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Review

Arsenic in Drinking Water and Urinary Tract Cancers: A Systematic Review Update

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Abstract: Problem: There remains uncertainty around cancer risk at lower levels of arsenic in drinking water. This study updates evidence from our previous review on the relationship between arsenic in drinking water and urinary bladder and kidney cancers (updated search January 2013 to February 2023). **Method**: Thirty-four studies were retained for review; six met criteria for inclusion in meta-analysis. Risk estimates for bladder and kidney cancer incidence and mortality were analyzed separately using Bayesian multilevel linear models. **Results**: For bladder cancer incidence, the estimated posterior mean relative risks (RRs) were 1.25 (0.92–1.73), 2.11 (1.18–4.22) and 3.01 (1.31–8.17) at arsenic concentrations of 10, 50 and 150 µg/L, respectively, with posterior probabilities of 92%, 99% and 100%, respectively, for the RRs to be >1. The corresponding RRs for kidney cancer were 1.37 (1.07–1.77), 1.95 (1.44–2.65) and 2.47 (1.74–3.52), with posterior probabilities of 100%. For bladder cancer, the posterior mean mortality ratios were 1.36 (0.35–6.39), 2.92 (1.24–7.82) and 4.88 (2.83–9.03) with posterior probabilities of 72%, 99% and 100%, respectively. **Conclusions**: The findings show increased bladder and kidney cancer risks at lower levels of arsenic in drinking water. Given that many people worldwide are exposed to lower levels of arsenic in drinking water, the public health impacts are substantial.

Keywords: arsenic; drinking water; urinary bladder; kidney; cancer risks; systematic review; Bayesian meta-analysis

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1. Introduction

Arsenic (As) is a toxic metalloid that occurs naturally in the Earth's crust. Human exposure to As involves multiple pathways [1–7], with drinking water being the primary route of exposure for the majority of highly exposed populations [2,7,8]. Inorganic As in drinking water is classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC), constituting a significant public health issue and impacting millions of people worldwide [1]. Various acute and chronic morbidities and malignancies have been observed in populations exposed to high concentrations of inorganic As in drinking water, particularly in arsenic-endemic areas in northern Chile, Taiwan, Argentina and Bangladesh [9–11].

Most ingested As is excreted predominantly in urine through the urinary system [12]; thus, urinary tract organs are a key target for As-induced carcinogenesis. Urinary tract cancers, comprising primarily cancers of the urinary bladder and kidney, are a major consequence of long-term exposure to inorganic As. Many epidemiological studies involving highly exposed populations have shown strong associations and dose–response relationships between As in drinking water and bladder cancer and potential associations with kidney cancer [13–16]. The carcinogenic effect of inorganic As is further exacerbated when As exposure is combined with cigarette smoking, which is itself an independent risk factor

for urinary tract cancers [17,18]. Although the exact mechanism of As-induced carcinogenesis is poorly understood, several hypotheses have been postulated, mostly dependent on the mode of As metabolism in the human body once the metalloid is ingested through drinking water. In humans, As compounds may be associated with several tumorigenesis mechanisms, including modifying epigenetic regulation through inhibiting activities of DNA methyltransferase enzymes and the oxidative methylation of arsenite, direct or indirect damage to DNA, the alteration of cell proliferation and oxidative stress [19–21]. Arsenic might also exert genotoxic effects through direct and indirect damage to DNA, through the disruption of the DNA repair processes and could interfere with signal transduction pathways and promote immunosuppression [19]. Specifically for bladder cancer, As has been observed to interrupt cellular homeostasis through stem cell activators, reprogramming healthy epithelial cells to adopt a malignant phenotype [22].

While the carcinogenic risk at high levels of As in drinking water is well established for urinary tract organs [23–30], there remains uncertainty around the risk at lower levels of exposure, particularly at levels around the current World Health Organization (WHO) maximum acceptable concentration (MAC) of 10 μg/L [31,32]. Most epidemiological studies to date that have established strong associations and dose–response relationships typically report on areas of severe exposure where levels of As in drinking water range from 150 to over 1000 ug/L. However, at lower levels of exposure (<150 μg/L), the extent to which health effects may develop remains unclear [31,32].

Previously, we conducted a systematic review and meta-analysis of over 30 years of epidemiological studies on As exposure and bladder and kidney cancer outcomes. The findings showed that exposure to As levels as low as 10 ug/L could double the risk of bladder cancer or, at the very least, increase it by 40%, providing evidence of health effects around the WHO MAC [33]. Given the substantial public health consequences associated with exposure to As in drinking water and the potentially large number of people worldwide exposed to lower concentrations of As in drinking water, there may be a need to reassess the provisional WHO advisory limit. Currently, the limit is a provisional guideline related to the capacity of treatment options for individual households [8].

Since our last publication, several studies have been conducted examining associations between As exposure, including lower As levels, and urinary tract cancers. Combining evidence from our previous review with the new studies ensures that the analysis reflects the most current evidence, provides more accurate estimates of the magnitude of the relationship and supports a better understanding the health impacts of As, particularly at lower levels of exposure. Additionally, we updated our analytical approach by applying Bayesian multilevel modeling, which provides more robust results for the association between As exposure and bladder and kidney cancer outcomes. This current work aims, therefore, to summarize and update the evidence from our previous systematic review. Adding the most recent 10 years of data, we present a combined review and meta-analysis to include over 40 years of evidence from multiple studies, examining a continuous range of As exposure from which to better assess and predict cancer risks associated with varying levels of arsenic in drinking water.

2. Materials and Methods

2.1. Eligibility Criteria

The review protocol was registered on the PROSPERO website (protocol reference #CRD42022381522) [34]. Given our previous review included studies published prior to January 2013, the current search results included publications between January 2013 and February 2023. This systematic review included observational epidemiological studies such as ecological, cohort or case–control studies. The following criteria for the inclusion of studies in the review were applied: (1) studies among human participants; (2) arsenic, as the exposure of primary interest, in drinking water, toenail or urine; (3) reported urinary tract cancer incidence, mortality rates and relative effect size estimates (e.g., relative risk,

odds ratio or hazard ratio) and their corresponding variability measures; (4) published in the English language and (5) peer reviewed publications.

2.2. Electronic Searches

For this review, the original search strategy for the MEDLINE database was updated by including relevant free-text keywords and medical subject heading (MESH) terms [33]. In brief, the search strategy was developed based on the key research question concepts in accordance with the PICO format: population—all populations; exposure—various concentration levels of arsenic in drinking water (also arsenic measurements in urine and toenail); outcome—incidence and mortality of urinary tract cancers, including urinary bladder cancer and kidney cancer; and comparator—people not exposed to arsenic or general population. The search included studies that contained keywords or MESH terms such as "arsenic", "bladder cancer", "kidney cancer", "urinary tract cancer", "carcinoma, renal cell", "water", "well water", "water supply", "toenail" and other relevant key terms (Figure S1).

The MEDLINE search strategy was modified and adapted to the specifics of other bibliographic databases considering their search methods, the use of thesauri and search operators. A comprehensive search for relevant published studies was performed in the MEDLINE (Ovid; Table S1), Embase (Ovid; Table S2), Web of Science Core Collection (Table S3), Scopus (Table S4) and Google Scholar (Table S5) bibliographic databases. Adapting the MEDLINE search strategy, additional searches were undertaken for grey literature in the Agricultural & Environmental Science Collection, Europe Pre-print Database and Open Access Theses and Dissertations (Table S6). Lastly, a hand search was performed for relevant studies, and authors were contacted if a full text of a study was not available or important information in a study was missing.

2.3. Study Selection

After importing all retrieved information from electronic searches into the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia), two independent reviewers (AA and BA) performed duplicate screening and retrieved title and abstract records for inclusion in the review, applying the eligibility criteria for studies. After selecting studies based on the title and abstract screening, the full texts of the pre-selected studies were obtained. Similarly, two reviewers (AA and BA) independently screened the full-text studies for inclusion by applying the eligibility criteria. Any disagreements during titles and abstracts or full-text screenings were resolved between two reviewers (AA and BA). If consensus was not reached, a third and a fourth reviewer (NSJ and TJBD) resolved the disagreement. The inclusion and exclusion process of studies in the review is illustrated in the PRISMA flow diagram [35] (Figure 1).

2.4. Data Extraction

The Data Extraction and Assessment Template created by the Cochrane Public Health Group was used to guide us in developing and piloting a data extraction form [36]. Using Covidence, two reviewers (AA and BA) independently abstracted data from the selected studies. Any disagreements in the extracted data between the two reviewers (AA and BA) were resolved through discussions. If no consensus was reached, a third and a fourth reviewer (NSJ and TJBD) resolved any disagreement. The following study information was abstracted: study-level characteristics (i.e., study design, location, publication year, funding source, inclusion or exclusion criteria, number of participants, participant recruitment/selection, number of cases, missing data and study follow-up time), exposure characteristics (i.e., individual or group arsenic exposure assessment, arsenic concentrations), outcome definition and measurement (i.e., type of outcome, International Classification of Diseases code, outcome measures—incidence or mortality), absolute and/or relative risk estimates (i.e., mortality rate, standardized mortality ratio (SMR), hazard ratio (HR), odds ratio (OR) and relative risk (RR) and their corresponding confidence intervals, whether

confounders or effect modifiers were determined and adjusted in the analysis). If study data were not present, the study authors were contacted requesting missing information.

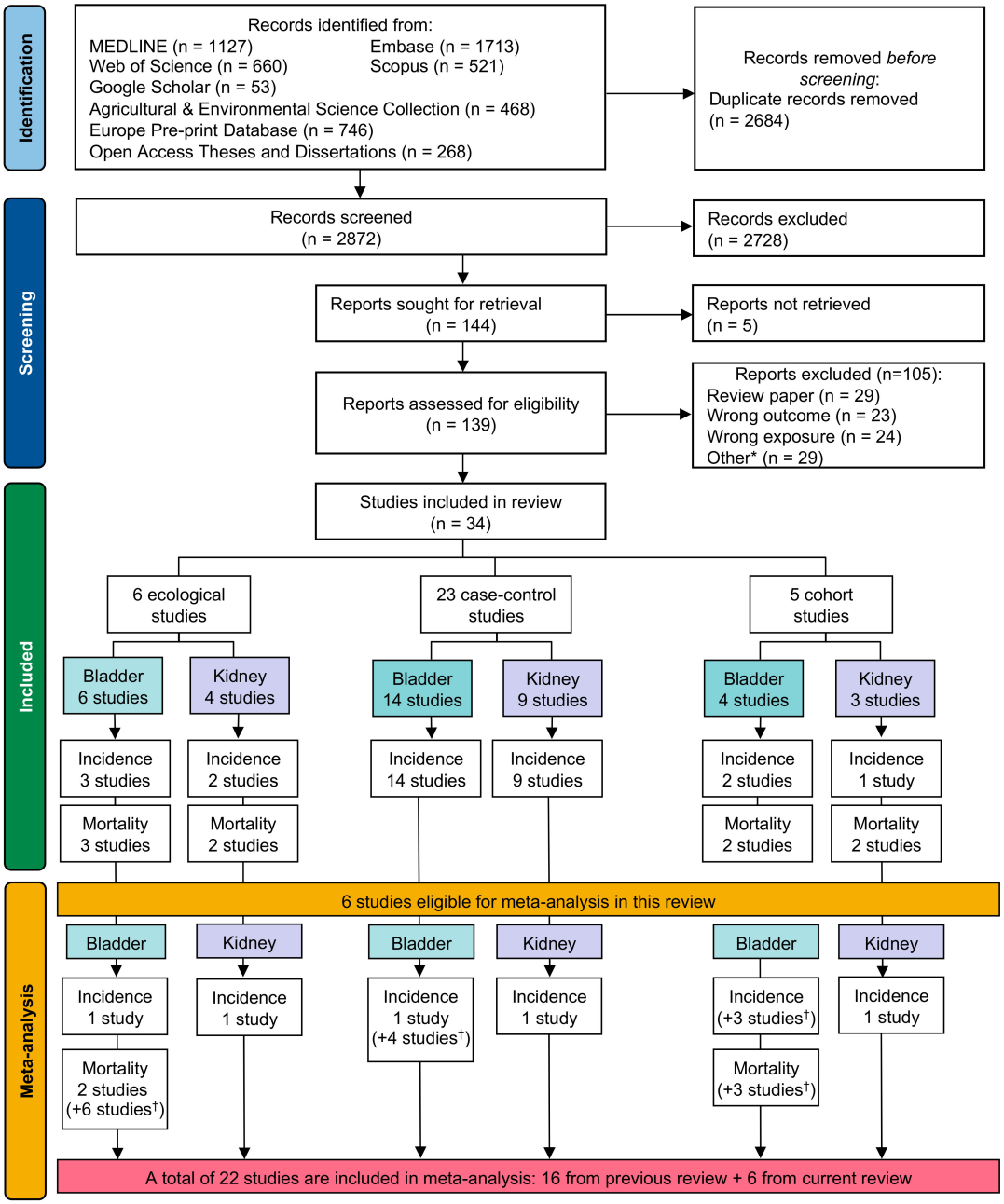

Figure 1. PRISMA flowchart illustrating the study selection process for the review and meta-analysis. Note that some studies reported on more than one cancer site. * ongoing study, wrong comparison group, not peer-reviewed, not in English, data missing or included in the previous review † Data from the previous review [33].

2.5. Data Analysis

Study inclusion for meta-analyses followed the same criteria as those reported in Saint-Jacques et al. [33]. Briefly, studies providing point estimates of As concentrations in drinking water were included, and those reporting annual average As ingestion, cumulative As exposure, duration of artesian water consumption and As levels in urine were excluded. Risk estimates from this current review (6 studies) were combined with those included in our previous review (16 studies; Figure 1), allowing us to examine associations over a broader and more continuous range of concentrations and with a larger number of studies.

Risk estimates for bladder cancer mortality (11 studies) were analyzed separately from risk estimates for bladder cancer incidence (9 studies). Studies reporting risk estimates on incidence for kidney cancer (3 studies) were also analyzed separately.

Bayesian hierarchical/multilevel models were used to estimate bladder and kidney cancer incidence relative risk (RR, OR, HR) and the bladder cancer standardized mortality ratio (SMR) in relation to arsenic exposure. Overall, the Bayesian approach considers both the data and model parameters as random variables, in contrast to frequentist methods. By treating model parameters as unknown random variables, it becomes possible to specify prior distributions for these. The joint prior probability density function for all the model parameters was then combined with the model likelihood function to obtain the joint posterior probability density function. This posterior distribution reflects the updated beliefs about the parameters after incorporating the observed data [37]. The approach specified a Gaussian observation submodel for log(Risk) with corresponding standard errors obtained from publications, also known as a random-effects meta-analysis model [38]. For bladder cancer, the models assumed random slopes and intercepts (Figures S2 and S3), while for kidney cancer, due to the small number of studies, a random intercept model was used (Figure S4). Posterior mean relative risk estimates, their corresponding 95% credible intervals (CrI) and exceedance probabilities were obtained at 5, 10, 20, 50, 100 and 150 µg/L As concentrations in drinking water.

The analyses were performed using the "brms" R package [39], a front end to the STAN computational platform [40]. Non-informative priors were used for model parameters. For each model, four chains of 5000 MCMC (Markov Chain Monte Carlo) samples were run. The first 2500 samples were discarded as the burn-in. Convergence of the MCMC sequences to the posterior distributions was assessed using an R-hat diagnostic statistic (R-hat = 1), effective sample size statistics (>1000) and examining trace plots of simulations. All analyses were performed using R 4.2.2 version [41].

3. Results

3.1. Study Characteristics

The electronic searches generated a total of 5556 records. After removing 2684 duplicate records, 2872 papers were retrieved for title and abstract screening, of which 144 studies were retained for full text review (Figure 1). A total of 110 reports were excluded for a variety of reasons, see Figure 1 for details. In total, 34 original studies met the inclusion criteria: 23 case–control, six ecological and five cohort studies. Of these, 16 studies reported on bladder cancer, nine on kidney cancer and nine on both cancers and other urinary tract cancers. Six studies met the criteria to be included in the meta-analyses: two reported on bladder cancer mortality, one on bladder cancer incidence, two on kidney cancer incidence and one reported incidence for both bladder and kidney cancers. Study regions included: northern Chile; Nova Scotia, Canada; rural USA; Taiwan; Bangladesh and Italy.

