronic cough	All All	Odds ratio 5.56 Odds ratio 12.0	2.68, 11.5 4.47, 32.0	For lifetime highest single year exposure. Adj: age, gender, smoking.
(Nardone et al., 2017) Cross-sectional	Chile n=751	Exp: in utero Out: 39-60 Male: 45	wAs>200 vs. wAs<11	Any symptom Cough Dyspnea	All All All	Odds ratio 4.07 Odds ratio 10.6 Odds ratio 4.47	2.15, 7.70 3.24, 29.2 1.87,10 .7	For lifetime highest single year exposure. Adj: sex, age, and smoking by categories of arsenic exposure and BMI.

Table 3 (continued)

(Siddique et al., 2020) Cross-sectional	Bangladesh n=842	Exp: Adults Out: Adults Male: 51	wAs:0.03-5.30 vs. wAs: 135-800	Asthma-like symptoms	All	Odds ratio 2.90	1.90, 4.43	Presence of one symptom: wheezing, coughs, dyspnea, and chest tightness. Adj: age, sex, BMI, smoking habits, income, education, and occupation.
Individual-level water arsenic publications								
Urinary arsenic publications								
(Powers et al., 2019) Longitudinal	USA n=2132	Exp: Adults Out: Adults Male: 40	uAs>16.7 vs. uAs<5.8	Cough Dyspnea	All All	Odds ratio 0.78 Odds ratio 1.02	0.65, 0.93 0.88, 1.17	In quartiles. Adj: age, sex, education, site, eGFR, tuberculosis, and BMI.

3.3.1 Strength of the evidence

Standardized respiratory symptom questionnaires for the three articles (Nardone et al., 2017; Siddique et al., 2020; Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016) were adapted from the British Medical Research Council respiratory questionnaire (Cotes, 1987), and the International Union Against Tuberculosis and Lung Disease Bronchial Symptoms Questionnaire (Ravault & Kauffmann, 2001).

Any respiratory symptoms. Two publications were incorporating several respiratory symptoms as an inclusive variable (Nardone et al., 2017; Siddique et al., 2020). Although these publications included slightly different combinations of symptoms, the positive correlation between InAs and “any respiratory symptom” was consistent and statistically significant. In (Nardone et al., 2017), the odds of any respiratory symptoms (defined as coughing, wheezing,

shortness of breath) among high exposure group (>200 μg/L) was 4.07 higher compared to low exposure group (<11 μg/L), after adjusting for sex, age, and smoking by categories of arsenic exposure and BMI. (Siddique et al., 2020) found high arsenic exposure group (135-1800 μg/L) had 2.90 higher odds of any asthma-like symptoms (defined as wheezing, coughs, shortness of breath and chest tightness) compared to low exposure group (0.03-5.3 μg/L), after adjusting for age, sex, BMI, smoking habits, income, education, and occupation. Exposure assessment was based on the presence or absence of skin lesions and residing in either an InAs-endemic or non-endemic village for at least five years.

Cough. Three publications evaluated the relationship between InAs and cough (Nardone et al., 2017; Powers et al., 2019; Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphiné, et al., 2016). Publications commonly classified cough by productive/non-productive and severity/frequency. In general, InAs was significantly positively correlated with coughing symptoms in two of the three publications, and each publication adjusted for potential confounding factors, including age, sex, and smoking, etc. (Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016) investigated the prevalence of chronic cough in Chilean adults exposed to very high levels of early exposure. For the highest single-year exposure, the odds for chronic cough among those exposed to wAs >200 μg/L was 12 times the odds among those exposed to wAs<11 μg/L after adjusting for age, gender and smoking (95% CI=4.47, 32.0). In (Nardone et al., 2017), for single year lifetime highest arsenic exposure, the odds for cough among those exposed to wAs>200 μg/L was 10.6 times the odds among those exposed to wAs<11 μg/L after adjusting for sex, age, smoking by categories of arsenic exposure and BMI (95% CI=3.24,29.2). However, (Powers et al., 2019) found urinary arsenic was inversely associated with cough. (Powers et al., 2019) prospectively investigated the relationship between InAs and self-

reported cough among 2132 American Indian adult participants in the Strong Heart Study. Curiously, they found participants in the highest quartile of uAs (>16.7 μg/g creatinine) had lower odds of cough compared to participants in the lowest quartile of uAs (<5.8 μg/g creatinine), after adjusting for age, sex, education, site, eGFR, tuberculosis and BMI (OR=0.78, 95% CI=0.65,0.93).

