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Microbiological and chemical drinking water contaminants and associated health outcomes in rural Appalachia, USA: A systematic review and meta-analysis

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ABSTRACT

In rural areas of the United States, an estimated ~1.8 million people lack reliable access to safe drinking water. Considering the relative dearth of information on water contamination and health outcomes in Appalachia, we conducted a systematic review of studies of microbiological and chemical drinking water contamination and associated health outcomes in rural Appalachia. We pre-registered our protocols, limiting eligibility to primary data studies published from 2000 to 2019, and searched four databases (PubMed, EMBASE, Web of Science, and the Cochrane Library). We used qualitative syntheses, meta-analyses, risk of bias analysis, and meta-regression to assess reported findings, with reference to US EPA drinking water standards. Of the 3452 records identified for screening, 85 met our eligibility criteria. 93 % of eligible studies (n = 79) used cross-sectional designs. Most studies were conducted in Northern (32 %, n = 27) and North Central (24 %, n = 20) Appalachia, and only 6 % (n = 5) were conducted exclusively in Central Appalachia. Across studies, *E. coli* were detected in 10.6 % of samples (sample-size-weighted mean percentage from 4671 samples, 14 publications). Among chemical contaminants, sample-size-weighted mean concentrations for arsenic were 0.010 mg/L (n = 21,262 samples, 6 publications), and 0.009 mg/L for lead (n = 23,259, 5 publications). 32 % (n = 27) of studies assessed health outcomes, but only 4.7 % (n = 4) used case-control or cohort designs (all others were cross-sectional). The most commonly reported outcomes were detection of PFAS in blood serum (n = 13), gastrointestinal illness (n = 5), and cardiovascular-related outcomes (n = 4). Of the 27 studies that assessed health outcomes, 62.9 % (n = 17) appeared to be associated with water contamination events that had received national media attention. Overall, based on the number and quality of eligible studies identified, we could not reach clear conclusions about the state of water quality, or its impacts on health, in any of Appalachia's subregions. More epidemiologic research is needed to understand contaminated water sources, exposures, and potentially associated health outcomes in Appalachia.

1. Introduction

The United Nations Sustainable Development Goal (SDG) target 6.1 is to "achieve universal and equitable access to safe and affordable drinking water for all" by 2030. However, as of 2020, ~2 billion people still lack access to safely managed drinking water source, as defined by the WHO/UNICEF's Joint Monitoring Program (JMP) (i.e., accessible on premises, available when needed, and free from fecal and priority chemical contamination) (UN-Water., 2021). Of the most impacted populations globally, people in low-income rural areas tend to have the lowest rates of access to safely managed drinking water (UN-Water., 2021; WHO/UNICEF, 2019). A recent JMP global progress estimate for safely managed drinking water service coverage in urban areas was 86 %, while in rural areas coverage was only 60 % (WHO/UNICEF,

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2021). Adding to this challenge, freshwater resources face mounting burdens in the coming decades due to climate change associated impacts, which are predicted to increase water related risks and adversely impact people and economies that rely on scarce, variable, and contaminated water sources and supplies (Zakar et al., 2020).

In the United States (US), according to JMP data, ~10 million Americans still lack access to a "safely managed" drinking water source nationally, suggesting that ~1.8 million Americans in rural areas lack access to safely managed drinking water (estimates based on JMP data, Annex 3) (WHO/UNICEF, 2021). For communities with utility-supplied water in the US, rurality and system size have been identified as predictors of increased risks of Safe Drinking Water (SDWA) health-based violations (Allaire et al., 2018; Marcillo and Krometis, 2019), and Central Appalachia in particular has been identified as a region with elevated levels of community water systems identified as SDWA Serious Violators (Mueller and Gasteyer, 2021). These disparities in access are often driven in part by aging, inadequate, or poorly managed community water systems (CWS), as well as vulnerabilities associated with private well water systems, such as close proximity to septic tanks and/or poor maintenance (Mueller and Gasteyer, 2021; Charrois, 2010; de Albuquerque, 2011; Hughes et al., 2005a). In rural Appalachia, impacts from industry including chemical spills and mining related impacts can contribute to increased levels of heavy metals like arsenic, copper, and lead in public and private water supplies (Kruse Daniels et al., 2021). There is scattered evidence of these issues, and occasional media attention spotlighting regional problems (Pytalski, 2018; US Water Alliance, 2019; WVPB, 2019); however, compared to many lower-income urban areas in the US, or to rural areas in some low- and middle-income countries (LMICs), there is relatively limited publicly available data describing regional drinking water contaminants or associated health impacts (Krometis et al., 2017; Marshall and Alcalde, 2017; Wies et al., 2020).

The Appalachian Regional Commission's (ARC) formal definition of Appalachia includes 423 counties across 13 states from southern New York to northern Mississippi (ARC, 2022a). As compared to the broader US, which is 20 % rural, 42 % of this 533,538 km (WHO/UNICEF, 2019) (206,000 miles (WHO/UNICEF, 2019)) region's population are classified as rural (Pollard and Jacobsen, 2021). Based on measures for median family income, poverty, and unemployment rates, in the fiscal year 2022 the ARC designated 81 counties as economically "distressed", and an additional 95 as "at-risk" (ARC, 2022b). There is a long history of large-scale mineral and resource extraction in the region and evidence of associated environmental health impacts in some communities and regions (Partridge et al., 2013).

Though water and sanitation related health outcome data is limited, other publicly available health data reveal a number of significant regional health disparities. Rates of lung cancer, heart disease, kidney disease, substance abuse, and diabetes are worse overall in the Appalachian region compared with the rest of the US (Marshall and Alcalde, 2017; Meit et al., 2019). Between 2009 and 2013, the gap in life expectancy between Appalachia and the rest of the US increased to 2.4 years for men and 2.2 years for women (Singh et al., 2017). Consistent with trends between rural and urban demographics, all-cause mortality in Appalachia was 5 % higher in 1990–92 and 18 % higher in 2009–13, when measured against the rest of the country (Singh et al., 2017).

Health disparities prevalent in Appalachia are partly explained and further complicated by poor economic conditions which are known to be direct determinants of health (Adler and Newman, 2002; Braveman et al., 2010; Steenland et al., 2004; Winkleby et al., 1992). Though the region is known for its wealth of natural resources, perhaps most notably thermal and metallurgical coal, the abundance of extraction industries has largely excluded Appalachian populations from the majority of associated wealth and power generated from these resources (Douglas and Walker, 2017; Zipper and Skousen, 2021). Perhaps not surprisingly, the Appalachian region has lagged behind the rest of the US on key development indicators, such as income disparity, unemployment, outmigration, educational attainment, health status, and housing availability (ARC, 2015). Extraction industries, including coal-mining and oil and gas development, have also created disproportionate environmental contaminant risks for surrounding communities (Krometis et al., 2017; Boyles et al., 2017; Werner et al., 2015). Both underground mining, which accounts for 81 % of coal production in the Appalachian region, and surface mining have had negative impacts on ground and surface water quality (*Energy Information Administration (EIA)*, 2021; *US EPA*, 1980). Mountaintop removal, in particular, a major method of surface coal mining in and around Central Appalachia, impacts the air, water, and soil, creating potential for adverse health effects in neighboring populations (Boyles et al., 2017).

Limited utility-supplied drinking water coverage, similar to other development metrics, is also more common in rural Appalachian households compared to the rest of the nation (Hughes et al., 2005a). Though significant progress has been made to increase utility coverage across the region, the percentage of the population in Appalachia connected to piped-drinking water services still falls behind the national average (74 % compared with 85 % of the population) (Hughes et al., 2005a). Where access to utility-supplied drinking water is common, reliance is primarily dependent on smaller community water systems (typically with higher per-capita operating costs), as opposed to systems serving > 5000 people (Hughes et al., 2005a).

The lack of basic water and sewer infrastructure in pockets of Appalachia has been acknowledged by the United Nations General Assembly in a report on the human right to safe drinking water and sanitation by the special rapporteur, emphasizing specific challenges faced by marginalized groups in rural areas (de Albuquerque, 2011). Though most of Appalachia's population (75 %) is served by utility-supplied drinking water, coverage is often unaffordable for many remote locations with lower population densities and mountainous terrain (Hughes et al., 2005a), resulting in dependence on private household wells, springs, and bottled water in remote rural areas. In portions of Central Appalachia, an analysis of U.S. Census data found that > 10 % of homes lacked access to piped water supply (Krometis et al., 2017). When public drinking water coverage is available, utilities in remote locations also face disproportionately higher instances of Safe Drinking Water Act (SDWA) violations and boil water advisories (Marcillo and Krometis, 2019). Although the SDWA regulates all public drinking water sources using health-based standards for harmful contaminants, in areas without utility coverage that rely on private water sources, the responsibility for monitoring drinking water quality falls directly to residents (Bowen et al., 2019). Compounding effects also result from both the hydrogeology of the region and impacts from extraction industries, which creates greater risk for natural and anthropogenic contaminants leaching into groundwater (Chapman et al., 2013). In a recent systematic review published on environmental health disparities associated with mountaintop removal mining, increased accounts of public drinking water violations were found to be directly related to exposures associated with the industry (Boyles et al., 2017). Other possible sources of contaminant exposure results from agricultural runoff, heavy rainfall, and proximity to septic systems (Hughes et al., 2005a; Dai et al., 2019; Hunter et al., 2021; Murphy et al., 2020). Collectively, these challenges potentially place many rural Appalachian households at a risk of consuming contaminated drinking water.

The overall objective of this work was to better understand the nature and extent of drinking water quality issues and associated health outcomes in rural Appalachia by extracting findings from published research. To do so, we conducted a comprehensive systematic review of the literature on drinking water contamination and water-related health outcomes in rural counties of the Appalachian region over a 20-year period. We restricted our search to published research papers that used primary data collection to measure or otherwise evaluate drinking water quality as well as measured or self-reported health outcomes with known or hypothesized associations to contaminated drinking water exposure. More broadly, our hope was that findings from this review and synthesis could be used to help identify potentially critical data gaps that may limit understanding of drinking water related health disparities, and to help inform efforts to further expand safe water access in rural Appalachia.