3.2. Risk of Bias Assessment

The risk of bias of the included studies varied in terms of the method of As exposure measurement, analytical approach, including controlling for potential confounding (particularly for tobacco smoking), handling of missing data and outcome measurement. Thirteen studies reported measures of As levels in well or tap drinking water, six studies reported cumulative As intake and 15 studies measured As concentrations in urine (Tables 1–6). The As concentrations in drinking water ranged from 0.5 µg/L to 3500 µg/L across the studies (Figure 2). Of the ecological studies, one estimated As exposure through linking residential history to previously collected individual-level measurements from wells [42], while the remaining studies relied on As exposure concentrations based on aggregate data. All of the cohort and most case–control studies evaluated As exposure either by directly measuring As levels in urine or in tap/well water or through the individual-level estimation of past As exposure based on residential history or the source of drinking water. Two case–control studies used aggregate data to estimate As exposure levels [43,44].

Table 1. Summary of results from ecological studies reporting on arsenic (As) exposure and the risk of bladder cancer.

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Exposure [1] (Comments)	ICD [2]	Outcome Measure	Cases	Risk Estimate (95% CI)
Mendez et al., 2017 [45] (Table Three)	1178 counties in 49 states, USA	Incidence 2006–2010	Mean county–level groundwater As concentration (μg/L) (per one unit log of mean county As increase) (Approximately, 31,000 As measurements from ground water sources in 1178 counties in 49 states were collected between 1971–2000. The average proportion of population served by public groundwater in the counties was 76%.)	ICD–9: 188	 RR_{male} RR_{female} (Adjusted for proportion groundwater dependence, education, household income, ethnicity, living in the same house, smoking status, rural–urban indicator, obesity, and age)	Counties 625 336	 1.00 (0.99–1.02) ‡ 1.03 (1.00–1.06)
* Roh et al., 2018 [46] (Table One)	Region II and the rest of Chile	Mortality 2001–2010	Annual average As concentration in drinking water for Antofagasta and Mejillones (Region II) of Chile ranging between <10 to 860 μg/L; compared with the rest of Chile; exposure generally < 10 μg/L. Data from historical records from 1950–2010. (Exposure data were based on where subjects died, without detailed residential history.)	ICD–9: 188	SMR_{male_birth} $SMR_{male\_1–10}$ $SMR_{male\_11–20}$ $SMR_{male\_21–30}$ $SMR_{male\_31–40}$ $SMR_{male\_\geq 40}$ SMR_{female_birth} $SMR_{female\_1–10}$ $SMR_{female\_11–20}$ $SMR_{female\_21–30}$ $SMR_{female\_31–40}$ $SMR_{female\_\geq 40}$ (Age at potential first exposure to high levels of As in drinking water; SMR_{male_birth} = mortality for males first exposed at birth)	17 28 32 65 39 13 7 7 27 47 41 9	16.8 (9.8–27.0) 7.9 (5.3–11.5) 4.8 (3.3–6.8) 5.9 (4.5–7.5) 4.4 (3.1–6.0) 4.9 (2.6–8.4) 13.6 (5.5–27.9) 5.3 (2.2–11.0) 9.9 (6.5–14.5) 8.8 (6.5–11.7) 6.4 (4.6–8.7) 3.6 (1.6–6.8)

Table 1. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Exposure [1] (Comments)	ICD [2]	Outcome Measure	Cases	Risk Estimate (95% CI)
* Saint–Jacques et al., 2018 [42] (Table Two)	Nova Scotia, Canada	Incidence 1998–2010	As concentration in drinking water (μg/L)	ICD-O: 188.0–188.9	Posterior Mean RR		
			<2 (referent) 2–5 ≥5	ICD-O 2/3: C67.0–C67.9	$RR\text{-}_{male}$	267 144 249	1.00 1.18 (0.91–1.51) 1.21 (0.96–1.49)
			<2 (referent) 2–5 ≥5		$RR\text{-}_{female}$	88 44 70	1.00 1.13 (0.73–1.69) 1.09 (0.74–1.55)
			<2 (referent) 2–5 ≥5		$RR\text{-}_{combined}$	355 188 319	1.00 1.16 (0.91–1.45) 1.18 (0.95–1.44)
			(Residential addresses linked to As measurements from 10,498 private wells (1991–1999), at 901 unique locations and aggregated over a set of continuous 25 km^2 cells. The maximum As level was 3900 μg/L and 17% of the wells had levels exceeding 10 μg/L.)		(Adjusted for material and social deprivation; SES used as a proxy for smoking)		
Smith et al., 2018 [47] (Table Two)	Region II in Chile, compared with the rest of Chile and unexposed Region V	Mortality 2001–2010	Northern Chile (Region II) with population weighted average As concentration in drinking water before 1958 was 116.8 μg/L between 1958–1970 up to 600 μg/L, and after installation of the As removal plant fell to 108.9 μg/L in 1978, to 10 μg/L between 2005–2010.	ICD–9: 188	$RR_{sex\_age\ at\ mortality}$		
					$RR_{male\_30–39}$	1	2.19 (0.28–16.8)
					$RR_{male\_40–49}$	23	13.0 (7.94–21.4)
					$RR_{male\_50–59}$	36	5.68 (3.98–8.11)
					$RR_{male\_60–69}$	48	4.18 (3.10–5.63)
					$RR_{male\_70–79}$	86	4.74 (3.79–5.93)
					RR_{male_80+}	58	4.07 (3.11–5.32)
					RR_{male_all}	252	4.79 (4.20–5.46)
					$RR_{female\_30–39}$	0	0 (Reference)
					$RR_{female\_40–49}$	6	7.03 (2.90–17.0)
					$RR_{female\_50–59}$	20	9.58 (5.83–15.7)
					$RR_{female\_60–69}$	35	7.25 (5.05–10.4)
					$RR_{female\_70–79}$	65	7.47 (5.74–9.74)
					RR_{female_80+}	51	4.78 (3.58–6.38)
					RR_{female_all}	177	6.43 (5.49–7.54)

Table 1. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Exposure [1] (Comments)	ICD [2]	Outcome Measure	Cases	Risk Estimate (95% CI)
* Lopez et al., 2020 [48] (Text–Results)	Antofagasta (Region II) and the rest of Chile	Mortality 1990–2016	From 1958 to 1971, As concentrations rose from 90 to up to 870 µg/L in Antofagasta compared to rest of Chile (mean concentration 570 vs. 50–178 µg/L)	ICD–9: 188, 189.1 and 189.2 ICD–10: C65, C66 and C67	MRR_{BC} † MRR_{UTUC} §	N/A 257	5.5 (5.2–5.9) 17.6 (13.5−22.9)
Krajewski et al., 2021 [49] (Table Two)	943 counties in 19 states, USA	Incidence 2011–2015	Aggregated cumulative county–level As concentrations (µg/year) <3.83 (referent) 3.83–7.18 7.18–12.89 >12.89 (Annual As concentrations in public water supplies were collected from 73,035 samples from 18,320 community water systems between 2000–2010. The annual median As concentration was close to 1 µg/L (three outliers with over 100 µg/L).)	N/A	RR (Adjusted for county population of black residents, percent of county population of males, percent of county population that lived in the same county for at least the last 5 years, percent of county population that ever smoked, environmental quality index of water, air, land, build, and sociodemographic and overall environmental quality)	Counties 236 235 237 235	 1.00 1.28 (1.08–1.53) 1.79 (1.47–2.18) 1.89 (1.53–2.35)

Note(s): [1] All ecological studies assessed As exposure at the group level. [2] ICD = International Classification for Disease for cancer site abstracted, which included bladder and urothelial/transitional cell carcinoma of the bladder. Transitional cell carcinoma of the renal pelvis often share the same etiology as bladder cancer and, as such, were treated as bladder within the meta–analysis as recommended by IARC [9]. * Study included in meta–analysis. ‡ Confidence intervals were derived from Supplementary Materials. † Urinary tract urothelial carcinoma. § Bladder cancer. N/A = not reported.

Table 2. Summary of results from case–control studies reporting on arsenic exposure and the risk of bladder cancer.

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Arsenic Exposure Assessment	Exposure (Comments)	Cases: Controls	All Participants		Never Smokers		Ever Smokers		Covariates Assessed
						n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
Chung et al., 2013 [50] (Table Two)	Taiwan	Incidence 2007–2011	Individual level 'measured'	As urine concentration (μg/g creatinine)	191:364							Age, sex
				<12.81 (referent)		29	1.00					
				12.81–23.30		44	1.64 (0.95–2.82)					
				≥23.30		118	4.63 (2.80–7.65)					
				(Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)								
Ferreccio et al., 2013 (a) [51] (Table Two, Supplementary Table Four)	Regions I and II, Northern Chile	Incidence 2007–2010	Individual level 'estimated'	Water As concentration (μg/L)	232:640							Age, sex, socioeconomic status, and second–hand tobacco smoke exposure.
				0–59 (referent)		23	1.00					
				60–199		27	0.84 (0.46–1.52)					
				200–799		60	2.50 (1.48–4.22)					
				≥800		122	4.44 (2.75–7.15)					
				Model 2								
				0–34				14	1.00	19	2.83 (1.22–6.58)	
				35–260				20	1.92 (0.90–4.11)	18	2.28 (0.98–5.31)	
				>260				31	5.27 (2.51–11.07)	41	15.30 (6.75–34.67)	
				(Average lifetime exposure up to 1971, when high exposure period in Antofagasta ended. As measurements were from the government, research and other sources (>97% of all drinking water sources in the study area.)								

Table 2. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Arsenic Exposure Assessment	Exposure (Comments)	Cases: Controls	All Participants		Never Smokers		Ever Smokers		Covariates Assessed
						n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
* Wang et al., 2013 [43] (Table Two)	Taipei, Taiwan	Incidence 1998–2009	Group level	As water concentration (μg /L)								Age, sex, cigarette smoking, alcohol consumption, and hazardous chemical
				Bladder Cancer	470:850							
				<350 (referent)		391	1.0	174	1.0	217	2.7 (1.9–3.6)	
				350–1140		79	2.4 (1.6–3.4)	36	2.5 (1.6–4.1)	43	5.7 (3.1–10.3)	
				UUTUC §								
				<350 (referent)	260:850	215	1.0	146	1.0	69	2.2 (1.4–3.4)	
				350–1140		45	2.5 (1.6–3.8)	27	2.3 (1.3–3.9)	18	6.4 (3.1–13.3)	
				(Period of As water samples collection not reported. Participants used artesian well water for > 10 years when recruited. The interview included history of well–water consumption, residential history, lifestyle factors. As water concentration in Peimen, Hsuechia, Putai and Ichu townships ranged between 350–1140 μg /L (BFD–endemic area), in surrounding areas was <350 μg /L.								
				Core zone (350–1140 + BFD) Zone 1 (>350) Zone 2 (<350))								

Table 2. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Arsenic Exposure Assessment	Exposure (Comments)	Cases: Controls	All Participants		Never Smokers		Ever Smokers		Covariates Assessed
						n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
Wu et al., 2013 (a) [52] (Table Two, Three)	Taipei, Taiwan	Incidence 2002–2009	Individual level 'measured'	Total urinary As (μg /g creatinine)	261:672							Age, sex, educational level, and alcohol consumption
				<11.50 (referent)		36	1.00					
				11.50–20.40		55	1.50 (0.95–2.39)					
				≥20.40		170	4.68 (3.06–7.14)					
				No second–hand smoke exposure <15.40 (referent)					1.00		2.93 (1.28–6.71)	
				≥15.40					3.06 (1.55–6.01)		5.55 (2.67–11.5)	
				Second–hand smoke exposure <15.40					1.72 (0.75–3.94)		3.00 (1.28–7.04)	
				≥15.40					5.55 (2.72–11.3)		10.8 (5.16–22.7)	
				(Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)								
Wu et al., 2013 (b) [53] (Table Two)	Taipei, Taiwan	Incidence 2002–2009	Individual level 'measured'	Total urinary As (μg /g creatinine)	299:594							Age, sex, education level, alcohol drinking, tea or coffee consump-tion, cumulative cigarette smoking, pesticide exposure, analgesic use and disease history
				≤11.74 (referent)		44	1.00					
				11.74–20.94		63	1.42 (0.90–2.25)					
				>20.94		192	4.13 (2.69–6.35)					
				(Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)								

Table 2. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Arsenic Exposure Assessment	Exposure (Comments)	Cases: Controls	All Participants		Never Smokers		Ever Smokers		Covariates Assessed
						n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
Melak et al., 2014 [54] (Table Four)	Regions I and II, Northern Chile	Incidence 2007–2010	Individual level 'measured'	Proportion of monomethylarsonic acid in urine (%)	117:347							Age, sex, smoking
				All:								
				<12.5 (referent)								
				≥12.5		75	1.00					
						42	1.41 (0.89–2.23)					
				Water As <200 µg/L:								
				<12.5 (referent)								
				≥12.5		14	1.00					
						13	2.37 (1.01–5.57)					
				Water As ≥200 µg/L:								
				<12.5								
						61	6.42 (3.29–12.53					
				≥12.5		29	6.96 (3.27–14.8)					
				(Residential history was collected; each city/town was linked to a water As measurement for that city/town so that an As concentration could be assigned to each year of each subject's life.)								
Steinmaus et al., 2014 [55] (Table Four)	Regions I and II, Northern Chile	Incidence 2007–2010	Individual level 'estimated'	As water concentration (µg/L)								Age, sex and smoking
				Exposed only in utero or as children	90:286							
				≤110 (referent)		29	1.00					
				111–800		13	2.94 (1.29–6.70)					
				>800		48	8.11 (4.31–15.3)					
				Exposed only as adults								
				≤110 (referent)	84:332	30	1.00					
				111–800		12	2.21 (1.03–4.74)					
				>800		42	4.71 (2.61–8.48)					
				(Residential history was collected; each city/town was linked to a water As measurement for that city/town so that an As concentration could be assigned to each year of each subject's life.)								

Table 2. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Arsenic Exposure Assessment	Exposure (Comments)	Cases: Controls	All Participants		Never Smokers		Ever Smokers		Covariates Assessed
						n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
Mostafa et al., 2015 [56] (Table Three)	Bangladesh	Incidence 2008–2011	Individual level 'estimated'	As water concentration (μg/L)	1446: 1078							Age, sex and smoking status
				TCC [£]								
				≤10 (referent)		238	1.00					
				10–50		319	1.52 (1.08–2.14)					
				50–100		204	1.07 (0.73–1.57)					
				100–200		278	0.99 (0.69–1.41)					
				200–300		251	1.63 (1.08–2.46)					
				≥300		156	0.89 (0.55–1.43)					
				(3535 wells were sampled (1998–1999) in 61/64 districts in Bangladesh, 27% of hand–pumped tube wells contained >50 μg/L of As. The mean As concentration data was linked to where participants lived during a biopsy.)								

Table 2. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Arsenic Exposure Assessment	Exposure (Comments)	Cases: Controls	All Participants		Never Smokers		Ever Smokers		Covariates Assessed
						n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
Baris et al., 2016 [57] (Table Three)	Maine, New Hampshire, and Vermont states, USA	Incidence 2001–2004	Individual level 'estimated'	Average drinking water As concentration (µg/L)	1079: 1287							Age, sex, Hispanic ethnicity, state of residence, smoking, education, employment in a high–risk occupation, and exposure to disinfection by–products (total tri-halomethanes)
				Unlagged								
				≤ 0.5 (referent)		303	1.00					
				>0.5–1.0		226	0.77 (0.60–0.98)	–	–	–	–	
				>1.0–2.1		281	0.97 (0.76–1.24)	–	–	–	–	
				>2.1–7.0		225	0.98 (0.74–1.28)	–	–	–	–	
				>7.0–10.4		18	0.64 (0.33–1.23)	–	–	–	–	
				>10.4		26	1.10 (0.61–2.00)	–	–	–	–	
				Lagged 40 years				–	–	–	–	
				≤ 0.4		280	1.00					
				>0.4–0.7		260	0.91 (0.71–1.17)	–	–	–	–	
				>0.7–1.6		233	0.93 (0.72–1.20)	–	–	–	–	
				>1.6–5.7		220	1.06 (0.81–1.40)	–	–	–	–	
				>5.7–8.7		26	0.92 (0.51–1.66)	–	–	–	–	
				>8.7		37	1.49 (0.85–2.61)	–	–	–	–	
				(Direct measurements of As in water samples collected between 2001–2004 (range 0–20.7 [95th percentile]). When direct estimates were unavailable historical records from 1971–2005 were collected (range 0–30.5 [95th percentile]). Residential history from interview combined with water sample measurements or prediction estimates.)								