Dyspnea. Three publications examined InAs and a symptom relating to shortness of breath/dyspnea (Nardone et al., 2017; Powers et al., 2019; Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016). In general, except for one publication (Powers et al., 2019), the association's direction was consistently positive for all. Two publications used standardized questionnaires and graded scales of dyspnea based on different situations (Nardone et al., 2017; Powers et al., 2019). (Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016) and (Nardone et al., 2017) found participants exposed to high levels of wAs had a significant positive association with dyspnea symptoms. (Powers et al., 2019) did not correlate arsenic and dyspnea, but positively correlated with stopping for breath while walking (OR=1.41, CI= 1.19, 1.69).

3.3.2 Early life exposure

Two of the four articles looking at in utero exposure found a statistically significant increase in adults' respiratory symptoms (Nardone et al., 2017; Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016). Among adults, those exposed to wAs levels >200 μg/L during ages 0-20 years, had increased odds of shortness of breath, chronic cough, wheeze, and asthma compared to adults who were exposed to <11 μg/L during ages 0-20 years (Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016). Among adults, single year lifetime highest arsenic exposures>200 μg/L were also associated with increases in cough,

shortness of breath, and any symptom when compared to the low exposure group (<11 μg/L). Although their exposure indicator was the single highest year, most of the subjects were born between 1958 and 1970 (the high exposure period in Antofagasta) and thus had early life exposure (Nardone et al., 2017).

3.3.3 Sex differences

(Nardone et al., 2017) found the odds ratios for cough, shortness of breath, wheeze, and any symptom was greater for females than for males; however, results did not reach statistical significance.

Table 4 Evidence table on InAs and acute respiratory tract infections

Reference Study design	Location Size	Age (yrs) Male (%)	Exposure level	Outcome	Effect estimate	95%CI/ P-value	Comments
Ecological- level water arsenic publications							
(Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphiné, et al., 2016) Cross-sectional	Chile n=795	Exp: in utero Out: Adults Male: 51	wAs>200 vs. wAs<11	Child hospitalization	Odds ratio 3.94	1.97, 7.87	For the highest age 0-20 years. Adj: age, gender, smoking. Ever hospitalized for a respiratory infection as a child.

3.4 Acute Respiratory Tract Infections

There was one publication on InAs and respiratory tract infections (Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016) (Table 4). (Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016) reported a statistically significant

increase in child hospitalization (defined as ever hospitalized for a respiratory infection as a child) among those exposed to wAs levels >200 μg/L during ages 0-20 years compared to those exposed to wAs levels<11 μg/L during ages 0-20 years, after adjusting for age, gender, smoking (OR=3.94, CI=1.97, 7.87).

3.5 Chronic Non-malignant Lung Disease

Two publications investigated the relationship between InAs and chronic non-malignant lung disease (Table 5). The specific disease outcomes include emphysema and chronic bronchitis.

Table 5 Evidence table on InAs an chronic non-malignant lung disease

Reference Study design	Location Size	Age (yrs) Male (%)	Exposure level	Outcome	Effect estimate	95%CI	Comments
Ecological- level water arsenic publications							
(Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphiné, et al., 2016) Cross-sectional	Chile n=795	Exp: in utero Out: Adults Male: 51	wAs>200 vs. wAs<11	Chronic bronchitis	Odds ratio 2.70	0.93, 7.84	For the highest age 0-20 years. Adj: age, gender, smoking.
Individual-level water arsenic publications **Urinary arsenic publications**							
(Powers et al., 2019)	USA n=2132	Exp: Adults Out: Adults Male:40	uAs>16.7 vs. uAs<5.8	Chronic bronchitis emphysema	Odds ratio 1.16 Odds ratio 1.66	0.92, 1.47 1.29, 2.15	In quartiles. Adj: age, sex, education, site, eGFR, tuberculosis, and BMI.