2. Methods

2.1. Protocol and registration

Prior to initiating our search, we piloted our search terms/sets and then pre-registered our study protocol on PROSPERO (Cohen et al., 2020), and uploaded our protocol and search terms/sets to Open Science Framework (https://osf.io/vjsh8/). We prepared our manuscript in accordance with the PRISMA reporting guidelines (Page et al., 2021); a completed checklist is provided in the Supplementary Information (SI).

2.2. Eligibility criteria

Papers were eligible for inclusion provided that at least some primary data was collected in at least one county in the Appalachian region (as determined by the ARC definition updated on May 2009), data collection was completed on or after January 1, 2000, and drinking water was tested for indicators of microbiological and/or chemical contamination, or if health outcomes directly related to drinking water were measured, and papers were published before December 31, 2019. We pre-specified collecting data from papers in rural and urban areas, however after the initial screening stage we amended our inclusion eligibility to limit the scope of the review to include only papers conducted in predominately rural areas of Appalachia (based on Metropolitan Statistical Area designations, or rural-related language study authors used when county specific location information was not reported) (HHS, 2022). Primary data collection was pre-specified to include samples from one or more drinking water sources that were then measured, quantified, evaluated, tested, or otherwise assessed for water quality parameters or contaminants (this included, but was not limited to, utility supplied piped water, well water, surface water, spring water, bottled water, or rainwater) and/or the direct measurement of health outcomes related to drinking water quality. We did not include papers that only assessed nonhuman populations (e.g., benthic macroinvertebrates). No restrictions were placed on the type of study design or sample size.

2.3. Search strategy

Four databases were searched to identify potentially eligible records: PubMed, EMBASE, Web of Science, and the Cochrane Library. We searched for all records (using title, abstract, and index/keyword search fields) containing any combination of search terms related to drinking water and names of US states in the ARC region. Search terms, sets, and explanations of the Boolean operators used, are provided in Table S1. Pre-specified and registered database searches were conducted on May 12, 2020 (additional details, including search code used for each database, are provided in Tables S2–5).

2.4. Screening

After the databases were searched, results were imported and organized via Endnote (version X9; Thomson Reuters, New York, NY). Duplicates were removed using Endnote's automated process as well as a manual search/review. After duplicate removal, spreadsheets were created with only three variables from each record: a unique ID, article title, and article abstract (as available). A random sequence was generated (by AC, using www.random.org) to split the records into two sets, with an overlap such that a random subset of 10 % of all the records would be screened by multiple reviewers (AD, HP, RG, JM). We pre-specified that if the inter-rater reliability for the randomly selected subset of overlapping records was not $>K = 0.65$, all records would be screened independently by two reviewers.

Full texts were assessed for eligibility based on multiple levels of criteria via a custom-designed decision tree (Fig. S1). Full-text records deemed eligible by only one of two reviewers per pair were then randomly reassigned to be screened a second time by the other two reviewers (unresolved decisions were arbitrated by AC). Additional details on our screening process are provided in the Supplementary Material Text S2.

2.5. Data extraction

Data from eligible papers were extracted and entered into a standardized spreadsheet (by AD & HP). Where possible we extracted or calculated the following information from eligible papers: study setting; study population; sampling protocols; source water; baseline characteristics; water quality data; details of the study design; all available outcomes; as well as information for a risk of bias assessment. Population estimates for each state were derived from American Community Survey data summarized in a recent ARC report (Pollard and Jacobsen, 2021). We pre-specified that we would extract data for chemical and microbiological contaminants or indicators with known or suspected links to health, and/or any health outcomes with direct, assumed, or hypothesized links to water exposures or consumption based on WHO's drinking water guidelines (World Health Organization, 2011). For records in which study authors did not report effect measures, such as mean drinking water concentrations, raw data were extracted as available and summary statistics were calculated manually. Maximum reported concentrations for contaminants were extracted when available, in addition to data on sampling location, sampling time, and the presence of water treatment. We also extracted data on author-hypothesized or stated reasons for observed contamination and/or health outcomes. To assess the accuracy of initial data extraction and entry, data from a random selection of $\sim$10 % of the eligible full text records were also extracted and entered independently (by RG & JM). Per our pre-specified protocol, in cases of incomplete or missing reported data we did not attempt to contact any study authors. Additional details on our data extraction methods are provided in the Supplementary Material Text S3.

2.6. Data analyses

We pre-specified comparing reported water parameter/quality data with current US EPA SDWA standards (US EPA, 2022), as well as subgroup analysis by drinking water source and ARC subregion. We also pre-specified using sample sized based weighting (as well as unadjusted measures of central tendency) for our meta-analyses, to reduce the potential that results from smaller studies would contribute disproportionately to calculated measures of central tendency (Borenstein et al., 2010; Higgins et al., 2019). Chemical and microbial data were summarized using summary statistics including mean concentrations as well as the proportion of samples above the detection limit and a binary variable for whether or not mean concentrations were above or below the US EPA SDWA standards, as applicable. Where possible, standard deviations were derived from reported results. Forest plots were used to summarize reported associations between exposures to contaminated drinking water and reported health outcomes. Observations below the detection level were treated as zero. Statistical analyses were conducted using R (v.4.1.1) as well as Stata (v.16); primary analyses (by AD) were independently replicated (by MR, with assistance from AC); meta-regression modelling was conducted by MR.

Given the quantity of data extracted, we could not reasonably summarize or present all the extracted data in this paper; we therefore encourage interested readers to consult the Supplementary Data excel file.

2.7. Assessment of bias

Given the relatively limited number of papers that assessed health outcomes, and the heterogeneity in study design and water quality parameters analyzed, we were unable to use a conventional, health-outcome focused, approach for risk of bias (ROB) assessment (which we pre-specified). Instead, papers were assigned a ROB score based on an index built on criteria used in previously published reviews (Bain et al., 2014; Cohen and Colford, 2017; Uribe-Leitz et al., 2016; Williams et al., 2015; Cohen et al., 2022a). Specifically, we used a composite index to calculate ROB scores for each study in order to classify papers as having a low, medium, or high ROB. The following six items (with scores ranging from 0 to 1, or 0 to 2) were used for our ROB index: Sample size reported; Study year and data collection duration/period reported; Some form of random sampling/selection used; Microbial or chemical outcome assessment protocols reported; Sufficient protocol information to allow for replication; State and county where study conducted reported (details provided in Table S7).

2.8. Meta-regression

Associations of interest across eligible papers were assessed through meta-regression using a generalized linear model with a logit link, binomial distribution, and cluster-robust standard errors (each publication served as a cluster, since many publications reported results from multiple sub-studies characterized by distinct timelines, drinking water source types, and/or locations). We used a binary outcome variable equal to one if the mean concentration was above the associated EPA maximum contaminant level (MCL) standard, and zero otherwise. The following four variables were used for our final analyses: (a) drinking water source (i.e., groundwater, utility-supplied, etc.); (b) Appalachian sub-region; (c) year study was initiated; and (d) number of sampling locations. Selection of final covariates was limited by available data, since many publications did not report sufficient data to allow for inclusion of other covariates of interest without considerably reducing the total sample size for the models. We anticipated inter-study variability (due to differences in study design, water sources, collection methods, analytic protocols, etc.), as well as random error, and therefore pre-specified conducting meta-regression with random-effects based weighting. Coefficients were exponentiated to report model results as Odds Ratios (OR), alongside corresponding 95 % confidence intervals (CI). Bivariate associations between each of the four covariates were assessed in isolation in addition to our final model which controlled for all four variables.

3. Results

3.1. Search results

The initial search yielded 4220 records from the four databases (Fig. 1). After duplicate removal, 3452 titles and abstracts were screened, 615 of which were deemed eligible for full text review. For the randomly selected sub-sample of overlapping 346 records for title/abstract review, inter-rater agreement was 86.7 % for two reviewers (AD, HP) (Kappa = 0.613, z = 11.4, $p < 0.001$) (Landis and Koch, 1977); because the Kappa statistic was less than our pre-specified threshold (Kappa = 0.65), we conducted additional duplicate review for the title/abstract screening stage so all records were screened by two reviewers (AD, HP, RG, JM). Of the 615 records eligible for full-text screening, 85 were selected for inclusion. Frequencies for exclusion reasons are reported in Table S6, with the most common reason being ineligible study location.

3.2. Study characteristics

Of the 85 papers eligible for inclusion, 41 reported results for only chemical outcomes (Aelion and Conte, 2004; Bamberger et al., 2019; Botner, 2018; Christian et al., 2016; Darrah et al., 2014; Darrah et al., 2015; Dasu et al., 2017; Drollette et al., 2015; Foreman et al., 2015; Harkness et al., 2017; Hughes et al., 2005b; Impellitteri et al., 2011; Jackson et al., 2013; Johnson et al., 2015; Jones and Allen, 2007; Kibuye et al., 2019; Kitto and Kim, 2005; Kreuzer et al., 2018; StTM et al., 2016; Lindstrom et al., 2011; Llewellyn et al., 2015; Lu et al., 2015; McMahon et al., 2019; Osborn et al., 2011; Palmer et al., 2019; Pehrsson et al., 2006; Penningroth et al., 2013; Pieper et al., 2015a; Reilly et al., 2015; Rhodes and Horton, 2015; Shiber, 2005; Siegel et al., 2015; Sinkevich et al., 2005; Szabo et al., 2012; Tomlinson et al., 2019; Vengosh et al., 2016; Vinson et al., 2008; Wang et al., 2017; Wigginton et al., 2007; Woda et al., 2018; Zhu et al., 2018), 10 reported microbiological & chemical (Alawattegama et al., 2015; Allevi et al., 2013; Arcipowski et al., 2017; Krometis et al., 2019; Law et al., 2017; Pieper et al., 2015b; Smith et al., 2014; Stanish et al., 2016; Swistock et al., 2015; Swistock et al., 2013), 7 reported only microbiological results (Okeke et al., 2011; Qin et al., 2017; Reed and Rasnake, 2016; Trzyna et al., 2010; Wedgworth et al., 2014; Wedgworth et al., 2015; Won et al., 2013), 17 reported health outcomes only (Anderson-Mahoney et al., 2008; Bartell et al., 2010; Clarkson et al., 2010; Darrow et al., 2013; Emmett et al., 2006; Frisbee et al., 2009; Frisbee et al., 2010; Javins et al., 2013; Knox, 2011; Looker et al., 2014; Schade et al., 2015; Stein et al., 2013; Stein et al., 2014; Vaughn et al., 2013; Watkins et al., 2013; Winquist et al., 2013; Worley et al., 2017), 4 reported microbiological & health outcomes (Baker and Hegarty, 2001; Stauber et al., 2016; Tallon et al., 2008; Wedgworth and Brown, 2013), and 6 reported chemical & health outcomes only (Elliott et al., 2018; Pieper et al., 2018; Unrine et al., 2019; Whelton et al., 2015; Zierold et al., 2004; Zimeri et al., 2015) (Table 2). Overall, 67 % (n = 57) of eligible papers reported results for chemical parameters in drinking water samples, while microbiological parameters were reported in 25 % (n = 21) of papers overall (Supplementary Data Excel File). Data on health outcomes associated with drinking water were reported in 32 % (n = 27) of papers.