Table 2. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Arsenic Exposure Assessment	Exposure (Comments)	Cases: Controls	All Participants		Never Smokers		Ever Smokers		Covariates Assessed
						n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
Chang et al., 2016 [58] (Table Three)	Taichung, Taiwan	Incidence 2011–2013	Individual level 'measured'	Urinary As concentration (μg/L)	205:406							Age, sex, education level, cumulative cigarette smoking, herbal medicine use, exposure to dye and pesticide use
				<46 (referent)		59	1.00					
				46–86.8		58	0.94 (0.59–1.50)					
				≥86.8		88	1.52 (0.98–2.37)					
				(Average urinary As level in controls was 95.6 μg/L (range = 3.8–1312.4 μg/L); in cases was 68.1 μg/L (range = 3.8–2819.6 μg/L).)								
Huang et al., 2016 (a) [59] (Table One)	Taipei, Taiwan	Incidence 2007–2009	Individual level 'measured'	Urinary total As concentration (μg/g creatinine)	167:334							Age, sex, education level, and cigarette smoking status
				≤12.24 (referent)		13	1.00					
				12.24–21.80		35	2.44 (1.19–5.02)					
				>21.80		119	8.44 (4.25–16.8)					
				(Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)								

Table 2. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Arsenic Exposure Assessment	Exposure (Comments)	Cases: Controls	All Participants		Never Smokers		Ever Smokers		Covariates Assessed
						n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
Huang et al., 2018 [60] (Table Two)	Taipei, Taiwan	Incidence 2007–2011	Individual level 'measured'	Total urinary As concentration (μg/L)	428:813							Age, sex, schools, father's educational level, cigarette smoking, alcohol, tea and coffee drinking, pesticide contact, urinary tract calculus, hypertension and diabetes history, and urinary creatinine
				UTUC^{+} and bladder cancer:								
				≤9.78 (referent)		177	1.00					
				9.78–17.91		112	1.52 (1.01–2.26)					
				17.91–30.28		76	1.67 (1.05–2.67)					
				>30.28		63	3.49 (2.01–6.06)					
				Bladder cancer: ≤9.78 (referent)		72	1.00					
				9.78–17.91		64	1.94 (1.18–3.20)					
				17.91–30.28		46	2.09 (1.18–3.69)					
				>30.28		34	3.52 (1.77–6.96)					
				UTUC:$^{+}$ ≤9.78 (referent)		105	1.00					
				9.78–17.91		48	1.40 (0.83–2.38)					
				17.91–30.28		30	1.91 (0.99–3.69)					
				>30.28		29	4.80 (2.22–10.4)					
				(Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)								

Table 2. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Arsenic Exposure Assessment	Exposure (Comments)	Cases: Controls	All Participants		Never Smokers		Ever Smokers		Covariates Assessed
						n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
Koutros et al., 2018 [61] (Table One, Two, Three)	Maine, New Hampshire, and Vermont states, USA	Incidence 2001–2004	Individual level 'estimated'	Cumulative As exposure (mg) Unlagged 0–15.7 (referent)	1079: 1287	228	1.0	50	1.0	108 64	1.0[†] 1.0[‡]	Age, sex, ethnicity, state of residence, smoking, disinfection by products and high–risk occupation
				>15.7–34.5		288	1.2 (0.92–1.5)	41	1.2 (0.7–2.1)	151 89	1.1 (0.8–1.6) [†] 1.5 (0.8–2.6) [‡]	
				>34.5–77.0		263	1.1 (0.87–1.5)	36	0.9 (0.5–1.5)	139 86	1.3 (0.9–1.8) [†] 1.3 (0.7–2.3) [‡]	
				>77.0–291.0		235	1.3 (1.00–1.7)	37	1.1 (0.6–1.9)	152 104	1.4 (0.9–2.0) [†] 1.6 (0.9–3.0) [‡]	
				>291.0–483.6		33	1.3 (0.7–2.3)					
				>483.6		32	1.6 (0.90–2.9)					
				Lagged 40 years 0–3.52 (referent)		233	1.0	48	1.0	94 83	1.0[†] 1.0[c]	
				>3.52–8.77		269	1.1 (0.87–1.5)	33	1.0 (0.5–1.7)	149 83	1.1 (0.8–1.6) [†] 1.7 (0.9–3.0) [‡]	
				>8.77–22.42		260	1.2 (0.92–1.6)	40	1.3 (0.7–2.3)	140 75	1.2 (0.8–1.7) [†] 1.3 (0.7–2.3) [‡]	
				>22.4–83.5		213	1.3 (0.95–1.7)	37	1.1 (0.6–2.0)	162 91	1.6 (1.1–2.4) [†] 1.6 (0.9–3.0) [‡]	
				>83.5–124.8		34	1.7 (0.96–3.1)					
				>124.8		47	2.2 (1.3–3.9)					
				(Period of As water sample collection not reported. Residential history from interview combined with water sample measurements or prediction estimates.)								

Table 2. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Arsenic Exposure Assessment	Exposure (Comments)	Cases: Controls	All Participants		Never Smokers		Ever Smokers		Covariates Assessed
						n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
Lin et al., 2018 [62] (Table Four)	Taipei, Taiwan	Incidence 2007–2011	Individual level 'measured'	Urinary total As concentration (μg/L)	216:648							Age, sex, education level, cigarette smoking, and urine creatinine level
				≤9.71 (referent)		72	1.00					
				9.71–17.98		64	2.02 (1.25–3.27)					
				17.98–30.51		46	2.36 (1.36–4.09)					
				>30.51		34	3.23 (1.68–6.20)					
				(Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)								

Note(s): * Study included in meta-analysis. [§] Upper urinary tract urothelial carcinoma; [£] Transitional cell carcinoma; [+] Urinary tract urothelial carcinoma; [†] Former smokers; [‡] Current smokers. ICD codes were not reported for any of the studies.

Table 3. Summary of results from cohort studies reporting on arsenic (As) exposure and the risk of bladder cancer.

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	ICD [1]	As Exposure Assessment	Exposure (Comments)	Outcome Measure	Cohort Size	Cases	Risk Estimate (95% CI)	Covariates Assessed
Yang et al., 2013 [63] (Table One, Two)	18 villages in four townships in the Lanyang Basin, North–eastern Taiwan	Incidence 1991–1994	ICD–9: 188, 189.0, 189.1–189.9	Individual level 'measured'	As concentration (μg/L)	RR	6876			Cigarette smoking
					<10 (referent)			3	1.00	
					10–99			9	2.18 (0.59–8.01)	
					≥100			17	8.71 (2.49–30.5)	
					Non–Smokers					
					<10 (referent)			2	1.00	
					10–99			3	1.14 (0.20–6.66)	
					≥100			6	4.64 (0.89–24.2)	
					Smokers					
					<10 (referent)			1	1.00	
					10–99			6	4.19 (0.51–34.5)	
					≥100			11	16.50 (2.12–128.6)	
					Cumulative As exposure (μg/L*y)					
					<500 (referent)			4	1.00	
					500–4999			11	2.46 (0.78–7.72)	
					≥5000			16	9.36 (3.03–28.9)	
					Non–Smokers					
					<500 (referent)			3	1.00	
					500–4999			3	0.91 (0.19–4.43)	
					≥5000			5	4.95 (1.21–20.2)	
					Smokers					
					<500 (referent)			1	1.00	
					500–4999			8	7.14 (0.88–58.1)	
					≥5000			11	23.45 (3.02–182.3)	
					(As levels in shallow well ranging from < 0.15 to 3590 μg/L and collected from 3901 well water samples between 1991–1994.)					

Table 3. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	ICD [1]	As Exposure Assessment	Exposure (Comments)	Outcome Measure	Cohort Size	Cases	Risk Estimate (95% CI)	Covariates Assessed
D'Ippoliti et al., 2015 [64] (Table Three)	17 municipalities, Viterbo province, Lazio Region, Italy	Mortality 1990–2010	ICD–9: 188	Individual level 'estimated'	Cumulative As intake (μg) Males ≤ 204.9 (referent) 204.9–804.0 >804.0 Females ≤ 204.9 (referent) 204.9–804.0 >804.0 (Residential history combined with local water records used to assess exposure. As concentration data were only available for 2005–2010, it was assumed that the As concentrations were stable in the study period. As levels ranged 0.5 μg/L to 80.4 μg/L (mean=19.3 μg/L).)	HR	68,758 70,042	13 56 88 5 18 15	1.00 0.82 (0.43–1.58) 1.32 (0.67–2.60) 1.00 0.91 (0.31–2.67) 0.71 (0.23–2.24)	Age, calendar period, socioeconomic level, occupation in the ceramic industry, smoking sales and radon exposure
Tsai et al., 2021 [65] (Table Four)	18 villages in four townships in the Lanyang Basin, North–eastern Taiwan	Incidence 1991–1994	ICD–9: 188	Individual level 'measured'	Cumulative exposure to As in well water (μg/L) <874.2 (referent) ≥874.2 Total urinary As concentration (μg/g creatinine) <97.14 (referent) ≥97.14 (As levels in shallow well ranging from < 0.15 to 3590 μg/L and collected from 3901 well water samples between 1991–1994.)	HR	771	1 11 1.00 2.78 (0.75–10.4)	1.00 11.38 (1.48–87.7)	Age, sex, education level and cigarette smoking.

Table 3. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	ICD [1]	As Exposure Assessment	Exposure (Comments)	Outcome Measure	Cohort Size	Cases	Risk Estimate (95% CI)	Covariates Assessed
Nuvolone et al., 2023 [66] (Table Five)	Five municipalities in Mt. Amiata area; Tuscany, Italy	Mortality 1998–2016	N/A	Individual level 'estimated'	Time–weighted average As concentration in drinking water (μg/L) ≤ 5 (referent) 5–10 >10 (As concentration in tap water were available from 2005 to 2010. It was assumed that As concentrations were stable before 2005, given no mitigation action prior to 2010 and widely known levels in groundwater. Long–term exposure to As for each subject was analyzed by overlapping home coordinates with the water supply units and sampling points.)	HR	30,910	11 27 34	1.00 0.56 (0.26–1.24) 0.63 (0.31–1.29)	Sex, socioeconomic status, calendar period

Note(s): [1] ICD = International Classification for Disease for cancer site abstracted, which included bladder and urothelial/transitional cell carcinoma of the bladder. Transitional cell carcinoma of the renal pelvis often share the same etiology as bladder cancer and, as such, were treated as bladder within the meta-analysis as recommended by IARC [9].

Table 4. Summary of results from ecological studies reporting on arsenic (As) exposure and the risk of kidney cancer.

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Exposure [1] (Comments)	ICD [2]	Outcome Measure	Cases	Risk Estimate (95% CI)
Roh et al., 2018 [46] (Table One)	Region II and the rest of Chile	Mortality 2001–2010	Annual average As concentration in drinking water for Antofagasta and Mejillones (Region II) of Chile ranging between <10 to 860 µg/L; compared with the rest of Chile; exposure generally < 10 µg/L. Data from historical records from 1950–2010. (Exposure data were based on where subjects died, without detailed residential history.)	ICD–9: 189	$SMR_{sex\_age\ at\ exposure}$ SMR_{male_birth} $SMR_{male\_1–10}$ $SMR_{male\_11–20}$ $SMR_{male\_21–30}$ $SMR_{male\_31–40}$ $SMR_{male\_\geq 40}$ SMR_{female_birth} $SMR_{female\_1–10}$ $SMR_{female\_11–20}$ $SMR_{female\_21–30}$ $SMR_{female\_31–40}$ $SMR_{female\_\geq 40}$	 4 18 32 29 16 3 4 7 17 17 22 4	 0.9 (0.2–2.3) 1.7 (1.0–2.6) 2.1 (1.4–3.0) 1.7 (1.2–2.5) 2.2 (1.2–3.5) 2.0 (0.4–5.9) 2.2 (0.6–5.6) 1.8 (0.7–3.7) 2.6 (1.5–4.2) 1.9 (1.1–3.0) 3.4 (2.1–5.1) 2.1 (0.6–5.4)
* Saint–Jacques et al., 2018 [42] (Table Three)	Nova Scotia, Canada	Incidence 1998–2010	As concentration in drinking water (µg/L) <2 (referent) 2–5 ≥5 <2 (referent) 2–5 ≥5 <2 (referent) 2–5 ≥5 (Participant residential addresses were linked to As measurements collected from 10,498 private wells between 1991–1999, pooled at 901 unique locations and aggregated over a set of continuous 25 km^2 cells. The maximum As level was 3900 µg/L and 17% of the wells had levels exceeding 10µg/L.)	ICD–O: 189.0 ICD–O 2/3: C64.9	Posterior Mean RR $RR\text{-}_{male}$ $RR\text{-}_{female}$ $RR\text{-}_{combined}$ (Adjusted for material and social deprivation; SES used as a proxy for smoking)	 132 66 123 89 40 74 221 106 197	 1.00 1.10 (0.78–1.51) 1.15 (0.86–1.51) 1.00 0.99 (0.66–1.43) 1.10 (0.79–1.51) 1.00 1.05 (0.79–1.37) 1.14 (0.89–1.44)

Table 4. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	Exposure [1] (Comments)	ICD [2]	Outcome Measure	Cases	Risk Estimate (95% CI)
Smith et al., 2018 [47] (Table Two)	Region II in Chile, compared with the rest of Chile and unexposed Region V	Mortality 2001–2010	Northern Chile (Region II) with population weighted average As concentration in drinking water before 1958 was 116.8 μg/L between 1958–1970 up to 600 μg/L, and after installation of the As removal plant fell to 108.9 μg/L in 1978, to 10 μg/L between 2005–2010.	ICD–9: 189	$RR_{sex\_age\ at\ mortality}$ $RR_{male\_30–39}$ $RR_{male\_40–49}$ $RR_{male\_50–59}$ $RR_{male\_60–69}$ $RR_{male\_70–79}$ RR_{male_80+} RR_{male_all} $RR_{female\_30–39}$ $RR_{female\_40–49}$ $RR_{female\_50–59}$ $RR_{female\_60–69}$ $RR_{female\_70–79}$ RR_{female_80+} RR_{female_all}	 0 8 29 45 47 25 154 0 5 12 18 31 26 92	 0 (Reference) 0.99 (0.49–2.00) 1.52 (1.05–2.21) 1.74 (1.29–2.35) 1.95 (1.46–2.61) 2.47 (1.65–3.70) 1.75 (1.49–2.05) 0 (Reference) 1.55 (0.63–3.81) 1.80 (1.00–3.21) 1.81 (1.13–2.90) 2.32 (1.61–3.33) 2.60 (1.75–3.86) 2.09 (1.69–2.57)
Krajewski et al., 2021 [49] (Table Two)	943 counties in 19 states, USA	Incidence 2011–2015	Aggregated cumulative county–level As concentrations (μg–year) <3.83 (referent) 3.83–7.18 7.18–12.89 >12.89 (Annual As concentrations in public water supplies were collected from 73,035 samples from 18,320 community water systems between 2000–2010. The annual median As concentration was close to 1 μg/L (three outliers with over 100 μg/L).)	N/A	RR (Adjusted for county population of black residents, percent of county population of males, percent of county population that lived in the same county for at least the last 5 years, percent of county population that ever smoked, environmental quality index of water, air, land, build, and sociodemographic and overall environmental quality.)	Counties 236 235 237 235	 1.00 1.15 (0.97–1.37) 1.60 (1.32–1.94) 1.69 (1.37–2.09)

Note(s): * Study included in meta-analysis. [1] All ecological studies assessed As exposure at the group level. [2] ICD = International Classification of Disease.

Table 5. Summary of results from case–control studies reporting on arsenic (As) exposure and the risk of kidney cancer.

Study [Reference] (Table from Original Publication)	STUDY LOCALE	Outcome	ICD [1]	As Exposure Assessment	Exposure (Comments)	Cases: CONTROLS	n	OR, (95% CI)	Covariates Assessed
Ferreccio et al., 2013 (b) [67] (Table Four)	Regions I and II, Northern Chile	Incidence 2007–2010	ICD–10: C64–66	Individual level 'estimated'	Cumulative As exposure (mg)	122:640			Sex, age, smoking, mining work, present body mass index, socioeconomic status.
					<10 (referent)		80	1.00	
					10–25		28	0.96 (0.59–1.55)	
					>25		14	1.69 (0.87–3.26)	
					(Exposure for cumulative As intake based on typical water consumptions and As water concentrations in the 3 main exposure areas of Arica/Iquique, Calama, and Antofagasta where historical average levels ranged from <10ug/L to 860 ug/L over the period of 1930 to 1995.)				