3.5.1 Strength of the evidence

Chronic bronchitis. Two publications investigated the relationship between InAs and chronic bronchitis (Powers et al., 2019; Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016). (Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphiné, et al., 2016) found that among those exposed to wAs levels >200 μg/L during ages 0-20 years had a greater risk of chronic bronchitis compared to those exposed to wAs levels <11 μg/L during ages 0-20 years, after adjusting for age, gender, and smoking, however, results did not reach statistical significance (OR=2.70, 95% CI=0.93, 7.84). (Powers et al., 2019) also found a modest association (OR=1.16, 95% CI=0.92, 1.47) among uAs and self-reported chronic bronchitis after adjusted for age, sex, education, site, eGFR, tuberculosis, and BMI.

Emphysema. (Powers et al., 2019) also reported greater odds of self-reported emphysema among those with the highest quartile of uAs (>16.7 μg/g creatinine) than for those in the lowest quartile (<5.8 μg/g creatinine), after adjusting for age, sex, education, site, eGFR, tuberculosis and BMI (OR=1.66, 95% CI=1.29,2.15), which was statistically significant.

3.5.2 Early life exposure

(Steinmaus, Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphine, et al., 2016) was the only publication in this category with exposure assessment in early life (see Section 3.2.2).

3.6 Non-malignant lung disease mortality

None of the eight articles in this review mentioned non-malignant lung disease mortality.

4.0 Discussion

For this update, eight studies were incorporated in the review and examined how InAs exposure may be related to different aspects of respiratory health, including consistent evidence on lung function impairment, respiratory symptoms, and acute respiratory tract infections. This review also revealed some common limitations, including an incomplete history of exposure, ambiguous outcomes, and limited confounder control.

4.1 Limitations

Although there are important discoveries revealed by these studies, there are also limitations. Only eight publications on arsenic exposure and non-malignant respiratory illnesses met the inclusion criteria. The included studies focused on populations with high levels of arsenic exposure (>100 μg/L). Thus, the relationship between arsenic and non-malignant respiratory is poorly understood at exposure levels common in the U.S. (<10 μg/L). In about eight percent of samples across Pennsylvania, arsenic concentrations met or exceeded the U.S. Environmental Protection Agency's maximum pollutant concentration of 10.0 μg/L (Gross, et al., 2013). Further, as a systematic review, publication bias is inevitable. Although two complementary databases and an intensive gray literature search have been searched, it is inevitable to ignore literature that is harder to find, like government reports or unpublished studies. This study was also limited by the exclusion of foreign language studies, which caused language bias. During the screening process, some publications met the inclusion criteria but were published in Chinese or French, and then

they were excluded. The adapted quality assessment questionnaire also has some problems. Because the binary quality assessments fail to capture finer details, or authors failed to report the required details, the quality of Publications may appear to be higher or lower. Thus, it is necessary to be more careful when using quality assessment to evaluate how well a study did. Three of the included studies were ecological studies, and the exposure markers are aggregate data rather than individual data, making them susceptible to the ecological fallacy. Further, the exposure metric (mean arsenic water concentrations for the city) is a comprehensive measurement and does not represent the variability in exposure levels within a city.

4.2 Summary of Findings

In general, the addition of eight studies did not alter the conclusions drawn by the previous systematic review regarding the associations between InAs and respiratory health (Tiffany R Sanchez et al., 2016). In terms of lung function, this review found consistent evidence of the relationship between increasing InAs and decreasing in FVC and FEV1. This review also found consistent evidence of the positive associations between InAs and respiratory symptoms, including "any respiratory symptom," cough, and dyspnea. One publication on InAs and respiratory tract infections in this review reported a statistically significant positive association between InAs exposure and frequency of RTI, consistent with the previous review. Even though two publications in this review found a positive association between InAs exposure and chronic non-malignant lung disease, including emphysema and chronic bronchitis, the association was not statistically significant for chronic bronchitis. Still, the association was statistically significant for emphysema. Thus, there was additional evidence to support the relationship between InAs exposure and

emphysema. None of the eight articles in this review mentioned non-malignant lung disease mortality. Thus, there was no additional evidence to support the relationship between InAs exposure and increased non-malignant lung disease mortality.