Of the five subregions included in the ARC definition of Appalachia, only 6 % (n = 5) of the eligible papers (StTM et al., 2016; Wigginton et al., 2007; Zhu et al., 2018; Arcipowski et al., 2017; Unrine et al., 2019) collected data exclusively from counties in Central Appalachia (Fig. 2). The majority of papers reported data collection from locations in Northern (32 %, n = 27) and North Central (24 %, n = 20) Appalachia, which includes counties in the states of Pennsylvania, New York, West Virginia, Ohio, and Maryland (Table 1, Fig. 2). Nine publications (10.5 %) reported on studies conducted in multiple ARC subregions, including 3 (3.5 %) publications with some data collection in parts of Central Appalachia.

Cross-sectional studies accounted for the majority (93 %, n = 79) of study designs, followed by cohort studies (4 %, n = 3) and case-control studies (2 %, n = 2) (Table 1). Authors from 9 % of papers (n = 8) reported using some form of random selection of sampling location and/or selection of study participants, though sample selection methods were unclear in 35 % (n = 30) of the papers (Supplementary Data Excel File).

Among the eligible papers, 71 % (n = 60) collected samples from private wells and 45 % (n = 39) collected samples from utility-supplied water sources (Supplementary Data Excel File). Alternative drinking water sources such as bottled (1 %, n = 1) and spring water (7 %, n = 6) were only sampled in a small percentage of papers (Supplementary Data Excel File). In total, 56 % (n = 46) of papers provided

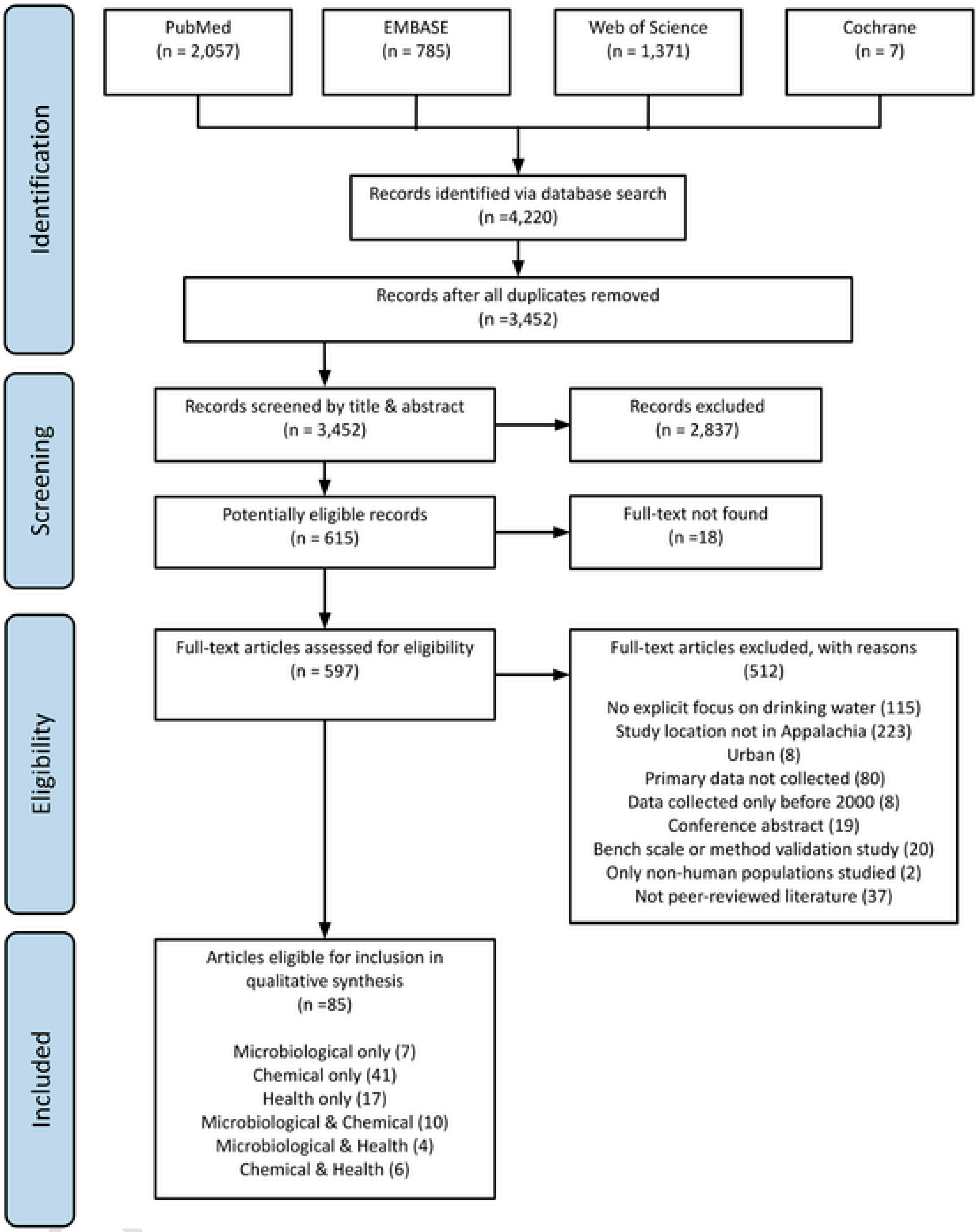

Fig. 1. Study screening and selection flow chart.

estimates of detection frequencies and 40 % (n = 34) reported arithmetic sample mean concentrations for microbial and chemical outcomes (Supplementary Data Excel File).

Of the papers that reported health outcomes associated with drinking water, odds ratios and other measures of association were reported or could be calculated from available data in only 30 % of health outcome papers (8/27) (Supplementary Data Excel File). Additional details for each paper, including specific outcomes, study design, and locations are provided in Table 2.

3.3. Chemical outcomes

67 % (38/57) of the papers which reported on chemical contaminants collected samples from private wells, and 23 % (13/57) collected samples from utility-supplied water (Supplemental Data Excel File). By subregion, Northern Appalachia (n = 110 reported chemical outcomes) was the most represented followed by the North Central (n = 30 chemical outcomes), South Central (n = 25 chemical outcomes), Central (n = 22 chemical outcomes), and Southern subregions (n = 22 chemical outcomes) (Fig. 3). Weighting by population in each Appalachian subregion, the number of papers reporting chemical outcomes per 1,000,000 people was highest for Northern (3.20 papers per 1,000,000), Central (2.70 papers per 1,000,000) Appalachia, and North

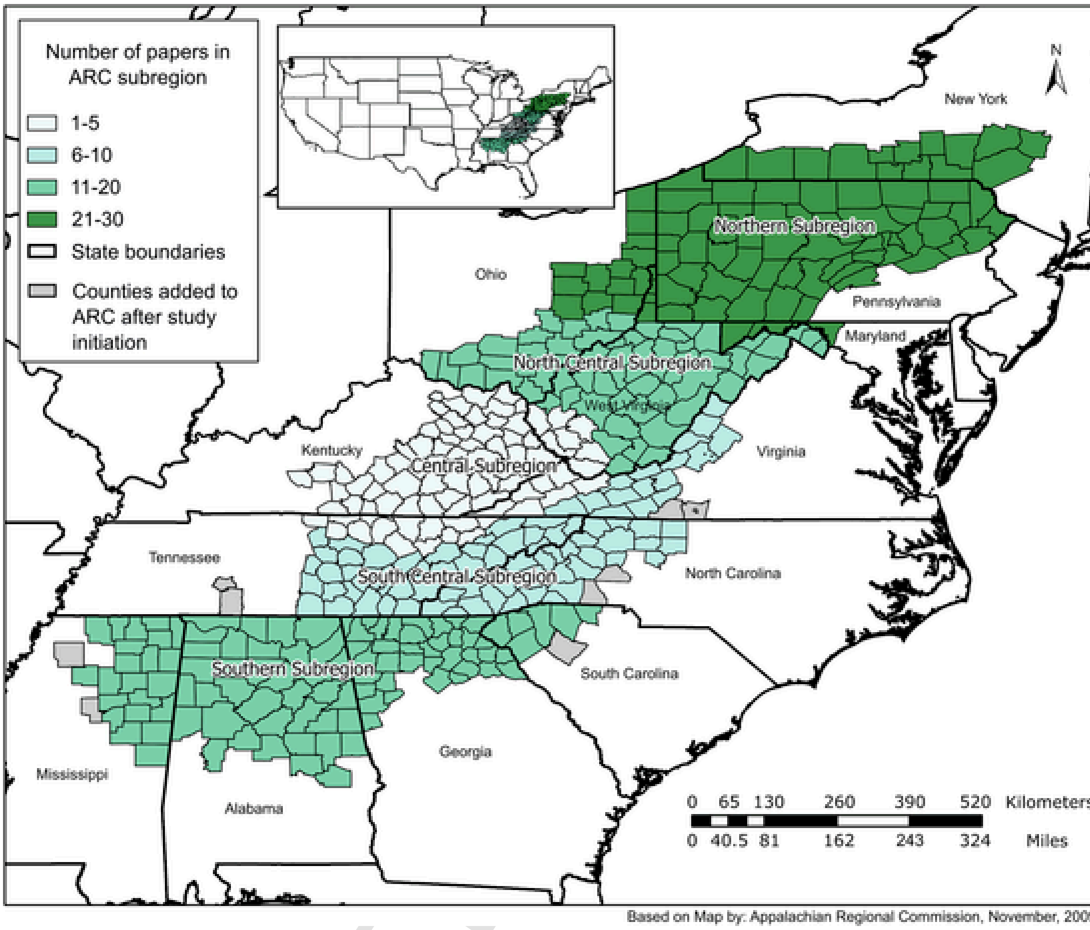

Fig. 2. Distribution of papers by appalachian state and subregion (excludes 9 publications reporting studies conducted in multiple regions, and 1 publication without sufficient data to identify the subregion).