Table 5. *Cont.*

Study [Reference] (Table from Original Publication)	STUDY LOCALE	Outcome	ICD [1]	As Exposure Assessment	Exposure (Comments)	Cases: CONTROLS	n	OR, (95% CI)	Covariates Assessed
* Mostafa et al., 2013 [68] (Table Three)	Bangladesh	Incidence 2008–2011	N/A	Individual level 'estimated'	As water concentration (μg/L)	986:503			Age, sex, ever smoked and for clustering within thana (smallest administrative area)
					RCC+TCC: [†]				
					<10 (referent)		216	1.00	
					10–50		149	1.29 (0.86–1.91)	
					50–100		123	2.12 (1.33–3.39)	
					100–200		150	2.41 (1.53–3.81)	
					200–300		197	3.84 (2.38–6.19)	
					≥300		151	6.00 (3.29–11.0)	
					RCC:				
					<10 (referent)		197	1.00	
					10–50		144	1.37 (0.92–2.06)	
					50–100		108	2.05 (1.27–3.32)	
					100–200		130	2.28 (1.42–3.64)	
					200–300		180	3.95 (2.42–6.44)	
					≥300		137	6.00 (3.24–11.1)	
					TCC:				
					<10 (referent)		19	1.00	
					10–50		5	0.51 (0.16–1.63)	
					50–100		15	4.59 (1.70–12.4)	
					100–200		20	4.94 (1.88–13.0)	
					200–300		17	4.83 (1.77–13.1)	
					≥300		14	7.70 (2.37–25.0)	
					(3535 wells were sampled between 1998–1999 in 61 out of 64 districts in Bangladesh, 27% of hand–pumped tube wells contained >50 μg/L of As. The mean As concentration data was linked to where participants lived during a biopsy.)				

Table 5. *Cont.*

Study [Reference] (Table from Original Publication)	STUDY LOCALE	Outcome	ICD [1]	As Exposure Assessment	Exposure (Comments)	Cases: CONTROLS	n	OR, (95% CI)	Covariates Assessed
Yang et al., 2015 [69] (Table Two)	Taipei, Taiwan	Incidence 2006–2009	N/A	Individual level 'measured'	Urinary total As (μg/L)	191:376			Age, sex, parental ethnicity, alcohol consumption, tea drinking, coffee drinking, and histories of hypertension, diabetes, urolithiasis, and creatinine
					≤10.52 (referent)		66	1.00	
					10.52–24.23		66	1.72 (0.96–3.08)	
					>24.23		59	4.07 (2.02–8.19)	
					(Results shown for renal cell carcinoma)				
					(Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)				
Huang et al., 2016 (b) [70] (Table Two)	Taipei, Taiwan	Incidence 2006–2012	N/A	Individual level 'measured'	Total urinary As (μg/L)	398:756			Individual urine creatinine level, age, sex, education level, cigarette smoking, alcohol consumption, history of hypertension and diabetes.
					≤12.35 (referent)		204	1.00	
					12.35–25.50		110	1.32 (0.92–1.91)	
					>25.50		84	1.90 (1.22–2.96)	
					(Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)				
Yang et al., 2016 [71] (Table Three)	Taipei, Taiwan	Incidence 2006–2014	N/A	Individual level 'measured'	Urinary total As (μg/L)	293:293			Age, sex, education level, parental ethnicity, BMI, cumulative cigarette smoking, alcohol consumption, tea drinking, coffee drinking, and histories of hypertension and diabetes
					≤10.80 (referent)		132	1.00	
					10.80–22.44		84	1.61 (0.94–2.77)	
					>22.44		77	2.86 (1.49–5.50)	
					(Results shown for clear cell renal carcinoma.)				
					(Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)				

Table 5. *Cont.*

Study [Reference] (Table from Original Publication)	STUDY LOCALE	Outcome	ICD [1]	As Exposure Assessment	Exposure (Comments)	Cases: CONTROLS	n	OR, (95% CI)	Covariates Assessed
Hsueh et al., 2017 [72] (Table Two)	Taipei, Taiwan	Incidence 2006–2012	N/A	Individual level 'measured'	Urinary total As (μg/g creatinine)	180:360			Age, sex, eGFR, diabetes and hypertension.
					≤11.70 (referent)		33	1.00	
					11.70–19.59		58	1.82 (1.08–3.07)	
					>19.59		89	2.87 (1.73–4.76)	
					(Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)				
Hsueh et al., 2018 [73] (Table One, Six)	Taipei, Taiwan	Incidence 2006–2012	N/A	Individual level 'measured'	Urinary total As (μg/L)	389:389			Model 1: age and sex
					Model 1: ≤9.29 (referent)		158	1.00	Model 2: age, sex, education level, smoking, alcohol drinking, diabetes, hypertension, BMI, ADIPOQ rs182052, and urinary creatinine levels
					9.29–16.78		86	1.20 (0.77–1.85)	
					16.78–29.24		83	1.94 (1.19–3.15)	
					>29.24		62	2.70 (1.52–4.79)	
					Model 2: ≤16.78 (referent)			1.00	
					>16.78 (Results shown for renal cell carcinoma)			2.27 (1.49–3.44)	
					(Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)				

Table 5. *Cont.*

Study [Reference] (Table from Original Publication)	STUDY LOCALE	Outcome	ICD [1]	As Exposure Assessment	Exposure (Comments)	Cases: CONTROLS	n	OR, (95% CI)	Covariates Assessed
Chen et al., 2021 [44] (Text–Results)	Taipei and Tainan, Taiwan	Incidence 2004–2011	ICD–9: 189.1, 189.2	Group Level	Arseniasis grades Grade 0 Grade 1 Grade 2 Grade 3 (As exposure was graded based on (1) As concentration >350 μg/L in well water; (2) Blackfoot disease cases; (3) signs of chronic arseniasis (skin lesions) in children. Grade 3—all three factors, Grade 2—factors 1 and 3; Grade 1—factor 1; Grade 0—As concentration <350 μg/L in well water.) (Results shown for upper tract urothelial carcinoma.)	2921:11684		 3.92 ‡ 4.71 5.31 8.35	Age
Hsueh et al., 2021 [74] (Table Two)	Taipei, Taiwan	Incidence 2006–2012	N/A	Individual level 'measured'	Total urinary As (μg/L) per SD increment (Average As concentration of tap water was 0.7 μg/L (range: 0–4.0 μg/L). All cases and controls lived far way (200–300 km) from As–contaminated areas.)	401:774		1.43 (1.19–1.72)	Age, cigarette use, second–hand smoking, alcohol drinking, coffee drinking, hypertension, diabetes mellitus, chronic kidney disease

Note(s): * Study included in meta-analysis. [1] ICD International Classification of Disease. ‡ Age-adjusted incidence rates per 100,000 person-years; † Renal cell carcinoma (RCC) and transitional cell carcinoma (TCC).

Table 6. Summary of results from cohort studies reporting on arsenic (As) exposure and the risk of kidney cancer.

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	ICD [1]	As Exposure Assessment	Exposure (Comments)	Outcome Measure	Cohort Size	Cases	Risk Estimate (95% CI)	Covariates Assessed
García–Esquinas et al., 2013 [75] (Table Three)	Arizona, Oklahoma and North/ South Dakota, USA	Mortality 1989–2008	ICD–9: 189	Individual level 'measured'	Urinary As concentration (µg/g) <6.91 (referent) 6.91–13.32 >13.32	HR	3909		1.00 0.69 (0.25–1.90) 0.44 (0.14–1.40)	Sex, age, education, smoking, alcohol, BMI, glomerular filtration rate, hypertension
D'Ippoliti et al., 2015 [64] (Table Three)	17 municipalities, Viterbo province, Lazio Region, Italy	Mortality 1990–2010	ICD–9: 189	Individual level 'estimated'	Cumulative As intake (µg) Males ≤ 204.9 (referent) 204.9–804.0 >804.0 Females ≤204.9 (referent) 204.9–804.0 >804.0 (Residential history combined with local water records to assess exposure. As concentration data only available for 2005–2010 and assumed stable. As levels ranged 0.5 µg/L to 80.4 µg/L (mean = 19.3 µg/L).)	HR	68758 70,042	 4 34 30 1 18	 1.00 1.95 (0.67–5.72) 1.93 (0.63–5.96) 1.00 4.51 (0.58–35.3) 3.03 (0.37–25.2)	Age, calendar period, socioeconomic level, occupation in the ceramic industry, smoking sales and radon exposure

Table 6. *Cont.*

Study [Reference] (Table from Original Publication)	Study Locale	Outcome	ICD [1]	As Exposure Assessment	Exposure (Comments)	Outcome Measure	Cohort Size	Cases	Risk Estimate (95% CI)	Covariates Assessed
*Tsai et al., 2021 [65] (Table Four)	18 villages in four townships in the Lanyang Basin, North–eastern Taiwan	Incidence 1991–1994	ICD–9: 189	Individual level 'measured'	Well As exposure (μg/L) <24.30 (referent) ≥24.30	HR	775	 7 9	 1.00 1.66 (0.53–5.15)	Age, sex, education level and cigarette smoking.
					Cumulative exposure to As in well water (μg/L) <874.2 (referent) ≥874.2			 6 10	 1.00 2.37 (0.72–7.82)	
					Total urinary As concentration (μg/g creatinine) <97.14 (referent) ≥97.14				 1.00 0.93 (0.32–2.69)	
					(As levels in shallow well ranging from < 0.15 to 3590 μg/L (95th percentile = 525.0 μg/L) and collected from 3901 well water samples between 1991–1994.)					

Note(s): * Study included in meta-analysis. [1] ICD International Classification of Disease.

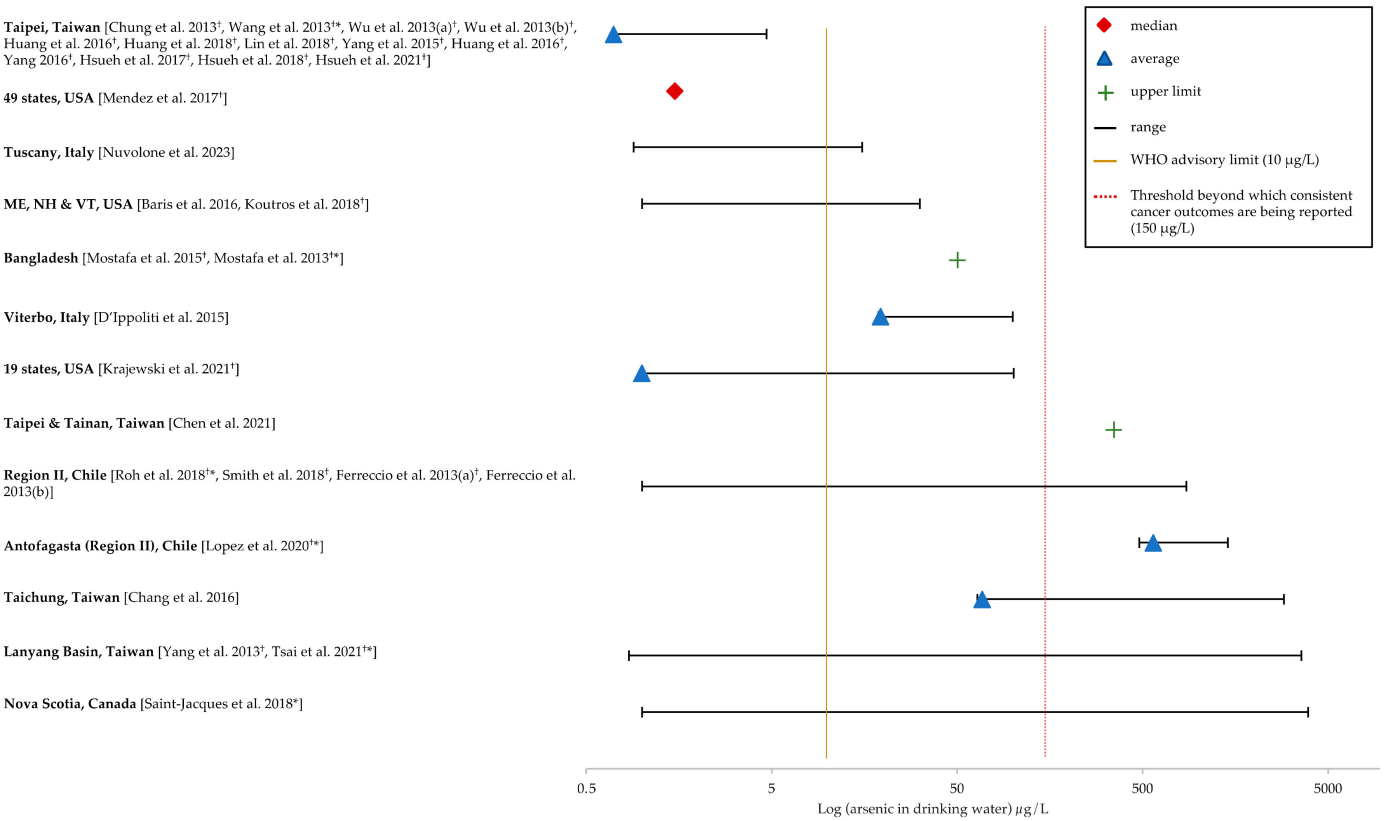

Figure 2. Arsenic concentrations (µg/L) from studies reporting on the association between urinary tract cancers and arsenic exposure in drinking water. † Studies reporting statistically significant associations, and square brackets indicate a citation number; * studies included in the meta-analysis. Of the 34 studies reviewed, three [38,39,60] studies did not report an arsenic concentration range. Abbreviations: WHO—World Health Organization, µg/L—micrograms per liter, ME—Maine state, NH—New Hampshire state, VT—Vermont state. References: Chung et al. [50], Wang et al. [43], Wu et al. (a–b) [52,53], Huang et al. [70], Huang et al. [60], Lin et al. [62], Yang et al. [69], Huang et al. [59], Yang et al. [71], Hsueh et al. [72], Hsueh et al. [73], Hsueh et al. [74], Mendez et al. [45], Nuvolone et al. [66], Baris et al. [57], Koutros et al. [61], Mostafa et al. [56], Mostafa et al. [68], D'Ippoliti et al. [64], Krajewski et al. [49], Chen et al. [44], Roh et al. [46], Smith et al. [47], Ferreccio et al. (a–b) [51,67], Lopez et al. [48], Chang et al. [58], Yang et al. [63], Tsai et al. [65], Saint-Jacques et al. [42].

Three of the six ecological studies accounted for tobacco smoking, either directly adjusting for smoking [45,49] or controlling for a proxy variable for tobacco smoking, such as social and material deprivation indices [42]. Nineteen of 23 case–control studies adjusted for tobacco smoking [44,50,69,72], two of which also controlled for second-hand smoking exposure [51] or education [52]. Five cohort studies accounted for tobacco smoking [63–66,75], one of which controlled for socioeconomic status as a surrogate for smoking [66].

Information about missing data and methods for handling missing data were rarely described in the included studies. Sixteen of the 34 studies did not provide any information regarding missing data [43,45,46,48,50,53,58–60,62,68,70–74], whereas nine excluded >10% of the data due to missingness without attempting to handle the missing data [42,44,51,55,63–65,67,75]. The studies also varied in terms of measuring outcomes. Although all the studies used robust methods to identify cases (incidence or mortality), including retrieving data from cancer registries, vital statistics registries, medical records or histopathological diagnoses records, over 60% of the studies (21 of 34) did not report a standardized classification such as international classification of diseases (ICD-9, ICD-10 or ICD-O) to report cases.

3.3. Arsenic Exposure and Bladder Cancer

3.3.1. Ecological Studies

Three of the six ecological studies reported on bladder cancer incidence, two of which observed a significant increase in risk at lower concentrations of arsenic (Table 1). Saint-Jacques et al. [42] and Krajewski et al. [49] reported an increased risk at As concentrations below the current WHO MAC (10 ug/L). Mendez et al. [45] found an increased risk per unit increase in the logged As concentration.

The ecological studies reporting on bladder cancer mortality were all conducted in the arsenic-endemic Region II area of Chile (Table 1). Of these, Roh et al. [46] found that an increased bladder cancer mortality was associated with an early age at first exposure to arsenic in drinking water, with the highest risk being found in exposures around birth (SMR = 16.0, 95% CI: 10.3–23.8). In a separate study, Smith et al. [47] confirmed that an increased mortality risk from bladder cancer persisted in both males and females even up to 40 years after As exposure reduction. Lopez et al. [48] reported increased mortality rates in the arsenic-endemic area than in the rest of Chile (mortality rate ratio = 5.5, 95% CI: 5.2–5.9).