Although the results from this systematic review showed that the evidence of a general link between InAs and non-malignant respiratory diseases is consistent, the relationship between InAs and any single non-malignant respiratory outcome in the pathological process is still poorly understood. Arsenic may cause a variety of non-malignant lung diseases through various mechanisms, including aberrant wound repair, impaired immune function, and disrupted matrix and barrier function. However, the mode of action of these mechanisms in response to arsenic exposures and cause non-malignant lung disease is still uncertain and should be further investigated.

This review found consistent evidence of an inverse association between InAs and both FEV1 and FVC, but no consistent association for FEV1/FVC. (T. R. Sanchez et al., 2018) also found the same relationships. In a restrictive pattern lung function test, FEV1 and FVC are generally reduced, but FEV1/FVC is stable or higher. This review provides additional evidence of a potential link between arsenic-related lung function defects and restrictive pattern lung disease. Determine a specific pattern of lung function defects associated with arsenic exposure that could guide future studies aimed at understanding the pathophysiological pathways involved and the population at risk.

Early life exposure. Emerging evidence showed that early life InAs exposure has lasting detrimental health effects throughout the lifespan. This review finds that in utero InAs exposure leads to adverse respiratory consequences, including lower lung function levels, increased respiratory symptoms, and increased child hospitalization due to respiratory infection (Steinmaus,

Ferreccio, Acevedo, Balmes, Liaw, Troncoso, Dauphiné, et al., 2016). Evidence on the potential effects of arsenic exposure in early adolescence is still lacking. The mechanisms that lead to the development of the latent disease is still poorly understood.

Sex differences. Only three publications in this review described sex differences. In general, effect estimates for InAs and lung function seem to be stronger in men than in women, consistent with previous studies. (Nardone, Ferreccio et al. 2017) found effect estimates for InAs and respiratory symptoms are stronger in women than in men, which is inconsistent with previous publications; however, it did not reach statistical significance. Arsenic metabolism is through a series of reduction and methylation reactions. InAs is reduced from pentavalent arsenate (AsV) to trivalent arsenite (AsIII), and then the methyl is oxidized to monomethyl arsonic acid(MMA), and then the methyl is oxidized to arsonic dimethyl acid (DMA) (Tseng, 2009). The intermediate MMA(III) and DMA(III) are highly toxic. Arsenic methylation is influenced by diet, exposure, genes, hormones, weight, race, age, and smoking habits. In addition, some studies have reported that women excrete more DMA with lower InAs and MMA than men, which indicates that women's overall ability to methylate As increases (Hopenhayn-Rich, Biggs, Smith, Kalman, & Moore, 1996; Hsueh et al., 1998; Loffredo, Aposhian, Cebrian, Yamauchi, & Silbergeld, 2003; Torres-Sanchez et al., 2016).

Dosimetry. Although I followed the previous review to perform subgroup analysis on lower levels wAs exposure (wAs<100 μg/L), wAs levels in most publications were>100 μg/L; thus, the effects of low to moderate arsenic exposures are still unclear. Also, publications used different exposure measurement methods and included different exposure comparisons; thus, it is difficult to study whether similar exposure levels produce similar effect estimates.

5.0 Conclusion

In this systematic review, eight epidemiological works of literature of different ways of InAs related to respiratory health have been updated, to provide evidence for stakeholders in this field better and determine future research directions. In brief, the link between InAs and respiratory health has been noted throughout the lifespan: in infancy, there is increasing evidence that InAs exposure in utero is associated with an increase in the frequency and severity of respiratory tract infections; respiratory symptoms also begin to appear in childhood; in adulthood, there is consistent evidence that InAs exposure is related with lung function defects (especially FVC) and increased reporting of cough and Dyspnea. Common limitations include potential language bias, potential publication bias; incomplete exposure histories; ecological fallacy; and the incomparability of each publication's measurement outcomes. More research and testing are required to better understand the sex differences and low-level dose-response relationship between InAs and respiratory health. Early life InAs exposure has lasting detrimental health effects on the respiratory system throughout the lifespan. Combined with the previous review, this updated review could instruct future research to identify potential relevant pathogenic mechanisms and implement effective public health interventions.

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