Central (2.09 papers per 1,000,000), and lower for the South Central (1.62 papers per 1,000,000) and Southern (0.83 papers per 1,000,000) regions (Pollard and Jacobsen, 2021) (Supplementary Data Excel File).

Results for mean concentrations and detection frequencies for chemical contaminants are reported in Table 3. Across all 85 eligible papers, arsenic (n = 21; 25 %), nitrate (n = 20; 24 %), barium (n = 18; 21 %), and lead (n = 15; 18 %) were the most commonly measured contaminants (Figs. 3, S5). To control for the number of sampling locations per study, we calculated means and medians for our outcome variables (mean concentration and detection frequency) weighted by sample size (i.e., extracted sample sizes from papers with eligible data were multiplied by the outcome variable, summed, and divided by total number of sampling locations across papers). Across extracted means and rates of detection for chemical outcomes, we used the weighted mean, and the maximum extracted mean, as our primary measures for outcome reporting. The total number of sampling points across papers for each chemical outcome are provided alongside summary statistics in Table 3.

Though sample and source water varied across papers, most calculated weighted means for mean concentrations were below EPA MCLs, with a notable exception for uranium (weighted mean = 0.30 mg/L; from 4 papers reporting results from 36 sampling locations (Table 3). However, maximum extracted means from papers were at or above EPA limits for nine chemical outcomes (nitrate, arsenic, barium, bromodichloromethane, PFOA, PFOS, radium 226, uranium, and lead). The unweighted mean and maximum reported mean across papers for lead, for instance, were 0.0104 and 0.0434 mg/L respectively, with the maximum mean (extracted from Pieper et al., 2018) approximately three times higher than the EPA limit (Fig. S6). For arsenic, summary statistics were either near or above the EPA MCL of 10 μg/L (weighted mean = 9.91 μg/L; maximum reported mean = 10 μg/L) (Fig. S7). Across papers reporting on *per*- and polyfluoroalkyl substances (PFAS) in water supplies, the weighted mean and maximum reported mean for Perfluorooctanoic acids (PFOAs) were 103 ng/L and 444 ng/L respectively. Though PFAS are not included in the EPA's current National Primary Drinking Water Regulations (NPDWRs), reported PFOA levels across eligible papers were higher than both the EPA's lifetime health advisory level set in 2016, 70 ppt, and the EPA advisory levels amended on June 15, 2022 to 0.004 ppt (USEPA, 2022).

To derive more conservative estimates of contaminant levels, and to report results from samples taken from "source" water, as opposed to results that included contaminants associated with premise plumbing, when both first draw samples and samples taken after flushing the tap were reported, we only included concentrations for samples tested after flushing. That is, for those studies that reported data from first flush and post flush samples, we only extracted and reported post-flushing results to better approximate source water quality. For example, Pieper et al. (2018), found a mean and maximum concentration of 0.249 mg/L and 1.75 mg/L respectively for lead in first draw samples across 15 household private well systems in North Carolina, whereas the mean concentration after flushing was 0.0434 mg/L.

When comparing parameters by source water type, we observed a lower weighted mean in utility water samples for arsenic (1.53 μg/L, from 1 paper, 17 total sampling locations) compared to private well water (9.95 μg/L, from 4 papers, 21,208 total sampling locations) (Table S17). However, there was a lack of sufficient sample size, in the case of

Table 1
Overview of eligible records (n = 85).

	Microbio. Only (n = 7)		Chemical only (n = 41)		Microbio. & chemical (n = 10)		Health only (n = 17)		Microbio. & Health (n = 4)		Chemical & Health (n = 6)		Total (n = 85)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Primary author affiliations														
Government agencies	1	14 %	5	12 %	1	10 %	3	18 %	0	0 %	0	0 %	10	12 %
Universities	5	71 %	27	66 %	9	90 %	9	53 %	3	75 %	4	67 %	57	67 %
University & government	1	14 %	6	15 %	0	0 %	3	18 %	1	25 %	2	33 %	13	15 %
Other (NGOs, companies)	0	0 %	3	7 %	0	0 %	2	12 %	0	0 %	0	0 %	5	6 %
Primary water source[a]														
Bottled	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %
Groundwater (unspecified)	0	0 %	2	5 %	0	0 %	0	0 %	0	0 %	0	0 %	2	2 %
Utility supplied	4	57 %	6	15 %	1	10 %	1	6 %	1	25 %	3	50 %	16	19 %
Private wells	1	14 %	29	71 %	4	40 %	0	0 %	1	25 %	2	33 %	37	44 %
Spring	1	14 %	0	0 %	2	20 %	0	0 %	1	25 %	0	0 %	4	5 %
Multiple sources	1	14 %	4	10 %	2	20 %	15	88 %	1	25 %	1	17 %	24	28 %
Not specified	0	0 %	0	0 %	1	10 %	1	6 %	0	0 %	0	0 %	2	2 %
Study design														
Case-control	0	0 %	0	0 %	0	0 %	1	6 %	0	0 %	1	17 %	2	2 %
Cohort	0	0 %	0	0 %	0	0 %	3	18 %	0	0 %	0	0 %	3	4 %
Cross-sectional	7	100 %	41	100 %	10	100 %	13	76 %	3	75 %	5	83 %	79	93 %
No clear study design	0	0 %	0	0 %	0	0 %	0	0 %	1	25 %	0	0 %	1	1 %
Primary ARC sub region[a]								0 %						
Northern	1	14 %	21	51 %	3	30 %	0	0 %	1	25 %	1	17 %	27	32 %
North central	1	14 %	3	7 %	1	10 %	14	82 %	0	0 %	1	17 %	20	24 %
Central	0	0 %	3	7 %	1	10 %	0	0 %	0	0 %	1	17 %	5	6 %
South central	1	14 %	4	10 %	3	30 %	0	0 %	1	25 %	1	17 %	10	12 %
Southern	3	43 %	6	15 %	0	0 %	1	6 %	1	25 %	1	17 %	13	15 %
Multiple	1	14 %	3	7 %	2	20 %	1	6 %	0	0 %	0	0 %	7	8 %
Not specified	0	0 %	1	2 %	0	0 %	1	6 %	0	0 %	1	17 %	3	4 %
Primary study state[a]								0 %						
Alabama	3	43 %	3	7 %	0	0 %	1	6 %	2	50 %	0	0 %	9	11 %
Georgia	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %	1	17 %	1	1 %
Kentucky	0	0 %	3	7 %	1	10 %	0	0 %	0	0 %	1	17 %	5	6 %
Maryland	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %
Mississippi	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %
New York	0	0 %	6	15 %	0	0 %	0	0 %	0	0 %	0	0 %	6	7 %
North Carolina	0	0 %	3	7 %	0	0 %	0	0 %	1	25 %	1	17 %	5	6 %
Ohio	1	14 %	1	2 %	0	0 %	0	0 %	0	0 %	1	17 %	3	4 %
Pennsylvania	0	0 %	8	20 %	3	30 %	0	0 %	1	25 %	0	0 %	12	14 %
South Carolina	0	0 %	2	5 %	0	0 %	0	0 %	0	0 %	0	0 %	2	2 %
Tennessee	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %
Virginia	0	0 %	1	2 %	3	30 %	0	0 %	0	0 %	0	0 %	4	5 %
West Virginia	1	14 %	2	5 %	1	10 %	1	6 %	0	0 %	1	17 %	6	7 %
Multiple	2	29 %	12	29 %	2	20 %	15	88 %	0	0 %	0	0 %	31	36 %
Not specified	0	0 %	0	0 %	0	0 %	1	6 %	0	0 %	1	17 %	1	1 %

Notes: Microbio. = Microbiological |

[a] To summarize all eligible papers and to avoid double counting, results are presented categorically. Consequently, true counts for the number of papers in a specific category may not be represented if the paper type was classified as "multiple sources" or "multiple states". Please see the Supplementary Excel Data File for true counts.

arsenic in utility supplied water, to compare differences between source water with statistical confidence. Similarly, the aggregate mean for uranium in utility water was 11.2 μg/L (from 2 papers, 23 sampling locations) compared with 582 μg/L in private well water (from 2 papers, 13 sampling locations), revealing analogous indicators of the influence of source water type, though limited due to insufficient sample size (Table S17). In the same manner, our ability to evaluate the trends induced by comparable factors such as sampling point (e.g., kitchen tap) and sampling time (e.g., first draw, after flushing) were also limited by the sample size across papers.

Calculated summary statistics for data we extracted on the percent of samples reported above detection limits for chemical outcomes are summarized in Table 3. Barium (weighted mean = 95.4 %), strontium (weighted mean = 92.3 %), PFOA (weighted mean = 73.9 %), and nitrate (weighted mean = 50.1 %) all had relatively high reported detection frequencies (Table 3).