3.3.2. Case–Control Studies

All 14 case–control studies reporting on the relationship between As exposure and bladder cancer focused on incidence (Table 2). Eight were from Taiwan and mostly used urinary As concentrations as the measure of exposure. A higher concentration of urinary As was consistently associated with a higher risk of bladder cancer incidence in Taiwan [50,52,53,59,60,62]. Wu et al. [52] reported increased odds of developing bladder cancer at urinary As concentrations $\geq$ 20.4 μg/g creatinine (OR = 4.68, 95% CI: 3.06–7.14), with the highest risk being found in those who smoked and were exposed to second-hand smoking at urinary As concentration $\geq$ 15.4 μg/g creatinine (OR = 10.8, 95% CI: 5.16–22.69). One study from Taiwan reporting on drinking water As concentrations observed a significant increase in bladder cancer risk (OR = 2.4, 95% CI: 1.6–3.4) at high As levels (midpoint levels, 745 μg/L vs. 175 μg/L); the effect increased with smoking (OR = 5.7, 95% CI: 3.1–10.3) [43].

In the case–control studies from the USA, Baris et al. [57] and Koutros et al. [61] found no evidence of increased bladder cancer risk at low levels of As in drinking water. However, when the average As exposure was lagged by 40 years, a moderate association with bladder cancer incidence was found in the 'highest' As level (>8.7 μg/L) considered (OR = 1.49, 95% CI: 0.85–2.61). Both current and former smokers had a similar increased risk compared to non-smokers exposed to the same higher level of cumulative As intake (OR = 1.6, 95% CI: 0.9–3.0). Mostafa et al. (2015) found no consistent dose–response association for transitional cell carcinoma of the bladder with increasing As concentrations [56].

The remaining case–control studies reporting on bladder cancer came from the well-known As-endemic areas in Regions I and II in northern Chile. Ferreccio et al. 2013(a) found an increased odds of bladder cancer incidence with increasing As concentrations in drinking water (OR = 4.44, 95% CI: 2.75–7.15) and a much higher OR in smokers for the highest level of As (>260 μg/L) in drinking water (OR = 15.30, 95% CI: 6.75–34.67) [51]. Melak et al. [54] also found a similar positive association when considering the percentage of monomethylarsonic acid present in urine. Similarly, Steinmaus et al. [55] observed increasing odds of bladder cancer incidence from exposure to high levels of As in drinking water in relation to age at first exposure, with the highest ORs being found in those exposed in utero or as children (OR = 8.11, 95% CI: 4.31–15.25).

3.3.3. Cohort Studies

Four cohort studies reported on the relationship between As exposure and bladder cancer incidence or mortality (Table 3). Both Yang et al. [63] and Tsai et al. [65] measured bladder cancer incidence in an As-exposed cohort from 18 villages in northeast Taiwan. Yang et al. [63] consistently observed an increased risk of developing bladder cancer at

As levels ≥ 100 µg/L in well water; the observed risk in the whole cohort was 8.71 (95% CI: 2.49–30.48), and, separately, in non-smokers it was 4.64 (95% CI: 0.89–24.2) and in smokers it was 16.5 (95% CI: 2.12–128.6). Similarly, Tsai et al. [65] also reported increased risk of bladder cancer incidence with higher levels of cumulative exposure to As in well water (HR = 11.38, 95% CI: 1.48–87.74) and urinary As concentrations (HR = 2.78, 95% CI: 0.75–10.39).

Two separate studies from Italy, D'Ippoliti et al. [64] and Nuvolone et al. [66], did not find any excess risk of mortality from bladder cancer with increased cumulative As exposure or As in drinking water, respectively. However, the analyses in both studies were limited by an incomplete adjustment for important individual risk factors such as smoking.

3.4. Arsenic Exposure and Kidney Cancer

3.4.1. Ecological Studies

Four ecological studies reported on kidney cancer, with half of these reporting on incidence (Table 4). Saint-Jacques et al. [42] observed increased kidney cancer incidence in Nova Scotia, Canada, at As levels ≥ 5 µg/L in drinking water for males and both sexes combined. Similarly, Krajewski et al. [49] observed a strong association between the incidence of kidney cancer with increasing quartiles of cumulative As exposure in the USA.

The two ecological studies on kidney cancer mortality were from the arsenic-endemic Region II area of Chile. Unlike for bladder cancer in the same study, Roh et al. [46] did not find a significant association between kidney cancer mortality and age at first exposure to high levels of As in drinking water. Instead, those exposed very early in life (at birth) had the lowest risk for kidney cancer (SMR = 1.3, 95% CI: 0.6–2.5). However, Smith et al. [47] found an elevated risk of mortality from kidney cancer that persisted in both males and females even up to 40 years after As exposure reduction.

3.4.2. Case–Control Studies

All nine case–control studies reporting on the relationship between As exposure and kidney cancer focused on incidence, and these were mostly from Taiwan (n = 7) (Table 5). Six studies [69–74] used urinary As concentrations as the metric of exposure and observed a consistent dose–response relationship between the incidence of kidney cancer and the concentration of urinary As. Similarly, Chen et al. [44] found a positive relationship between the incidence of kidney cancer and an increasing arseniasis grade, reporting rates of 3.92, 4.71, 5.31 and 8.35 per 100,000 person-years for arseniasis grades 0, 1, 2 and 3, respectively.

Mostafa et al. [68] found a consistent dose–response association between increasing concentrations of As in drinking water and the incidence of kidney cancer in Bangladesh (OR = 1.37, 95% CI: 0.92–2.06; OR = 2.05, 95% CI: 1.27–3.32; OR = 2.28, 95% CI: 1.42–3.64; OR = 3.95, 95% CI: 2.42–6.44 and OR = 6.0, 95% CI: 3.24–11.12 for As levels 50–100 µg/L, 100–200 µg/L, 200–300 µg/L and ≥300 µg/L, respectively). In contrast, Ferreccio et al. [67] did not find an association between increasing cumulative As exposure and the incidence of kidney cancers; however, when stratifying by kidney cancer subtypes, a significant dose–response relationship was observed between cancer of the renal pelvis and ureter and cumulative As exposure (OR = 5.49, 95% CI: 2.02–14.9 and OR = 10.35, 95% CI: 2.57–41.64 for 10–25 mg and >25 mg, respectively).

3.4.3. Cohort Studies

Three cohort studies reported on the relationship between As exposure and kidney cancer incidence or mortality (Table 6). Tsai et al. [65] explored kidney cancer incidence in an As-exposed cohort from 18 villages in northeast Taiwan and found an increased risk at higher levels of As in well drinking water (HR = 1.66, 95% CI: 0.53–5.15) and cumulative exposure to As in well water (HR = 2.37, 95% CI: 0.72–7.82). D'Ippoliti et al. [64] reported a similar magnitude of effect for kidney cancer mortality in both males (HR = 1.93, 95% CI: 0.63–5.96) and females (HR = 3.03, 95% CI: 0.37–25.22) using a cumulative As exposure metric. However, using urinary As concentrations as the metric of exposure, García-Esquinas et al. [75] did

not find any excess mortality from kidney cancer; rather, the hazard ratios decreased with increasing urinary As levels (HR = 0.44, 95% CI: 0.14–1.40).

3.5. Meta-Analyses

Twenty-two studies were considered in the meta-analyses (16 from the previous review). Among these, nine studies reported on bladder cancer incidence, 11 on bladder cancer mortality and three on kidney cancer incidence. All studies used As in drinking water as the metric of exposure. Similar to the previous review, we found that exposure to increasing levels of As in drinking water was associated with an increased risk of bladder cancer incidence and bladder cancer mortality (Figures 3–5). For bladder cancer, the posterior mean relative risks estimated at 10, 50 and 150 ug/L were 1.25 (95% CrI: 0.92–1.73), 2.11 (95% CrI: 1.18–4.22) and 3.01, (95% CrI: 1.31–8.17), respectively (Table 7). Exceedance probabilities for the estimated risks to be above 1 were consistently above 90%, suggesting a significant excess risk from exposure to arsenic in drinking water (Table 7; Figure 5A). The corresponding effect sizes for bladder cancer mortality were 1.36 (95% CrI: 0.35–6.39), 2.92 (95% CrI: 1.24–7.82) and 4.88 (95% CrI: 2.83–9.03). The probability for the risk of dying began to increase at arsenic exposure levels between 5 and 10 ug/L and became significantly higher thereafter (Figure 5B). For kidney cancer, the posterior mean relative risks estimated at 10, 50 and 150 ug/L were 1.37 (95% CrI: 1.07–1.77), 1.95 (95% CrI: 1.44–2.65) and 2.47 (95% CrI: 1.74–3.52), respectively. There was a 91% probability for the risk to exceed 1 at levels of arsenic exposure as low as 5 ug/L (Figure 5C). Overall, exceedance probabilities above 80%, which are generally considered to be consistent with a significant excess risk within a Bayesian framework [76,77], were observed at arsenic levels of 4 ug/L, 8 ug/L and 13 ug/L for kidney and bladder cancer incidence and bladder cancer mortality, respectively (Figure 5).

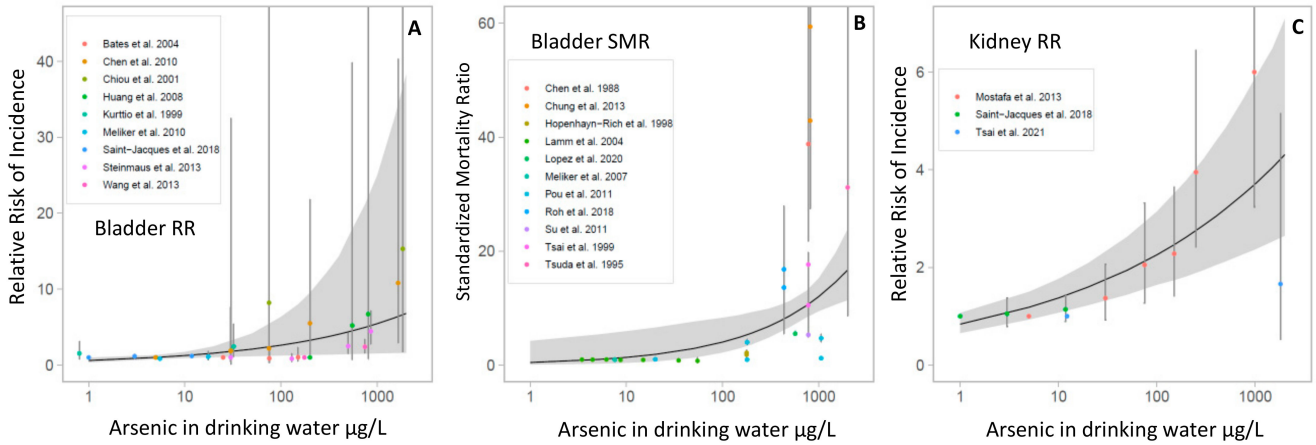

Figure 3. Risk estimates for varying levels of arsenic in drinking water in relation to: (**A**) bladder cancer incidence relative risk (RR); (**B**) standardized bladder cancer mortality ratio (SMR); and (**C**) kidney cancer incidence relative risk (RR). Solid lines show the predicted risks from the random-effects meta-analysis model and their corresponding 95% credible intervals. References: Bates et al. [78], Chen et al. [14], Chiou et al. [30], Huang et al. [79], Kurttio et al. [80], Meliker et al. [81], Saint-Jacques et al. [42], Steinmaus et al. [82], Wang et al. [43], Chen et al. [28], Chung et al. [83], Hopenhayn-Rich et al. [84], Lamm et al. [85], Lopez et al. [48], Meliker et al. [86], Pou et al. [87], Roh et al. [46], Su et al. [88], Tsai et al. [26], Tsuda et al. [89], Mostafa et al. [68], Tsai et al. [65].

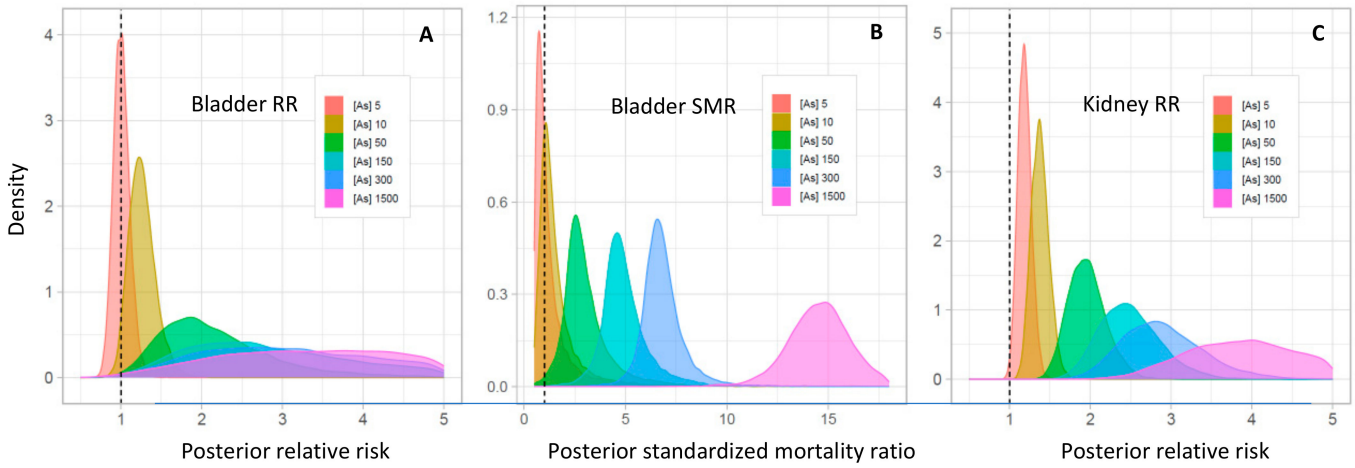

Figure 4. Posterior predictions for: (**A**) bladder cancer incident relative risk (RR); (**B**) standardized bladder cancer mortality ratio (SMR); and (**C**) kidney cancer incident relative risk (RR) estimated at varying levels of arsenic concentrations (5, 10, 50, 150, 300 and 1500 µg/L) in drinking water.

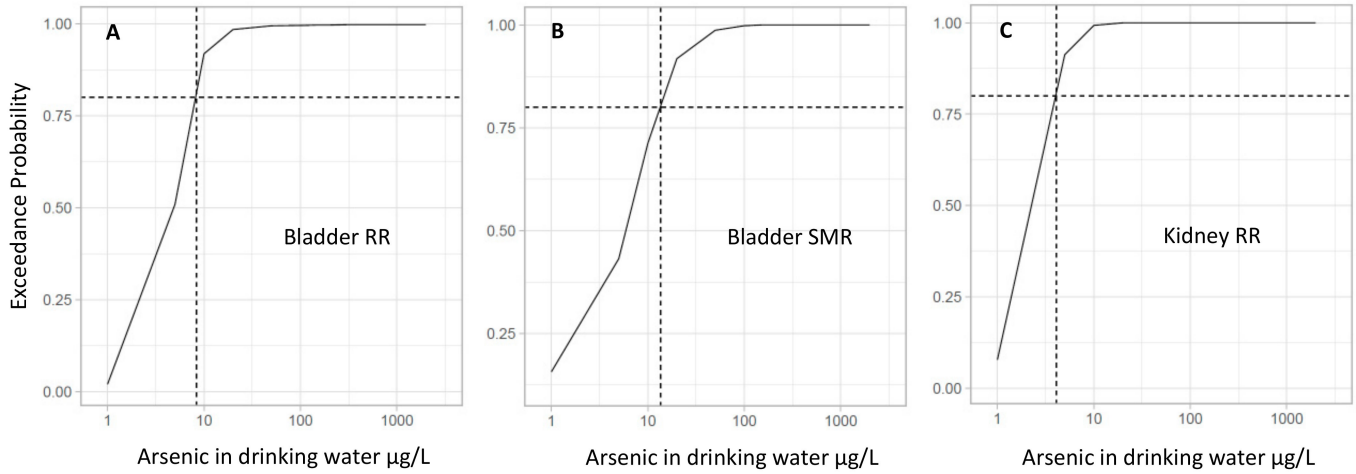

Figure 5. Exceedance probability profile for estimated risk as a function of varying levels of arsenic in drinking water. Results are shown for: (**A**) bladder cancer incident relative risk (RR); (**B**) standardized bladder cancer mortality ratio (SMR); and (**C**) kidney cancer incident relative risk (RR).