3.4. Microbiological outcomes

Of the papers reporting microbiological outcomes, fecal indicator organisms such as *Escherichia coli* (*E. coli*) (n = 16), total coliform (n = 14), and *Enterococci* (n = 3) were the most commonly reported (Table 4; Figs. 4; S8). Several papers also reported results for specific pathogens including *Cryptosporidium* (n = 1), *Campylobacter* spp. (n = 1), *Giardia lamblia* (n = 1), *Mycobacterium* spp. (n = 2), *Legionella* (n = 1), and *Pseudomonas aeruginosa* (n = 1) (Fig. 4) (Stanish et al., 2016; Swistock et al., 2015; Qin et al., 2017; Won et al., 2013). Across all papers, weighted means for *E. coli* and total coliform were

Table 2
Eligible study locations, study designs, and reported outcome data.

First author & publication year	State/s	Arc subregion	Study design	Chemical outcome/s	Microbiological outcome/s	Health outcome/s
Aelion, Marjorie 2004	Southern	SC	CS	1,1-Dichloroethylene, Tetrachloroethylene, 1,1,1-Trichloroethane, 1,2,4-Trimethylbenzene, cis-1,2-Dichloroethene, Bromodichloromethane (BDCM), Nitrate, Trichloroethylene, VOCs (unspecified), Methyl tert-butyl ether (MTBE)	–	–
Alawattegama, Shyama K. 2015	Northern	PA	CS	Aluminum, Fluoride, Nitrate, Antimony, Arsenic, Barium, Cadmium, Chromium (total), Copper, Lead, Selenium, Sodium, Strontium, Uranium (total)	*Escherichia coli*, Total Coliform	–
Allevi, Richard 2013	South Central	VA	CS	Nitrate, Fluoride, Copper, Sodium	HF183, Total Coliform, *Escherichia coli*	–
Anderson-Mahoney, Pamela 2008	North Central	WV, OH	CS	–	–	Cardiovascular problems, High blood pressure, Kidney disease, Chronic bronchitis, Thyroid problems, Liver problems
Arcipowski, Erin 2017	Central	KY	CS	Arsenic, Mercury, Aluminum, Sodium, Nitrate	*Escherichia coli*	–
Baker, Katherine 2001	Northern	PA	CS	–	*Helicobacter pylori*, *Escherichia coli*	*Helicobacter pylori* infection
Bamberger, Michelle 2019	Northern	PA	CS	Aryl hydrocarbon receptor activity	–	–
Bartell, Scott 2010	North Central	WV, OH	CS	–	–	PFOA in blood serum
Botner, E. Claire 2018	Northern	OH	CS	Methane	–	–
Christian, Kayla 2016	Northern	NY	CS	Barium, Sodium, Nitrate, Strontium, Lead, Chlorine, Selenium	–	–
Clarkson, L.S. 2010	Multiple	GA, TN	CC	–	–	Salmonella Javiana infection
Darrah, Thomas 2014	Northern	PA	CS	Methane	–	–
Darrah, Thomas H. 2015	Northern	NY, PA	CS	Barium	–	–
Darrow, Lyndsey 2013	North Central	OH, WV	CH	–	–	Preterm birth, Pregnancy-induced hypertension (PIH), Low birth weight, PFOA in blood serum, PFOS in blood serum
Dasu, Kavitha 2017	North Central	OH, WV	CS	PFBS, PFHxS, PFOS, PFHpA, PFOA	–	–
Drollete, Brian 2015	Northern	PA, NY	CS	Diesel range organic compounds (DROs), Gasoline Range Organic Compounds (GROs)	–	–
Elliott, Elise 2018	Northern	OH	CS	Benzene, Ethylbenzene, Toluene, m-xylene plus p-xylene, Bromodichloromethane (BDCM), Bromoform, Dibromochloromethane (DBCM), Tetrachloroethylene, Gasoline Range Organic Compounds (GROs), Diesel range organic compounds (DROs), 1,2,4-Trichlorobenzene	–	Respiratory symptoms, Dermal symptoms, Acute gastrointestinal Illness
Emmett, Edward Anthony 2006	North Central	WV, OH	CS	–	–	PFOA in blood serum
Foreman, William 2014	North Central	WV	CS	4-Methylcyclohexanemethanol (MCHM)	–	–
Frisbee, Stephanie 2009	North Central	WV, OH	CS	–	–	PFPsA in blood serum, PFHxA in blood serum, PFHS in blood serum, PFPpA in blood serum, PFOA in blood serum, PFOS in blood serum, PFNA in blood serum, PFDA in blood serum, PFUnA in blood serum, PFDoA in blood serum
Frisbee, Stephanie 2010	North Central	WV, OH	CS	–	–	PFOA in blood serum, PFOS in blood serum
Harkness, Jennifer 2017	North Central	WV	CS	Arsenic, Barium, Nitrate, Strontium	–	–
Hughes, Lara 2005	Southern	SC	CS	Uranium (total), Radium 226, Radium 228, Radon 222, 210 Lead	–	–
Impellitteri, Christopher 2011	North Central	PA, WV, VA	CS	Perchlorate	–	–
Jackson, Robert 2013	Northern	PA, NY	CS	Methane	–	–
Javins, Ben 2013	North Central	WV, OH	CS	–	–	PFOA in blood serum, PFOS in blood serum

(*continued on next page*)

Table 2 (*continued*)

First author & publication year	State/s	Arc subregion	Study design	Chemical outcome/s	Microbiological outcome/s	Health outcome/s
Johnson, Jason 2015	Northern	PA, NY	CS	Barium, Sodium, Strontium, Nitrate	–	–
Jones, Russel L. 2007	Southern	AL	CS	Aldicarb carbamate residue	–	–
Kibuye, Faith 2019	Northern	PA	CS	Acetaminophen, Ampicillin, Caffeine, Naproxen, Oflaxacin, Sulfamethoxazole, Trimethoprim	–	–
Kitto, Michael 2005	Northern	NY	CS	Radium 226, Gross alpha radioactivity, Gross beta radioactivity, Radium 228, Radium (total), Uranium (total)	–	–
Knox, Sarah 2011	North Central	WV, OH	CS	–	–	PFOA in blood serum, Thyroid problems, PFOS in blood serum
Kreuzer, Rebecca 2018	Northern	NY	CS	Barium, Strontium, Sodium, Chlorine	–	–
Krometis, Leigh-Anne 2019	Multiple	WV, TN, KY, VA, NC	CS	Uranium (total), Cadmium, Selenium, Aluminum, Copper, Fluoride, Arsenic, Lead, Nitrate, Sodium	Total Coliform, *Escherichia coli*	–
Law, R. K. 2017	North Central	WV	CS	Antimony, Arsenic, Beryllium, Barium, Cadmium, Chromium (total), Copper, Cyanide, Fluoride, Lead, Mercury, Nitrate, Selenium, Radon 222	*Escherichia coli*, Total Coliform	–
LeDoux, St. Thomas M. 2016	Central	KY	CS	Sodium, Nitrate	–	–
Lindstrom, Andrew B. 2011	Southern	AL	CS	PFNA, PFOA, PFHpA, PFDA, PFHxA, PFPeA, PFBA, PFOS, PFHxS, PFBS	–	–
Llewellyn, Garth 2015	Northern	PA	CS	Barium, Strontium, Nitrate, Methane	–	–
Looker, Claire 2014	Multiple	WV, OH	CS	–	–	PFOA in blood serum, PFOS in blood serum
Lu, Zunli 2015	Northern	NY	CS	Bromine	–	–
McMahon, Peter 2019	Northern	NY, PA	CS	Barium, Nitrate, Arsenic, Strontium, Benzene, Toluene, Ethylbenzene, m-xylene plus p-xylene, o-xylene, 1,2,4-Trimethylbenzene, Butane, n-Pentane, Hexane, Napthalene, sec-Butylbenzene, Methyl tert-butyl ether (MTBE), Tetrachloroethene, Tetrachloromethane, Trichloroethene, 1,1,1-Trichloroethane, cis-1,2-Dichloroethene	–	–
Okeke, Benedict C. 2011	Southern	AL	CS	–	*Escherichia coli*, Enterococci, Total Coliform	–
Osborn, Stephen 2011	Northern	PA, NY	CS	Methane, Sodium, Radium 226	–	–
Palmer, Anna 2019	Southern	AL	CS	Lithium	–	–
Pehrsson, P.R. 2006	Multiple	VA, NC	CS	Fluoride	–	–
Penningroth, Stephen 2013	Northern	NY	CS	Gross alpha radioactivity, Gross beta radioactivity, Barium, Arsenic, Strontium, Benzene, Ethylbenzene, Toluene, Xylenes (total)	–	–
Pieper, Kelsey 2015	South Central	VA	CS	Lead	–	–
Pieper, Kelsey 2015	South Central	VA	CS	Arsenic, Cadmium, Chromium (total), Fluoride, Nitrate, Copper, Lead	Total Coliform, *Escherichia coli*	–
Pieper, Kelsey 2018	South Central	NC	CS	Lead, Cadmium	–	Blood lead levels
Qin, Ke 2017	Multiple	WV, OH	CS	–	Acanthamoeba, Mycobacterium spp., Legionella, *Pseudomonas aeruginosa*	–
Reed, Brian 2016	South Central	PA	CS	–	Total Coliform, *Escherichia coli*	–
Reilly, Darren 2015	Northern	PA	CS	Nitrate, Arsenic, Aluminum, Barium, Strontium	–	–
Rhodes, Amy 2015	Northern	PA	CS	Barium, Nitrate, Arsenic, Cadmium, Chromium (total), Copper, Lead, Strontium, Sodium	–	–
Schade, Charles 2015	North Central	WV	CS	–	–	Illness related to chemical spill, Diarrhea
Shiber, John G. 2005	Multiple	KY, WV, OH, TN	CS	Arsenic	–	–

(*continued on next page*)

Table 2 (*continued*)

First author & publication year	State/s	Arc subregion	Study design	Chemical outcome/s	Microbiological outcome/s	Health outcome/s
Siegel, D. I. 2015	Multiple	OH, PA, WV	CS	Arsenic, Benzene, Cadmium, Chromium (total), Ethylbenzene, Lead, Mercury, Selenium, Sodium, Strontium, Toluene, Xylenes (total), Barium	–	–
Sinkevich, Michael 2005	Northern	NY	CS	Atrazine	–	–
Smith, Tamara 2014	South Central	VA	CS	Nitrate	general fecal Bacteroides marker, HF183, Total Coliform, *Escherichia coli*	–
Stanish, Lee 2016	Multiple	OH, WV, KY, PA	CS	Arsenic, Cadmium, Chromium (total), Copper, Antimony, Selenium, Fluoride, Sodium, Nitrate, Barium	Mycobacterium spp.	–
Stauber, Christine 2016	Southern	AL	CS	–	*Escherichia coli*, Total Coliform	Acute gastrointestinal Illness
Stein, Cheryl 2013	North Central	WV, OH	CS	–	–	in utero PFOA concentration
Stein, Cheryl R 2014	North Central	WV, OH	CS	–	–	PFOA in blood serum
Swistock, Bryan R. 2013	Northern	PA	CS	Lead, Arsenic, Nitrate	Total Coliform, *Escherichia coli*	–
Swistock, Bryan R. 2015	Northern	PA	CS	Barium, Arsenic, Lead, Nitrate, Copper, Aluminum	Total Coliform, *Escherichia coli*, *Giardia lamblia*, Cryptosporidium	–
Szabo, Zoltan 2011	Southern	AL, MS	CS	Radon 222	–	–
Tallon, Lindsay 2008	South Central	NC	NC	–	*Escherichia coli*, Enterococci, Fecal coliforms	Acute Hepatitis A
Tomlinson, Martha Scott 2019	South Central	NC	CS	Copper, Arsenic, Cadmium, Chromium (total), Lead, Strontium	–	–
Trzyna, Wendy 2010	North Central	WV	CS	–	Acanthamoeba, Amoebae	–
Unrine, Jason 2019	Central	KY	CC	Arsenic, Selenium, Copper, Aluminum, Uranium (total), Lead, Cadmium, Chromium (total)	–	Lung cancer
Vaughn, Barry 2013	North Central	WV, OH	CH	–	–	Cancer, Bladder cancer, Liver cancer, Lung cancer, Kidney cancer, PFOA in blood serum
Vengosh, Avner 2016	South Central	NC	CS	Chromium (total), Chromium (VI), Strontium	–	–
Vinson, David 2008	South Central	NC	CS	Radon 222	–	–
Wang, Yuxin 2017	Northern	PA	CS	Bromide, Trihalomethanes (TTHM), Halocetic acids (HAA5), Chloroform, Bromodichloromethane (BDCM), Dibromochloromethane (DBCM)	–	–
Watkins, Deborah 2013	North Central	WV, OH	CS	–	–	PFOA in blood serum, Poor kidney function
Wedgworth, Jessica 2013	Southern	AL	CS	–	Fecal coliforms	Acute gastrointestinal Illness
Wedgworth, Jessica 2014	Southern	AL	CS	–	Total Coliform	–
Wedgworth, Jessica 2015	Southern	AL	CS	–	Total Coliform, *Escherichia coli*, Enterococci	–
Whelton, Andrew 2015	North Central	WV	CS	4-Methylcyclohexanemethanol (MCHM), Arsenic, Barium, Beryllium, Cadmium, Chromium (total), Copper, Lead, Aluminum, Nitrate, Fluoride	–	Self-reported illness, Diarrhea
Wigginton, Andrew 2007	Central	KY	CS	Arsenic, Cadmium, Chromium (total), Copper, Mercury, Lead, Selenium, Barium	–	–
Winquist, Andrea 2013	North Central	WV, OH	CH	–	–	Osteoarthritis, Coronary artery disease, Hypertension, Stroke, Diabetes, Lupus, Multiple sclerosis, Thyroid disease, Kidney disease, Liver disease, Ulcerative colitis, Crohn's disease, Parkinson's disease, Chronic obstructive pulmonary disease, Asthma, Malignancies, Rheumatoid arthritis with medication, High cholesterol with medication, Myocardial infarction, PFOA in blood serum

(*continued on next page*)

Table 2 (*continued*)

First author & publication year	State/s	Arc subregion	Study design	Chemical outcome/s	Microbiological outcome/s	Health outcome/s
Woda, Josh 2018	Northern	PA	CS	Barium, Methane, Strontium, Arsenic, Uranium (total)	–	–
Won, Gayeon 2013	Northern	OH	CS	–	*Escherichia coli*, Pathogenic *Escherichia coli*, Campylobacter, Total Coliform	–
Worley, Rachel Rogers 2017	Southern	AL	CS	–	–	PFOA in blood serum, PFOS in blood serum
Zhu, Junfeng 2018	Central	KY	CS	Sodium, Methane	–	–
Zierold, Kristina 2004	Multiple	NR	CS	Arsenic	–	Heart disease, Angina
Zimeri, Anne Marie 2015	Southern	GA	CS	PCBs (total), mono- PCB, Di PCB, Tri-PCB, Tetra-PCB, Penta-PCB, Hexa-PCB, Hepta PCB compound, Octo PCB compound, Uranium (total)	–	Arsenic in plasma, Aluminum in plasma, Bromine in plasma, Cadmium in plasma, Lead in plasma, Uranium in plasma

Notes: CS = Cross-sectional study, CH = Cohort Study, CC = Case-control, NC = No clear study design; PFOA: Perfluorooctanoic acid; PCBs: Polychlorinated biphenyls; VOC: Volatile organic compound; PFOS: Perfluorooctane sulfonic acid; NR: Not Reported.

11.8 MPN/100 mL (unweighted mean = 12.8 MPN/100 mL) and 69 MPN/100 mL (unweighted mean = 105 MPN/100 mL), respectively (Table 4; Table S13). Of the papers that collected data on bacterial and fecal indicator organisms (n = 17), 92 % of those reporting concentrations of total coliform (12/13) and 81 % of those reporting concentrations of *E. coli* (13/16) reported sample means above the EPA MCLs (Supplementary Data Excel File). Considering EPA standards for most indicator bacteria are set at 0 % detection rates, weighted averages for detection rates of *E. coli* (weighted mean = 10.6 %), total coliform (weighted mean = 35.2 %), and *Enterococci* (weighted mean = 44.3 %) were also all relatively high (Table 4). Compared with other subregions, few studies situated in Central and North Central Appalachian collected primary data on total coliform and *E. coli*, or microbiological outcomes in general (Fig. 4). The number of papers reporting microbiological outcomes by subregion weighted by their respective population estimates was highest for North Central (1.26 papers per 1,000,000 people) and South Central (1.22 papers per 1,000,000 people) and lower for the Northern (0.62 papers per 1,000,000 people), Central (0.54 papers per 1,000,000 people), and Southern (0.60 papers per 1,000,000 people) regions (Pollard and Jacobsen, 2021) (Supplementary Data Excel File). Three papers documented the presence of opportunistic pathogens in utility supplied drinking water (Stanish et al., 2016; Qin et al., 2017; Trzyna et al., 2010) and two papers reported tracking common microbial source targets associated with human sewage intrusion (Allevi et al., 2013; Smith et al., 2014) (Fig. 4; Table 2) (the number of genome copies/L for specified assays are provided in our Supplemental Data Excel file).

3.5. Health outcomes

While most eligible papers alluded to the possible public health impacts of drinking water contamination, only 32 % (n = 27) specifically assessed associations between drinking water exposures and health outcomes; details for these papers are summarized in Table 5 and Table S16. The most commonly studied outcomes were gastrointestinal illness (19 %, 5/27), concentrations of per fluorinated compounds in blood serum (48 %, 13/27), cardiovascular-related outcomes (15 %, 4/27), poor kidney function (11 %, 3/27), and poor thyroid function (11 %, 3/27) (Figs. 5 & S4).

Most papers reporting health outcomes were based on cross sectional study designs (78 %, 21/27), while 11 % (3/27) were cohort studies, and 7 % (2/27) were case-control studies (Supplemental Excel Data File). Three of these 27 papers were outbreak investigations (Clarkson et al., 2010; Baker and Hegarty, 2001; Tallon et al., 2008). Pathogens associated with these outbreaks included *Salmonella* (serotype Javiana), *Helicobacter pylori*, and hepatitis A Virus (HAV). We were only able to extract odds ratios, or sufficient data to calculate odds ratios, from 30 % (8/27) of the papers that collected data on health outcomes (Table S8). Due to heterogeneity in study design and outcome assessment methods, while we present odds ratios for reported health outcomes using a forest plot in Fig. 6, we chose not to present pooled odds ratios by outcome.

For example, although we were able to extract odds ratios for acute gastrointestinal illness (AGI) from four papers (Fig. 6) (Stauber et al., 2016; Wedgworth and Brown, 2013; Elliott et al., 2018; Whelton et al., 2015), there were considerable differences in the type of exposures and methods used (Table S8; details in Supplemental Excel Data File). Study populations for papers reporting odds ratios for AGI targeted homes with existing or likely elevated exposures (e.g. households whose drinking water tested positive for fecal coliform), had frequent water supply interruptions, whose distribution systems had low water pressure, or who were in close proximity to oil and gas wells (Stauber et al., 2016; Wedgworth and Brown, 2013; Elliott et al., 2018). Additional data on odds ratios and prevalence rates are reported in our Supplemental Excel Data File.

3.6. Risk of bias assessment

Low, medium, and high ROB scores were assigned to each study based on measures outlined in Table S7 and the distributions of ROB levels (low, medium, high) by paper type are provided in Table S9. ROB scores ranged from 0 to 11, with lower scores indicative of a higher risk of bias. The majority of papers (87 %, n = 74) were assessed to have high ROB scores (i.e., lower risk of bias) based on our criteria (Table S9). High risk of bias was observed for one health and chemical outcome focused paper (Zierold et al., 2004), and of the 10 papers assessed to have medium ROB scores, 50 % (n = 5) reported on chemical outcomes only.