Table 7. Modeled mean risk, credible intervals and associated exceedance probabilities for bladder and kidney cancer outcomes estimated at varying levels of arsenic in drinking water.

Arsenic Concentration (µg/L)	Bladder Cancer Mean RR (95% CrI)	Exceedance Probability (RR > 1) *	Bladder Cancer Mean SMR (95% CrI)	Exceedance Probability (SMR > 1) *	Kidney Cancer Mean RR (95% CrI)	Exceedance Probability (RR > 1) *
5	1.00 (0.76–1.32)	0.50	0.98 (0.22–5.92)	0.44	1.18 (0.94–1.51)	0.91
10	1.25 (0.92–1.73)	0.92	1.36 (0.35–6.39)	0.72	1.37 (1.07–1.77)	1.00
20	1.57 (1.04–2.46)	0.99	1.89 (0.60–6.83)	0.92	1.60 (1.23–2.09)	1.00
50	2.11 (1.18–4.22)	0.99	2.92 (1.24–7.82)	0.99	1.95 (1.44–2.65)	1.00
100	2.64 (1.26–6.37)	1.00	4.04 (2.11–8.49)	1.00	2.26 (1.61–3.15)	1.00
150	3.01 (1.31–8.17)	1.00	4.88 (2.83–9.03)	1.00	2.47 (1.74–3.52)	1.00

Note(s): SMR:standardized mortality ratio, CrI:credible interval, RR:relative risk, µg/L:micrograms per liter.
* Exceedance probabilities > 0.8 are generally consistent with significant excess risk [76,77].

4. Discussion

4.1. Summary of Findings

This work updated evidence from our previous systematic review on the relationship between long-term exposure to As in drinking water and urinary bladder and kidney cancers. An additional 34 studies published between January 2013 and February 2023 were found. Among these, 16 studies from the USA, Chile and Taiwan reported statistically significant associations between As exposure and the risk of developing bladder cancer or dying from the disease (seven studies assessed As concentrations in drinking water, seven studies measured As levels in urine and two studies evaluated cumulative As exposure). Eleven studies, conducted in the USA, Bangladesh, Chile and Taiwan, reported a significant relationship between As exposure and the risk of developing kidney cancer or dying from the disease (four studies measured As levels in drinking water, six measured As levels in urine and one measured cumulative As exposure).

Although controlling for confounding is challenging in ecological studies, half of the included studies accounted for tobacco smoking, either directly or indirectly (e.g., using a proxy variable) [42,45,49]. All but four of the case–control studies and all cohort studies accounted for tobacco smoking behavior. Smoking is an independent risk factor for urinary tract cancers, and not adjusting for smoking may overestimate the magnitude of the association between As exposure and urinary tract cancers [90]. Indeed, studies that did not account for smoking [44,50,69] had a stronger dose–response relationship than studies that controlled for smoking. In addition, over 70% of the studies did not report information concerning missing data or excluded substantial proportions of the study participants due to missingness. Without properly testing the '*missing completely at random*' assumption, results based on a complete-case analysis should be interpreted with caution as these effect size estimates might be biased.

As exposure levels in most of the ecological studies and some of the case–control studies were determined based on geographic or group-level measurements, and their results might have been prone to nondifferential misclassification bias. Risk estimates from the studies evaluating As exposure in well or tap drinking water were measured within a limited range of As levels. Interestingly, these estimates varied considerably across the studies, within geographic areas or even in regions with the same As concentrations. These differences could be explained by variability in exposure (e.g., duration of exposure and As species), exposure measurement methods (e.g., historical data, longitudinal assessment, and measurement technique), individual factors (e.g., genetic susceptibility, lifestyle, and behavioral factors) and study methodological approaches (e.g., study design, participant sampling and data analysis).

4.2. Quantitative Synthesis of the Association between As Exposure and Bladder and Kidney Cancers

The association between As exposure in drinking water and bladder and kidney cancer outcomes were quantitatively assessed over a broad and continuous range of As concentrations. After controlling for study differences, we observed positive non-linear relationships of increased risks of developing bladder or kidney cancers or dying from bladder cancer with increasing As exposure levels; similar associations were reported in our previous review [33]. The results from the Bayesian random-effects meta-analysis models suggested that exposure to 10 μg/L of As in drinking water was associated on average with a 25% excess bladder cancer risk (posterior mean RR = 1.25, 95% CrI: 0.92–1.73). Exposure to As levels of 50 and 150 μg/L resulted on average in a doubling (posterior mean RR = 2.11; 95% CrI: 1.18–4.22) and tripling of the risk (3.01, 95% CrI: 1.31–8.17), respectively. The risk estimates for bladder cancer obtained from bootstrap resamplings in our previous review were of a similar magnitude (predicted RR = 1.4, 95% CI: 0.35–4.0; 2.3, 95% CI: 0.59–6.4; and 3.1, 95% CI: 0.80–8.9) for As levels at 10, 50 and 150 μg/L, respectively) [33]. Additionally, exposure to 10 μg/L of As in drinking water was associated on average with a 36% excess bladder cancer mortality (posterior mean RR = 1.36, 95% CrI: 0.35–6.39) and with a tripling (posterior mean RR = 2.92, 95% CrI: 1.24–7.82) and quintupling (posterior mean RR = 4.88,

95% CrI: 2.83–9.03) of risk at As levels of 50 and 150 μg/L, respectively. The mortality estimates from bootstrap resamplings reported in our previous review were moderate (predicted SMR = 1.0, 95% CI: 0.15–38; 1.7, 95% CI:0.49–40; and 2.2, 95% CI:0.54–41) for As levels at 10, 50 and 150 μg/L, respectively) in comparison to the current findings. The updated findings suggest a stronger relationship between lower concentrations of As in drinking water and bladder cancer mortality. Our reviews, which now summarize 40 years of epidemiological data, support evidence of an increased cancer risk around the current WHO MAC guideline limit (10 μg/L).

The findings reported here were in contrast with those from a recent systematic review, which reported no association between exposure to low-level As in drinking water (<150 μg/L) and bladder cancer risk [91]. However, it is important to note that the inconsistent findings were from a review of studies using different inclusion and exclusion criteria (e.g., excluding ecological studies and studies reporting at least two exposure categories), which might have resulted in reduced statistical power. In addition, the other review combined various As exposure measurements (e.g., cumulated, average lifetime exposure and yearly mean exposure) and diverse exposure categories, which could potentially result in the misclassification of exposure and likely trend the estimated risk towards the null. Another systematic review evaluated the relationship between As exposure in drinking water and the risk of bladder cancer by applying a meta-regression analysis [15]. Similar to our findings, they reported a non-linear dose–response relationship in support of an increased risk of bladder cancer with increasing As exposure levels. However, in their subgroup analyses, the authors noted that although the dose–response relationship was sustained at As levels < 100 μg/L, the association was not statistically significant.

In this study, we also modeled the risk of developing kidney cancer at various As levels in drinking water. The modeled estimates suggested that exposure to 10 μg/L of As in drinking water was associated on average with a 37% excess kidney cancer risk (posterior mean RR = 1.37, 95% CrI: 1.07–1.77), with the risk doubling (posterior mean RR = 1.95, 95% CrI: 1.44–2.65) and almost tripling (posterior mean RR = 2.47, 95% CrI: 1.74–3.52) at As levels of 50 and 150 μg/L, respectively. These results were aligned with our previous review findings, where we reported a dose–response relationship between increased kidney cancer mortality and increasing As concentrations in drinking water [33]. The results were also consistent with those of a recent systematic review that reported a significant increase in kidney cancer incidence and mortality in people exposed to drinking water contaminated with an As level > 100 μg/L [92]. Nonetheless, although we found an association at 10 μg/L of As in drinking water, studies reporting on lower concentrations of As exposure are lacking. Additional studies are required to confirm the excess risk of developing and dying from kidney cancer observed in our review and in the previous review.

Findings from this updated review support our previously published results [33], indicating that individuals exposed to As concentrations of 50 and 150 μg/L have two and three times the risk of developing bladder cancer, respectively. The updated evidence suggests that people exposed to As in drinking water at a concentration of 10 μg/L have a 25% increased bladder cancer risk; this is slightly lower than what has been previously reported. Also, in the current meta-analysis, we found a stronger association between As concentrations in drinking water and bladder cancer mortality compared to the previous review. For As concentrations of 50 and 150 μg/L, the risk increased three-fold and five-fold, respectively. Interestingly, our analysis also revealed that exposure to an As concentration of 10 μg/L in drinking water resulted in a 36% excess bladder cancer mortality, a finding that was not observed in our previous review. Kidney cancer incidence risk was not assessed in the previous review as none of the identified studies met the inclusion criteria for the meta-analysis. However, this updated review suggests that people exposed to 10 μg/L of As in drinking water have, on average, a 37% excess risk of kidney cancer. Notably, the risk substantially increased, with it doubling and nearly tripling at As levels 50 and 150 μg/L, respectively.

This systematic review and meta-analysis provides evidence of an excess risk of bladder and kidney cancer at lower concentrations of As in drinking water, particularly

around the WHO provisional MAC guideline limit of 10 μg/L. Recent modelling of As concentrations in groundwater suggests that 94 to 220 million people might be exposed to elevated levels of As (>10 μg/L) in drinking water [93]. Given that this large number of people may be exposed to these lower levels worldwide [94], the public health consequences of arsenic in drinking water are substantial.

Arsenic mitigation in drinking water is an important public health priority. Various mitigation measures, such as accessing alternative water sources and utilizing centralized and non-centralized drinking water treatment technologies, have proven to be effective in reducing exposure to arsenic [95,96]. The successful implementation of mitigation strategies often necessitates substantial behavioral change and community acceptance alongside the enforcement of public policies. Although there is no evidence indicating that lower socioeconomic status groups disproportionately reside in arsenic-affected areas, disparities in exposure arise from differences in rates of protective behaviors and psychological factors favoring such behaviors [97–99]. Measures such as the universal screening of private well water quality and state laws mandating arsenic testing during real estate transactions can partially address the socioeconomic disparity in water testing [100,101].

Moreover, the implementation of effective mitigation strategies poses financial challenges as it requires investments in the installation, operation and maintenance of treatment systems. This can be particularly daunting for communities, regions or countries with limited resources [102]. Therefore, it is crucial to invest in the research and development of cost-effective technologies, capacity building, policy reforms and community engagement to achieve sustainable and long-term solutions for reducing arsenic concentrations in drinking water.

4.3. Strengths and Weakness of the Review

This review has several strengths. First, it drew from multiple bibliographic databases to find the related published and grey literature on the topic. The search strategy followed established robust criteria, applying the PRESS Peer Review of Electronic Search Strategies Guideline and the PRISMA-S checklist [103,104]. A broad sensitive search strategy was adopted by not restricting the review to certain study designs; rather, we included all epidemiological designs—ecological, case–control and cohort studies—allowing all relevant findings to be qualitatively and quantitatively synthesized. Second, similar to our previous review, this update quantified the risks of developing or dying from urinary tract cancers over a wide range of As exposures, including lower levels (<150 μg/L), for which there is a clear knowledge gap. Third, the meta-analysis was performed using a Bayesian framework, which is known to be a robust analytical approach that accounts for the uncertainty around the heterogeneity of variance [105,106]. Fourth, conducting the meta-analysis on studies included in the current (6 studies) and previous (16 studies) reviews allowed for an inference over a broader and more continuous range of As concentrations and an increased statistical power. Finally, the independent analyses of incidence and mortality outcomes likely minimized biases related to exposure misclassification and ascertainment. Mortality data are prone to misclassification (e.g., inconsistent methods used to determine cause of the death) relative to incidence data.

This review has some limitations. First, publication bias may be present in the review, since we only included studies published in peer-reviewed scientific journals, which may favorably publish studies with significant results. However, such a bias should be minimal, as almost a third of the included studies reported non-significant findings, and more than half of the excluded studies found statistically significant associations. Second, we piloted the ROBINS-E tool [107] that was specifically developed to assess the risk of bias in non-randomized studies. However, the tool did not account for specific methodological and reporting characteristics of As-related exposure studies (e.g., various types of exposure matrix, challenges with measuring and defining or categorizing As exposure). As such, we evaluated studies based on simple core methodological aspects (e.g., whether a study adjusted for possible confounding factors, whether As exposure was

measured at the individual or group level, whether missing data were present and how these were handled). Third, the results from the meta-analysis performed on kidney cancer risk should be interpreted with caution given that the estimates were modeled based only on three studies [106]. Lastly, due to methodological heterogeneity (e.g., study designs and analytical approaches) among the studies with missing data and among the studies without missing data (or with near-complete data), we were not able to distinguish the direction and magnitude of bias related to missing data.

5. Conclusions

The present review provides consistent evidence of an association between moderate and higher As concentrations (≥50 µg/L) in drinking water with bladder and kidney cancer incidence and bladder cancer mortality. In addition, it shows an increased bladder and kidney cancer risk at lower levels of As around the current WHO provisional MAC of 10 µg/L. People exposed to 10 µg/L of As in drinking water may be at a 25% or 36% increased risk of developing or dying from bladder cancer, respectively, and a 37% increased kidney cancer risk. Moreover, the pooled analysis showed that people drinking water contaminated with As at concentrations as low as 5 µg/L could be at an excess risk of developing kidney cancer. However, as these results were derived from a small number of studies, it would be advisable to confirm the pattern once additional studies reporting on kidney cancer incidence become available. Additional research is necessary to further assess the relationship between urinary tract cancers and lower concentrations of As in drinking water, including exposure close to, or below, the current regulatory limits. In addition, given the challenges associated with the current As detection methods, future research should focus on development of cost-effective and reliable solutions that are applicable in real-world setting. This is particularly important given the fact that several millions of people worldwide are regularly drinking water containing naturally occurring As around the current WHO 10 µg/L MAC. The public health consequences of exposure to As in drinking water are both substantial and widespread. We suggest that the current policies and recommendations regulating As concentrations in drinking water should be revised, particularly through lowering the current WHO provisional MAC guideline limit.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/w15122185/s1, Figure S1: Search keywords; Table S1: Search strategy through Ovid MEDLINE ®and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions®, January 2013 to February 8, 2023; Table S2: Search strategy through Ovid Embase ®, January 2013 to February 8, 2023; Table S3: Search strategy through the Web of Science Core Collection, January 2013 to February 2023; Table S4: Search strategy through the Scopus database, January 2013 to February 2023; Table S5: Search strategy through the Google Scholar database, January 2013 to February 2023; Table S6: Search strategies through grey literature bibliographic databases, January 2013 to February 2023; Figure S2: Posterior distribution of slopes (log(As)) and intercepts, assuming random slopes and intercepts, for bladder cancer incidence; Figure S3: Posterior distribution of slopes (log(As)) and intercepts, assuming random slopes and intercepts, for standardized bladder cancer mortality; Figure S4: Posterior distribution of slopes (log(As)) and intercepts, assuming random intercepts only, for kidney cancer incidence.

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References

1. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Some Drinking-Water Disinfectants and Contaminants, Including Arsenic*; IARC: Lyon, France, 2004; Volume 844.
2. Singh, N.; Kumar, D.; Sahu, A.P. Arsenic in the environment: Effects on human health and possible prevention. *J. Environ. Biol.* **2007**, *28*.
3. Cantor, K.P.; Lubin, J.H. Arsenic, internal cancers, and issues in inference from studies of low-level exposures in human populations. *Toxicol. Appl. Pharmacol.* **2007**, *222*, 252–257. [CrossRef] [PubMed]
4. Mondal, D.; Banerjee, M.; Kundu, M.; Banerjee, N.; Bhattacharya, U.; Giri, A.; Ganguli, B.; Roy, S.S.; Polya, D.A. Comparison of drinking water, raw rice and cooking of rice as arsenic exposure routes in three contrasting areas of West Bengal, India. *Environ. Geochem. Heal.* **2010**, *32*, 463–477. [CrossRef] [PubMed]
5. Enterline, P.E.; Day, R.; Marsh, G.M. Cancers related to exposure to arsenic at a copper smelter. *Occup. Environ. Med.* **1995**, *52*, 28–32. [CrossRef]
6. Liu, J.; Zheng, B.; Aposhian, H.; Zhou, Y.; Chen, M.; Zhang, A.; Waalkes, M.P. Chronic Arsenic Poisoning From Burning High-Arsenic-Containing Coal In Guizhou, China. *J. Peripher. Nerv. Syst.* **2002**, *7*, 208. [CrossRef]
7. Silverman, D.T.; Devesa, S.S.; Moore, L.E.; Rothman, N. Bladder Cancer. In *Cancer Epidemiology and Prevention*; Schottenfeld, D., Fraumeni, J.F., Eds.; Oxford University Press: Oxford, UK, 2006.
8. WHO. Arsenic—World Health Organizaiton. Fact Sheets. 2018. Available online: https://www.who.int/news-room/fact-sheets/detail/arsenic (accessed on 17 April 2023).
9. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Arsenic, metals, fibres, and dusts. *IARC Monogr. Eval. Carcinog. Risks Hum.* **2012**, *100*, 11.
10. Palma-Lara, I.; Martínez-Castillo, M.; Quintana-Pérez, J.; Arellano-Mendoza, M.; Tamay-Cach, F.; Valenzuela-Limón, O.; García-Montalvo, E.; Hernández-Zavala, A. Arsenic exposure: A public health problem leading to several cancers. *Regul. Toxicol. Pharmacol.* **2020**, *110*, 104539. [CrossRef]
11. Lamm, S.H.; Boroje, I.J.; Ferdosi, H.; Ahn, J. A review of low-dose arsenic risks and human cancers. *Toxicology* **2021**, *456*, 152768. [CrossRef] [PubMed]
12. Buchet, J.P.; Lauwerys, R.; Roels, H. Urinary excretion of inorganic arsenic and its metabolites after repeated ingestion of sodium metaarsenite by volunteers. *Int. Arch. Occup. Environ. Heal.* **1981**, *48*, 111–118. [CrossRef]
13. Chu, H.-A.; Crawford-Brown, D.J. Inorganic Arsenic in Drinking Water and Bladder Cancer: A Meta-Analysis for Dose-Response Assessment. *Int. J. Environ. Res. Public Heal.* **2006**, *3*, 316–322. [CrossRef]
14. Chen, C.-L.; Chiou, H.-Y.; Hsu, L.-I.; Hsueh, Y.-M.; Wu, M.-M.; Wang, Y.-H.; Chen, C.-J. Arsenic in Drinking Water and Risk of Urinary Tract Cancer: A Follow-up Study from Northeastern Taiwan. *Cancer Epidemiology Biomarkers Prev.* **2010**, *19*, 101–110. [CrossRef] [PubMed]
15. Lynch, H.N.; Zu, K.; Kennedy, E.M.; Lam, T.; Liu, X.; Pizzurro, D.M.; Loftus, C.T.; Rhomberg, L.R. Quantitative assessment of lung and bladder cancer risk and oral exposure to inorganic arsenic: Meta-regression analyses of epidemiological data. *Environ. Int.* **2017**, *106*, 178–206. [CrossRef]
16. Christoforidou, E.P.; Riza, E.; Kales, S.N.; Hadjistavrou, K.; Stoltidi, M.; Kastania, A.N.; Linos, A. Bladder cancer and arsenic through drinking water: A systematic review of epidemiologic evidence. *J. Environ. Sci. Heal. Part A* **2013**, *48*, 1764–1775. [CrossRef] [PubMed]
17. Soria, F.; Marra, G.; Čapoun, O.; Soukup, V.; Gontero, P. Prevention of bladder cancer incidence and recurrence: Tobacco use. *Curr. Opin. Urol.* **2018**, *28*, 80–87. [CrossRef] [PubMed]
18. Mori, K.; Mostafaei, H.; Abufaraj, M.; Yang, L.; Egawa, S.; Shariat, S.F. Smoking and bladder cancer: Review of the recent literature. *Curr. Opin. Urol.* **2020**, *30*, 720–725. [CrossRef] [PubMed]
19. Zhou, Q.; Xi, S. A review on arsenic carcinogenesis: Epidemiology, metabolism, genotoxicity and epigenetic changes. *Regul. Toxicol. Pharmacol.* **2018**, *99*, 78–88. [CrossRef] [PubMed]
20. Saintilnord, W.N.; Fondufe-Mittendorf, Y. Arsenic-induced epigenetic changes in cancer development. *Semin. Cancer Biol.* **2021**, *76*, 195–205. [CrossRef] [PubMed]
21. Islam, R.; Zhao, L.; Wang, Y.; Lu-Yao, G.; Liu, L.-Z. Epigenetic Dysregulations in Arsenic-Induced Carcinogenesis. *Cancers* **2022**, *14*, 4502. [CrossRef]
22. Shukla, V.; Chandrasekaran, B.; Tyagi, A.; Navin, A.K.; Saran, U.; Adam, R.M.; Damodaran, C. A Comprehensive Transcriptomic Analysis of Arsenic-Induced Bladder Carcinogenesis. *Cells* **2022**, *11*, 2435. [CrossRef]
23. Chen, C.J.; Chuang, Y.C.; Lin, T.M.; Wu, H.Y. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: High-arsenic artesian well water and cancers. *Cancer Res.* **1985**, *45*, 5895–5899.
24. Chen, C.-J.; Kuo, T.-L.; Wu, M.-M. Arsenic and cancers. *Lancet* **1988**, *331*, 414–415. [CrossRef]
25. Wu, M.-M.; Kuo, T.-L.; Hwang, Y.-H.; Chen, C.-J. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Am. J. Epidemiol.* **1989**, *130*, 1123–1132. [CrossRef]

26. Tsai, S.-M.; Wang, T.-N.; Ko, Y.-C. Mortality for Certain Diseases in Areas with High Levels of Arsenic in Drinking Water. *Arch. Environ. Heal. Int. J.* **1999**, *54*, 186–193. [CrossRef] [PubMed]
27. Chiang, H.S.; Guo, H.R.; Hong, C.L.; Lin, S.M.; Lee, E.F. The Incidence of Bladder Cancer in the Black Foot Disease Endemic Area in Taiwan. *BJU Int.* **1993**, *71*, 274–278. [CrossRef] [PubMed]
28. Chen, C.J.; Wu, M.M.; Lee, S.S.; Wang, J.D.; Cheng, S.H.; Wu, H.Y. Atherogenicity and carcinogenicity of high-arsenic artesian well water. Multiple risk factors and related malignant neoplasms of blackfoot disease. *Arter. Off. J. Am. Hear. Assoc. Inc.* **1988**, *8*, 452–460. [CrossRef] [PubMed]
29. Chiou, H.Y.; Hsueh, Y.M.; Liaw, K.F.; Horng, S.F.; Chiang, M.H.; Pu, Y.-S.; Lin, J.S.; Huang, C.H.; Chen, C.J. Incidence of internal cancers and ingested inorganic arsenic: A seven-year follow-up study in Taiwan. *Cancer Res* **1995**, *55*, 1296–3000.
30. Chiou, H.Y.; Chiou, S.-T.; Hsu, Y.-H.; Chou, Y.-L.; Tseng, C.-H.; Wei, M.-L.; Chen, C.-J. Incidence of Transitional Cell Carcinoma and Arsenic in Drinking Water: A Follow-up Study of 8,102 Residents in an Arseniasis-endemic Area in Northeastern Taiwan. *Am. J. Epidemiol.* **2001**, *153*, 411–418. [CrossRef] [PubMed]
31. Mink, P.J.; Alexander, D.D.; Barraj, L.M.; Kelsh, M.A.; Tsuji, J.S. Low-level arsenic exposure in drinking water and bladder cancer: A review and meta-analysis. *Regul. Toxicol. Pharmacol.* **2008**, *52*, 299–310. [CrossRef]
32. Tsuji, J.S.; Alexander, D.D.; Perez, V.; Mink, P.J. Arsenic exposure and bladder cancer: Quantitative assessment of studies in human populations to detect risks at low doses. *Toxicology* **2014**, *317*, 17–30. [CrossRef]
33. Saint-Jacques, N.; Parker, L.; Brown, P.; Dummer, T.J. Arsenic in drinking water and urinary tract cancers: A systematic review of 30 years of epidemiological evidence. *Environ. Heal.* **2014**, *13*, 44. [CrossRef]
34. Issanov, A.; Adewusi, B.; Dummer, T.J.; Saint-Jacques, N. Arsenic in Drinking Water and Urinary Tract Cancers: A Systematic Review Update. PROSPERO 2022 CRD42022381522. Available online: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022381522 (accessed on 17 April 2023).
35. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Int. J. Surg.* **2021**, *88*, 105906. [CrossRef] [PubMed]
36. The Cochrane Public Health Group. Data Extraction and Assessment Template. 2011. Available online: https://ph.cochrane.org/sites/ph.cochrane.org/files/public/uploads/CPHG%20Data%20extraction%20template_0.docx (accessed on 17 April 2023).
37. Sutton, A.J.; Abrams, K.R. Bayesian methods in meta-analysis and evidence synthesis. *Stat. Methods Med. Res.* **2001**, *10*, 277–303. [CrossRef] [PubMed]
38. Gelman, A.; O'Reilly for Higher, E. *Bayesian Data Analysis*, 3rd ed.; CRC Press: Boca Raton, FL, USA, 2014.
39. Bürkner, P.-C. brms: An R package for Bayesian multilevel models using Stan. *J. Stat. Softw.* **2017**, *80*, 1–28. [CrossRef]
40. Gelman, A.; Lee, D.; Guo, J. Stan: A probabilistic programming language for Bayesian inference and optimization. *J. Educ. Behav. Stat.* **2015**, *40*, 530–543. [CrossRef]
41. R Core Team. *R: A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2020; Available online: https://www.R-project.org/ (accessed on 17 April 2023).
42. Saint-Jacques, N.; Brown, P.; Nauta, L.; Boxall, J.; Parker, L.; Dummer, T.J. Estimating the risk of bladder and kidney cancer from exposure to low-levels of arsenic in drinking water, Nova Scotia, Canada. *Environ. Int.* **2018**, *110*, 95–104. [CrossRef]
43. Wang, Y.-H.; Yeh, S.-D.; Wu, M.-M.; Liu, C.-T.; Shen, C.-H.; Shen, K.-H.; Pu, Y.-S.; Hsu, L.-I.; Chiou, H.-Y.; Chen, C.-J. Comparing the joint effect of arsenic exposure, cigarette smoking and risk genotypes of vascular endothelial growth factor on upper urinary tract urothelial carcinoma and bladder cancer. *J. Hazard. Mater.* **2013**, *262*, 1139–1146. [CrossRef]
44. Chen, C.-H.; Grollman, A.P.; Huang, C.-Y.; Shun, C.-T.; Sidorenko, V.S.; Hashimoto, K.; Moriya, M.; Turesky, R.J.; Yun, B.H.; Tsai, K.; et al. Additive Effects of Arsenic and Aristolochic Acid in Chemical Carcinogenesis of Upper Urinary Tract Urothelium. *Cancer Epidemiology Biomarkers Prev.* **2021**, *30*, 317–325. [CrossRef]
45. Mendez, W.M.; Eftim, S.; Cohen, J.; Warren, I.; Cowden, J.; Lee, J.S.; Sams, R. Relationships between arsenic concentrations in drinking water and lung and bladder cancer incidence in U.S. counties. *J. Expo. Sci. Environ. Epidemiol.* **2016**, *27*, 235–243. [CrossRef] [PubMed]
46. Roh, T.; Steinmaus, C.; Marshall, G.; Ferreccio, C.; Liaw, J.; Smith, A.H. Age at Exposure to Arsenic in Water and Mortality 30–40 Years After Exposure Cessation. *Am. J. Epidemiol.* **2018**, *187*, 2297–2305. [CrossRef] [PubMed]
47. Smith, A.H.; Marshall, G.; Roh, T.; Ferreccio, C.; Liaw, J.; Steinmaus, C. Lung, Bladder, and Kidney Cancer Mortality 40 Years After Arsenic Exposure Reduction. *Gynecol. Oncol.* **2017**, *110*, 241–249. [CrossRef] [PubMed]
48. López, J.F.; Fernández, M.I.; Coz, L.F. Arsenic exposure is associated with significant upper tract urothelial carcinoma health care needs and elevated mortality rates. *Urol. Oncol. Semin. Orig. Investig.* **2020**, *38*, 638.e7–638.e13. [CrossRef] [PubMed]
49. Krajewski, A.K.; Jimenez, M.P.; Rappazzo, K.M.; Lobdell, D.T.; Jagai, J.S. Aggregated cumulative county arsenic in drinking water and associations with bladder, colorectal, and kidney cancers, accounting for population served. *J. Expo. Sci. Environ. Epidemiology* **2021**, *31*, 979–989. [CrossRef]
50. Chung, C.-J.; Huang, C.-Y.; Pu, Y.-S.; Shiue, H.-S.; Su, C.-T.; Hsueh, Y.-M. The effect of cigarette smoke and arsenic exposure on urothelial carcinoma risk is modified by glutathione S-transferase M1 gene null genotype. *Toxicol. Appl. Pharmacol.* **2013**, *266*, 254–259. [CrossRef]
51. Ferreccio, C.; Yuan, Y.; Calle, J.; Benítez, H.; Parra, R.L.; Acevedo, J.; Smith, A.H.; Liaw, J.; Steinmaus, C. Arsenic, Tobacco Smoke, and Occupation. *Epidemiology* **2013**, *24*, 898–905. [CrossRef]