3.7. Meta-regression

Meta-regression analysis was conducted for studies reporting chemical water contaminant outcomes with MCLs under the SDWA (not enough data were available for studies reporting outcomes for microbiological parameters to conduct similar analyses). In Table 6, bivariate associations between model covariates and our outcome variable are presented in models 1–4, alongside results from our final model (model 5), after controlling for all covariates. Results from model 1 indicate that for every one-year increase in the year a study was initiated, the odds of being above the chemical EPA MCL were statistically signifi-

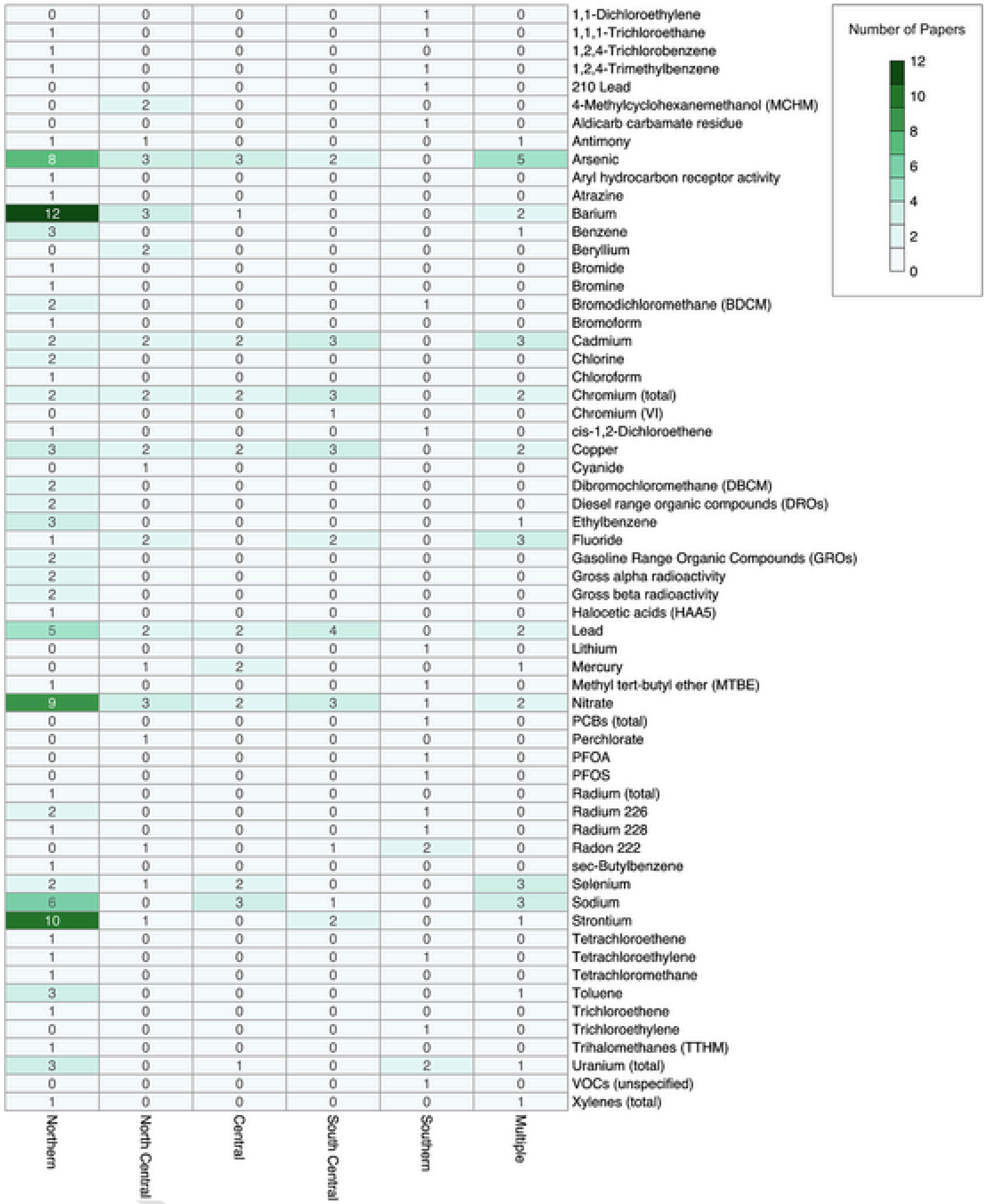

Fig. 3. Chemical outcome frequency by subregion.

cantly lower (OR = 0.857, p = 0.030, n = 132); i.e., overall, more recent studies were more likely to report chemical contaminants at levels below the MCL (Table 6). In model 2 we observed that as the number of water samples analyzed increased across studies, the odds of chemical concentrations exceeding the EPA MCLs decreased (OR = 0.742), though this association was not significant (p = 0.404), and a similar result was observed in the final model. While we did not observe any statistically significant associations in model 3, studies conducted in the North Central region were more likely (OR = 1.167, p = 0.861) to report chemical contaminants at levels above the EPA MCL. When analyzed without other variables incorporated into the model, chemical concentrations for private well water were more likely to be above EPA MCLs in comparison with utility-supplied water (model 4), but the reverse was observed after controlling for other covariates in the model 5 (OR = 0.183, p = 0.208), and neither association was statistically significant. In model 5 which included all variables, none of the associations approached statistical significance (at a $p < 0.05$ threshold) (Table 6). Although we pre-specified performing a sensitivity analysis by running model 5 with and without publications assessed to have a high or moderate risk of bias, this was not necessary since all of the studies included in the meta regression models had low ROB scores.

4. Discussion

As far as we are aware, this effort represents the first Appalachia-focused systematic review and meta-analysis study on drinking water quality and associated health outcomes. A number of overarching findings emerge from our review, including that: 1) the detection of micro-

Table 3
Summary statistics for chemical outcomes.

Chemical Outcome	EPA MCL	EPA SMCL	WHO guideline value	Units	Mean concentration reported				Data aggregated from:		Frequency Detected (as a percentage):				Data aggregated from	
					Weighted median	Maximum	Weighted mean	SD	Total papers	Total sampling points[a]	Weighted median	Maximum	Weighted mean	SD	Total papers	Total sampling points[a]
1,1,1-Trichloroethane	0.2	–	–	mg/L	–	–	–	–	–	–	1.43 %	1.43 %	0.833 %	0.825 %	2	125
1,2,4-Trimethylbenzene	–	–	–	–	–	–	–	–	–	–	1.43 %	6.67 %	1.67 %	3.51 %	2	125
Antimony	0.006	–	0.02	mg/L	–	–	–	–	–	–	7.90 %	22.4 %	9.48 %	10.2 %	2	156
Arsenic	10	–	10	μg/L	10.0	10.0	9.92	3.24	6	21,262	4.00 %	100 %	5.28 %	32.3 %	9	21,607
Barium	2	–	1.3	mg/L	0.390	2.40	0.308	0.637	10	21,896	97.0 %	100 %	95.4 %	2.68 %	5	21,525
Benzene	5	–	10	μg/L	0.500	0.600	0.530	0.311	2	21,099	0.060 %	10 %	0.155 %	3.96 %	4	21,279
Bromodichloromethane (BDCM)	0	–	–	μg/L	0.017	14.2	1.13	10.0	2	76	8.70 %	98.0 %	23.5 %	44.2 %	3	142
Cadmium	5	–	3	μg/L	1.00	1.00	1.00	0.576	2	21,061	0.450 %	85.0 %	0.80 %	33.8 %	5	21,260
Chromium (total)	100	–	50	μg/L	10.000	10.0	8.33	5.0	2	21,061	0.700 %	95.0 %	1.01 %	42.0 %	4	21,239
cis-1,2-Dichloroethene		–	0.05	mg/L	–	–	–	–	–	–	2.86 %	2.86 %	1.67 %	1.65 %	2	125
Copper	1.3	1	2	mg/L	0.005	0.0	0.01	0.01	2	54	41.7 %	100 %	59.5 %	25.3 %	4	216
Dibromochloromethane (DBCM)	0.06	–	0.1	mg/L	–	–	–	–	–	–	18.2 %	74 %	20.6 %	34.7 %	2	72
Diesel range organic compounds (DROs)	–	–	–	–	–	–	–	–	–	–	59.4 %	71.4 %	59.7 %	6.6 %	2	130
Ethylbenzene	0.7	–	0.3	mg/L	–	–	–	–	–	–	0.040 %	13.0 %	5.35 %	4.55 %	4	21,279
Fluoride	4	2	1.5	mg/L	0.930	0.930	0.743	0.419	2	117	99.3 %	100 %	95.0 %	14.40 %	4	210
Gasoline Range Organic Compounds (GROs)	–	–	–	–	–	–	–	–	–	–	97.8 %	100 %	72.8 %	41.8 %	2	130
Gross alpha radioactivity	–	–	0.5	Bq/L	–	–	–	–	–	–	60.0 %	100 %	62.4 %	28.3 %	2	1990
Lead	0.015	–	0.01	mg/L	0.007	0.043	0.009	0.014	5	23,259	10 %	100 %	12.2 %	36.5 %	7	21,478
Mercury	2	–	6	μg/L	–	–	–	–	–	–	0.180 %	0.250 %	0.208 %	0.127 %	3	21,184
Methyl tert-butyl ether (MTBE)	–	–	–	–	–	–	–	–	–	–	1.43 %	6.67 %	2.50 %	2.71 %	2	125
Nitrate	10	–	50	mg/L	1.08	106	7.41	27.1	10	1636	53.0 %	100 %	50.1 %	32.5 %	8	597
PFOA	0.000004[b]	–	–	ng/L	17.5	444	103	302	2	30	84.0 %	84.0 %	73.9 %	35.8 %	2	30
PFOS	0.00002[b]	–	–	ng/L	10.1	10.1	8.93	4.05	2	30	36.0 %	36.0 %	35.5 %	1.89 %	2	30
Radium 226	5	–	27	pCi/L	1.40	5.43	1.12	2.75	3	164	–	–	–	–	–	–
Radium 228	5	–	27	pCi/L	–	–	–	–	–	–	39.1 %	39.1 %	36.5 %	19.8 %	2	96
Selenium	50	–	40	μg/L	10.0	10.0	9.990	4.720	2	21,061	0.210 %	73.7 %	1.04 %	32.5 %	5	21,424
Sodium	–	–	–	mg/L	35.8	67.4	46.7	14.6	7	21,740	98.0 %	100 %	98.8 %	3.81 %	5	21,344
Strontium	–	–	–	mg/L	0.420	1.24	0.553	0.277	7	21,770	92 %	100 %	92.30 %	4.20 %	4	21,394
Tetrachloroethylene	–	–	0.04	mg/L	–	–	–	–	–	–	1.52 %	5.00 %	1.98 %	2.12 %	2	136
Toluene	1	–	0.7	mg/L	–	–	–	–	–	–	0.830 %	93.5 %	1.28 %	37.80 %	4	21,279
Uranium (total)[c]	0.03	–	0.03	mg/L	0.02	1.2	0.30	0.58	4	36	57.9 %	90.0 %	49.3 %	39.7 %	3	34
Xylenes (total)	10	–	0.5	mg/L	–	–	–	–	–	–	0.830 %	0.830 %	0.578 %	0.429 %	2	21,158