52. Wu, C.-C.; Chen, M.-C.; Huang, Y.-K.; Huang, C.-Y.; Lai, L.-A.; Chung, C.-J.; Shiue, H.-S.; Pu, Y.-S.; Lin, Y.-C.; Han, B.-C.; et al. Environmental tobacco smoke and arsenic methylation capacity are associated with urothelial carcinoma. *J. Formos. Med Assoc.* **2013**, *112*, 554–560. [CrossRef] [PubMed]
53. Wu, C.-C.; Huang, Y.-K.; Chung, C.-J.; Huang, C.-Y.; Pu, Y.-S.; Shiue, H.-S.; Lai, L.-A.; Lin, Y.-C.; Su, C.-T.; Hsueh, Y.-M. Polymorphism of inflammatory genes and arsenic methylation capacity are associated with urothelial carcinoma. *Toxicol. Appl. Pharmacol.* **2013**, *272*, 30–36. [CrossRef]
54. Melak, D.; Ferreccio, C.; Kalman, D.; Parra, R.; Acevedo, J.; Pérez, L.; Cortés, S.; Smith, A.H.; Yuan, Y.; Liaw, J.; et al. Arsenic methylation and lung and bladder cancer in a case-control study in northern Chile. *Toxicol. Appl. Pharmacol.* **2013**, *274*, 225–231. [CrossRef] [PubMed]
55. Steinmaus, C.; Ferreccio, C.; Acevedo, J.; Yuan, Y.; Liaw, J.; Durán, V.; Cuevas, S.; García, J.; Meza, R.; Valdés, R.; et al. Increased Lung and Bladder Cancer Incidence in Adults after In Utero and Early-Life Arsenic Exposure. *Cancer Epidemiology Biomarkers Prev.* **2014**, *23*, 1529–1538. [CrossRef]
56. Mostafa, M.G.; Cherry, N. Arsenic in Drinking Water, Transition Cell Cancer and Chronic Cystitis in Rural Bangladesh. *Int. J. Environ. Res. Public Heal.* **2015**, *12*, 13739–13749. [CrossRef] [PubMed]
57. Baris, D.; Waddell, R.; Freeman, L.E.B.; Schwenn, M.; Colt, J.S.; Ayotte, J.D.; Ward, M.H.; Nuckols, J.; Schned, A.; Jackson, B.; et al. Elevated Bladder Cancer in Northern New England: The Role of Drinking Water and Arsenic. *J. Natl. Cancer Inst.* **2016**, *108*, djw099. [CrossRef]
58. Chang, C.-H.; Liu, C.-S.; Liu, H.-J.; Huang, C.-P.; Huang, C.-Y.; Hsu, H.-T.; Liou, S.-H.; Chung, C.-J. Association between levels of urinary heavy metals and increased risk of urothelial carcinoma. *Int. J. Urol.* **2016**, *23*, 233–239. [CrossRef]
59. Huang, C.-Y.; Pu, Y.-S.; Shiue, H.-S.; Chen, W.-J.; Lin, Y.-C.; Hsueh, Y.-M. Polymorphisms of human 8-oxoguanine DNA glycosylase 1 and 8-hydroxydeoxyguanosine increase susceptibility to arsenic methylation capacity-related urothelial carcinoma. *Arch. Toxicol.* **2015**, *90*, 1917–1927. [CrossRef] [PubMed]
60. Huang, C.-Y.; Lin, Y.-C.; Shiue, H.-S.; Chen, W.-J.; Su, C.-T.; Pu, Y.-S.; Ao, P.-L.; Hsueh, Y.-M. Comparison of arsenic methylation capacity and polymorphisms of arsenic methylation genes between bladder cancer and upper tract urothelial carcinoma. *Toxicol. Lett.* **2018**, *295*, 64–73. [CrossRef] [PubMed]
61. Koutros, S.; Baris, D.; Waddell, R.; Freeman, L.E.B.; Colt, J.S.; Schwenn, M.; Johnson, A.; Ward, M.H.; Hosain, G.M.M.; Moore, L.E.; et al. Potential effect modifiers of the arsenic-bladder cancer risk relationship. *Int. J. Cancer* **2018**, *143*, 2640–2646. [CrossRef] [PubMed]
62. Lin, Y.-C.; Chen, W.-J.; Huang, C.-Y.; Shiue, H.-S.; Su, C.-T.; Ao, P.-L.; Pu, Y.-S.; Hsueh, Y.-M. Polymorphisms of Arsenic (+3 Oxidation State) Methyltransferase and Arsenic Methylation Capacity Affect the Risk of Bladder Cancer. *Toxicol. Sci.* **2018**, *164*, 328–338. [CrossRef]
63. Yang, T.-Y.; Hsu, L.-I.; Chen, H.-C.; Chiou, H.-Y.; Hsueh, Y.-M.; Wu, M.-M.; Chen, C.-L.; Wang, Y.-H.; Liao, Y.-T.; Chen, C.-J. Lifetime risk of urothelial carcinoma and lung cancer in the arseniasis-endemic area of Northeastern Taiwan. *J. Asian Earth Sci.* **2013**, *77*, 332–337. [CrossRef]
64. D'ippoliti, D.; Santelli, E.; De Sario, M.; Scortichini, M.; Davoli, M.; Michelozzi, P. Arsenic in Drinking Water and Mortality for Cancer and Chronic Diseases in Central Italy, 1990-2010. *PLOS ONE* **2015**, *10*, e0138182. [CrossRef] [PubMed]
65. Tsai, T.-L.; Kuo, C.-C.; Hsu, L.-I.; Tsai, S.-F.; Chiou, H.-Y.; Chen, C.-J.; Hsu, K.-H.; Wang, S.-L. Association between arsenic exposure, DNA damage, and urological cancers incidence: A long-term follow-up study of residents in an arseniasis endemic area of northeastern Taiwan. *Chemosphere* **2020**, *266*, 129094. [CrossRef]
66. Nuvolone, D.; Stoppa, G.; Petri, D.; Voller, F. Long-term exposure to low-level arsenic in drinking water is associated with cause-specific mortality and hospitalization in the Mt. Amiata area (Tuscany, Italy). *BMC Public Heal.* **2023**, *23*, 71. [CrossRef]
67. Ferreccio, C.; Smith, A.H.; Durán, V.; Barlaro, T.; Benítez, H.; Valdés, R.; Aguirre, J.J.; Moore, L.E.; Acevedo, J.; Vásquez, M.I.; et al. Case-Control Study of Arsenic in Drinking Water and Kidney Cancer in Uniquely Exposed Northern Chile. *Am. J. Epidemiology* **2013**, *178*, 813–818. [CrossRef]
68. Mostafa, M.; Cherry, N. Arsenic in drinking water and renal cancers in rural Bangladesh. *Occup. Environ. Med.* **2013**, *70*, 768–773. [CrossRef]
69. Yang, S.-M.; Huang, C.-Y.; Shiue, H.-S.; Huang, S.-P.; Pu, Y.-S.; Chen, W.-J.; Lin, Y.-C.; Hsueh, Y.-M. Joint Effect of Urinary Total Arsenic Level and VEGF-A Genetic Polymorphisms on the Recurrence of Renal Cell Carcinoma. *PLOS ONE* **2015**, *10*, e0145410. [CrossRef] [PubMed]
70. Huang, C.-Y.; Huang, Y.-L.; Pu, Y.-S.; Shiue, H.-S.; Chen, W.-J.; Chen, S.-S.; Lin, Y.-C.; Su, C.-T.; Hsueh, Y.-M. The joint effects of arsenic and risk diplotypes of insulin-like growth factor binding protein-3 in renal cell carcinoma. *Chemosphere* **2016**, *154*, 90–98. [CrossRef] [PubMed]
71. Yang, S.-M.; Huang, C.-Y.; Shiue, H.-S.; Pu, Y.-S.; Hsieh, Y.-H.; Chen, W.-J.; Lin, Y.-C.; Hsueh, Y.-M. Combined effects of DNA methyltransferase 1 and 3A polymorphisms and urinary total arsenic levels on the risk for clear cell renal cell carcinoma. *Toxicol. Appl. Pharmacol.* **2016**, *305*, 103–110. [CrossRef]
72. Hsueh, Y.-M.; Lin, Y.-C.; Chen, W.-J.; Huang, C.-Y.; Shiue, H.-S.; Pu, Y.-S.; Chen, C.-H.; Su, C.-T. The polymorphism XRCC1 Arg194Trp and 8-hydroxydeoxyguanosine increased susceptibility to arsenic-related renal cell carcinoma. *Toxicol. Appl. Pharmacol.* **2017**, *332*, 1–7. [CrossRef]

73. Hsueh, Y.-M.; Chen, W.-J.; Lin, Y.-C.; Huang, C.-Y.; Shiue, H.-S.; Yang, S.-M.; Ao, P.-L.; Pu, Y.-S.; Su, C.-T. Adiponectin gene polymorphisms and obesity increase the susceptibility to arsenic-related renal cell carcinoma. *Toxicol. Appl. Pharmacol.* **2018**, *350*, 11–20. [CrossRef]
74. Hsueh, Y.-M.; Lin, Y.-C.; Huang, Y.-L.; Shiue, H.-S.; Pu, Y.-S.; Huang, C.-Y.; Chung, C.-J. Effect of plasma selenium, red blood cell cadmium, total urinary arsenic levels, and eGFR on renal cell carcinoma. *Sci. Total. Environ.* **2020**, *750*, 141547. [CrossRef]
75. García-Esquinas, E.; Pollán, M.; Umans, J.G.; Francesconi, K.A.; Goessler, W.; Guallar, E.; Howard, B.; Farley, J.; Best, L.G.; Navas-Acien, A. Arsenic Exposure and Cancer Mortality in a US-Based Prospective Cohort: The Strong Heart Study. *Cancer Epidemiol. Biomarkers Prev.* **2013**, *22*, 1944–1953. [CrossRef] [PubMed]
76. Richardson, S.; Thomson, A.; Best, N.; Elliott, P. Interpreting posterior relative risk estimates in disease-mapping studies. *Environ. Health Perspect.* **2004**, *112*, 1016–1025. [CrossRef] [PubMed]
77. Yin, P.; Mu, L.; Madden, M.; Vena, J.E. Hierarchical Bayesian modeling of spatio-temporal patterns of lung cancer incidence risk in Georgia, USA: 2000–2007. *J. Geogr. Syst.* **2014**, *16*, 387–407. [CrossRef]
78. Bates, M.N.; Rey, O.A.; Biggs, M.L.; Hopenhayn, C.; Moore, L.E.; Kalman, D.; Steinmaus, C.; Smith, A.H. Case-Control Study of Bladder Cancer and Exposure to Arsenic in Argentina. *Am. J. Epidemiology* **2004**, *159*, 381–389. [CrossRef] [PubMed]
79. Huang, Y.-K.; Huang, Y.-L.; Hsueh, Y.-M.; Yang, M.-H.; Wu, M.-M.; Chen, S.-Y.; Hsu, L.-I.; Chen, C.-J. Arsenic exposure, urinary arsenic speciation, and the incidence of urothelial carcinoma: A twelve-year follow-up study. *Cancer Causes Control* **2008**, *19*, 829–839. [CrossRef]
80. Kurttio, P.; Pukkala, E.; Kahelin, H.; Auvinen, A.; Pekkanen, J. Arsenic concentrations in well water and risk of bladder and kidney cancer in Finland. *Environ. Health Perspect.* **1999**, *107*, 705–710. [CrossRef]
81. Meliker, J.R.; Slotnick, M.J.; AvRuskin, G.A.; Schottenfeld, D.; Jacquez, G.M.; Wilson, M.L.; Goovaerts, P.; Franzblau, A.; Nriagu, J.O. Lifetime exposure to arsenic in drinking water and bladder cancer: A population-based case–control study in Michigan, USA. *Cancer Causes Control.* **2010**, *21*, 745–757. [CrossRef]
82. Steinmaus, C.M.; Ferreccio, C.; Romo, J.A.; Yuan, Y.; Cortes, S.; Marshall, G.; Moore, L.E.; Balmes, J.R.; Liaw, J.; Golden, T. Drinking Water Arsenic in Northern Chile: High Cancer Risks 40 Years after Exposure CessationHigh Cancer Risks 40 Years after Arsenic Exposure. *Cancer Epidemiol. Biomark. Prev.* **2013**, *22*, 623–630. [CrossRef] [PubMed]
83. Chung, C.-J.; Huang, Y.-L.; Huang, Y.-K.; Wu, M.-M.; Chen, S.-Y.; Hsueh, Y.-M.; Chen, C.-J. Urinary arsenic profiles and the risks of cancer mortality: A population-based 20-year follow-up study in arseniasis-endemic areas in Taiwan. *Environ. Res.* **2013**, *122*, 25–30. [CrossRef]
84. Hopenhayn-Rich, C.; Biggs, M.L.; Smith, A.H. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. *Leuk. Res.* **1998**, *27*, 561–569. [CrossRef] [PubMed]
85. Lamm, S.H.; Engel, A.; Kruse, M.B.; Feinleib, M.; Byrd, D.M.; Lai, S.; Wilson, R. Arsenic in Drinking Water and Bladder Cancer Mortality in the United States: An Analysis Based on 133 U.S. Counties and 30 Years of Observation. *J. Occup. Environ. Med.* **2004**, *46*, 298–306. [CrossRef]
86. Meliker, J.R.; Slotnick, M.J.; AvRuskin, G.A.; Kaufmann, A.; Fedewa, S.A.; Goovaerts, P.; Jacquez, G.J.; Nriagu, J.O. Individual lifetime exposure to inorganic arsenic using a space–time information system. *Int. Arch. Occup. Environ. Heal.* **2006**, *80*, 184–197. [CrossRef]
87. Pou, S.A.; Osella, A.R.; Diaz, M.d.P. Bladder cancer mortality trends and patterns in Córdoba, Argentina (1986–2006). *Cancer Causes Control.* **2011**, *22*, 407–415. [CrossRef]
88. Su, C.-C.; Lu, J.-L.; Tsai, K.-Y.; Lian, I.-B. Reduction in arsenic intake from water has different impacts on lung cancer and bladder cancer in an arseniasis endemic area in Taiwan. *Cancer Causes Control.* **2010**, *22*, 101–108. [CrossRef] [PubMed]
89. Tsuda, T.; Babazono, A.; Yamamoto, E.; Kurumatani, N.; Mino, Y.; Ogawa, T.; Kishi, Y.; Aoyama, H. Ingested Arsenic and Internal Cancer: A Historical Cohort Study Followed for 33 Years. *Am. J. Epidemiol.* **1995**, *141*, 198–209. [CrossRef] [PubMed]
90. Freedman, N.D.; Silverman, D.T.; Hollenbeck, A.R.; Schatzkin, A.; Abnet, C.C. Association Between Smoking and Risk of Bladder Cancer Among Men and Women. *JAMA* **2011**, *306*, 737–745. [CrossRef]
91. Boffetta, P.; Borron, C. Low-Level Exposure to Arsenic in Drinking Water and Risk of Lung and Bladder Cancer: A Systematic Review and Dose–Response Meta-Analysis. *Dose-Response* **2019**, *17*. [CrossRef] [PubMed]
92. Jaafarzadeh, N.; Poormohammadi, A.; Almasi, H.; Ghaedrahmat, Z.; Rahim, F.; Zahedi, A. Arsenic in drinking water and kidney cancer: A systematic review. *Rev. Environ. Heal.* **2022**, *38*, 255–263. [CrossRef]
93. Podgorski, J.; Berg, M. Global threat of arsenic in groundwater. *Science* **2020**, *368*, 845–850. [CrossRef] [PubMed]
94. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Arsenic and arsenic compounds. In *Arsenic, Metals, Fibres and Dusts*; International Agency for Research on Cancer: Lyon, France, 2012.
95. Yadav, M.K.; Saidulu, D.; Gupta, A.K.; Ghosal, P.S.; Mukherjee, A. Status and management of arsenic pollution in groundwater: A comprehensive appraisal of recent global scenario, human health impacts, sustainable field-scale treatment technologies. *J. Environ. Chem. Eng.* **2021**, *9*, 105203. [CrossRef]
96. Punshon, T.; Jackson, B.P.; Meharg, A.A.; Warczack, T.; Scheckel, K.; Guerinot, M.L. Understanding arsenic dynamics in agronomic systems to predict and prevent uptake by crop plants. *Sci. Total. Environ.* **2016**, *581–582*, 209–220. [CrossRef]
97. Flanagan, S.V.; Spayd, S.E.; Procopio, N.A.; Marvinney, R.G.; Smith, A.E.; Chillrud, S.N.; Braman, S.; Zheng, Y. Arsenic in private well water part 3 of 3: Socioeconomic vulnerability to exposure in Maine and New Jersey. *Sci. Total. Environ.* **2016**, *562*, 1019–1030. [CrossRef]

98. Adeloju, S.B.; Khan, S.; Patti, A.F. Arsenic Contamination of Groundwater and Its Implications for Drinking Water Quality and Human Health in Under-Developed Countries and Remote Communities—A Review. *Appl. Sci.* **2021**, *11*, 1926. [CrossRef]
99. Krupoff, M.; Mobarak, A.M.; van Geen, A. Evaluating Strategies to Reduce Arsenic Poisoning in South Asia: A View from the Social Sciences. *Asian Dev. Rev.* **2020**, *37*, 21–44. [CrossRef]
100. Flanagan, S.V.; Spayd, S.E.; Procopio, N.A.; Chillrud, S.N.; Braman, S.; Zheng, Y. Arsenic in private well water part 1 of 3: Impact of the New Jersey Private Well Testing Act on household testing and mitigation behavior. *Sci. Total. Environ.* **2016**, *562*, 999–1009. [CrossRef]
101. Flanagan, S.V.; Spayd, S.E.; Procopio, N.A.; Chillrud, S.N.; Ross, J.; Braman, S.; Zheng, Y. Arsenic in private well water part 2 of 3: Who benefits the most from traditional testing promotion? *Sci. Total Environ.* **2016**, *562*, 1010–1018. [CrossRef]
102. Milton, A.H.; Hore, S.K.; Hossain, M.Z.; Rahman, M. Bangladesh arsenic mitigation programs: Lessons from the past. *Emerg. Heal. Threat. J.* **2012**, *5*, 7269. [CrossRef] [PubMed]
103. McGowan, J.; Sampson, M.; Salzwedel, D.M.; Cogo, E.; Foerster, V.; Lefebvre, C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J. Clin. Epidemiology* **2016**, *75*, 40–46. [CrossRef] [PubMed]
104. Rethlefsen, M.L.; Kirtley, S.; Waffenschmidt, S.; Ayala, A.P.; Moher, D.; Page, M.J.; Koffel, J.B.; PRISMA-S Group. PRISMA-S: An extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. *Syst. Rev.* **2021**, *10*, 39. [CrossRef]
105. Vuorre, M. Bayesian Meta-Analysis with R, Stan, and brms. Meta-Analysis is a Special Case of Bayesian Multilevel Modeling. Available online: https://mvuorre.github.io/posts/2016-09-29-bayesian-meta-analysis/ (accessed on 18 April 2023).
106. Hackenberger, B.K. Bayesian meta-analysis now–let's do it. *Croat. Med. J.* **2020**, *61*, 564. [CrossRef]
107. Bero, L.; Chartres, N.; Diong, J.; Fabbri, A.; Ghersi, D.; Lam, J.; Lau, A.; McDonald, S.; Mintzes, B.; Sutton, P.; et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: Concerns arising from application to observational studies of exposures. *Syst. Rev.* **2018**, *7*, 242. [CrossRef] [PubMed]