Notes: Statistics weighted by study sample sizes (note: sampling methods and water sources varied across papers). Summary statistics are only provided for chemical outcomes reported in (n > 1) papers (see Tables S10–S12 for additional outcomes).

[a] Total sampling points refers to aggregated number of sampling points across papers which reported the specific chemical or microbial concentration for which we reported summary statistics.

[b] Instead of a standard, in 2016 the U.S. Environmental Protection Agency (EPA) released a non-enforceable lifetime health advisory (HA) of 70 ng/L for perfluorooctanoic acid (PFOA) and perfluoro octane sulfonate (PFOS), individually or combined. In 2022, the EPA amended its lifetime health advisory levels for PFOA and PFOS to 0.004 ppt and 0.02 ppt, respectively (USEPA, 2022).

[c] Since the isotopic composition and thus the specific activity for uranium were not reported in Kitto and Kim, 2005, to get the most conservative estimate for uranium in μg/L we used 0.67 pCi/μg, the activity to mass conversion factor recommended by the EPA for uranium (NNDC, 2011; USEPA, 2000).

Table 4
Summary statistics for microbiological outcomes.

			Mean concentration				Data aggregated from:		Frequency detected (as a percentage):				Data aggregated from:	
Microbiological outcome	EPA MCL	Units	Weighted median	Maximum	Weighted mean	SD	Total papers	Total sampling points	Weighted median	Maximum	Weighted mean	SD	Total papers	Total sampling points
Acanthamoeba	–	–	–	–	–	–	–	–	16.00 %	25 %	15.7 %	12.5 %	2	13
E. coli	0	MPN/ 100 mL	11.8	43	11.8	13.3	5	884	10 %	100 %	10.6 %	27.7 %	14	4671
Enterococci	–	–	–	–	–	–	–	–	42.60 %	61.10 %	44.3 %	22.7 %	2	15
HF183	–	–	–	–	–	–	–	–	34 %	60 %	34.4 %	42.4 %	2	61
Total Coliform	5 %	MPN/ 100 mL	27.5	201	69	67.9	5	2330	42 %	100 %	35.2 %	34.1 %	13	5558

Notes: Statistics weighted by study sample sizes (note: sampling methods and water sources varied across papers). Summary statistics are only provided for microbiological outcomes reported in (n > 1) papers (see Tables S13–S15 for additional outcomes).

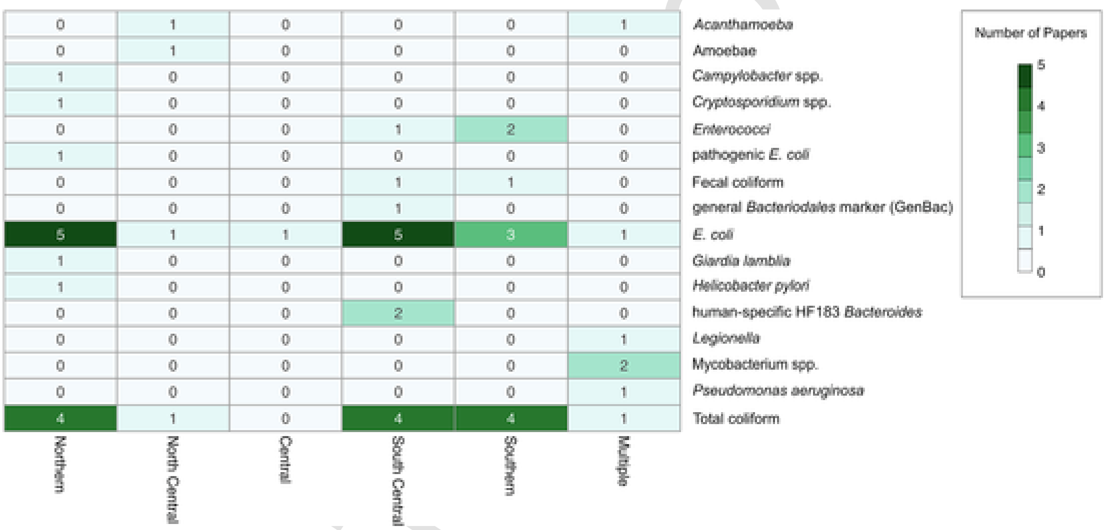

Fig. 4. Microbiological outcome frequency by subregion.

biological and chemical contaminants at levels above recommended standards is not uncommon for rural Appalachian drinking water sources; 2) most eligible studies were conducted in northern regions of Appalachia, and focused primarily on chemical contaminants; and 3) relatively few studies used epidemiologic research methods or direct health outcome assessment.

A number of other, more granular, findings also emerged for our review. For one, private wells were heavily represented in papers that collected primary data on health-related drinking water measures. The majority of sample means reported for fecal indicator organisms were also above EPA MCLs. Though influenced by site selection, as many studies examined areas pre-identified as at particular risk, some concentrations for uranium, lead, arsenic, nitrate and PFOA were also above EPA standards. The most consistently reported outcomes were inorganic contaminants, namely arsenic, nitrate, barium, and lead, in private well water. Of the papers that collected primary data on drinking water and evaluated health outcomes, it appears that most were conducted following water contamination events that received national media attention. Modeled odds ratios from our meta regression for chemical contaminants did not approach statistical significance for predictor variables in either bivariate models or the final model, limiting our understanding of which factors may or may not contribute to, or otherwise be associated with, MCL violations in the region or subregions. Overall, our findings highlight that more research on drinking water quality is needed to understand any potential health risks associated with drinking water exposures in the Appalachian region. More broadly, and beyond the scope of this review, our findings indicate that primary data on drinking water contaminants and associated health outcomes in other predominantly rural and resource-limited regions of the US may likewise be limited.

4.1. Health outcome studies and media-publicized water contamination events

The lack of research directly linking water and health is especially noteworthy with respect to Central Appalachia where indicators of poverty, life expectancy, and other health related metrics are more severe compared with the rest of the US (Mueller and Gasteyer, 2021; de Albuquerque, 2011; Hughes et al., 2005a; Krometis et al., 2017; Born, 2021; Chicago Tribune, 2019; Rappleye and Kaplan, 2021). Since most of the papers identified were cross-sectional in nature, authors were limited in their ability to make causal inferences about drinking water contamination events and health outcomes, pointing to the need for more longitudinal public health studies.

Of the studies that collected primary data on health outcomes (n = 27, 26 %), the majority of papers (n = 17, 62.9 %) appeared to be linked to contamination events which received national media attention (Supplementary Data Excel File), and so failed to capture baseline or typical exposures. Across eligible papers, a large number were focused on PFAS contamination as a result of a DuPont plant's chemical discharge (Anderson-Mahoney et al., 2008; Bartell et al., 2010; Darrow et al., 2013; Emmett et al., 2006; Frisbee et al., 2009; Frisbee et al., 2010; Javins et al., 2013; Knox, 2011; Looker et al., 2014; Stein et al., 2013; Stein et al., 2014; Vaughn et al., 2013; Watkins et al., 2013; Winquist et al., 2013), as well as two papers focused on the 2014 Charleston WV Elk River industrial spill (Whelton et al., 2015; Schade

Table 5
Health outcome summary table.

Outcomes	Populations	Exposures	Results	Paper/s
Acute gastrointestinal illness	Households relying on private wells or utility water supply in the Black belt Region of Alabama	Private wells and county water supply with known links to microbial contamination, specifically failing septic systems	•Study authors found a significant increase (OR 4.0, 95 % CI 1.3–14) in highly credible gastrointestinal risk for individuals whose drinking water sample was positive for Fecal Coliform. •The authors also identified associations between respondent-reported water supply interruption and any symptoms of GII (adjusted odds ratio (aOR): 3.01, 95 % confidence interval (CI) = 1.65–5.49), as well as low water pressure and any symptoms of GII (aOR: 4.51, 95 % CI = 2.55–7.97).	2 papers (Stauber et al., 2016; Wedgworth and Brown, 2013)
Acute Hepatitis A	Populations who spent time on a farm in western North Carolina with a suspected contaminated water supply.	Drinking water from a shallow spring	•Study authors recovered Hepatitis A Virus (HAV) from a fecally contaminated drinking water source that was identical to the sequenced region isolated from the sera of persons linked to the hepatitis A outbreak	1 paper (Tallon et al., 2008)
Birth Outcomes: Preterm birth, low birth weight, pregnancy induced hypertension	C8 Health Project participants living in PFOA contaminated water district	Any of six public water districts or from private water sources which contained >0.05 ppb PFOA	•No effect observed between serum PFOA or PFOS and preterm birth or low birth weight •Serum PFOA and PFOS were positively associated with pregnancy-induced hypertension, with adjusted odds ratios (ORs) per log unit increase in PFOA and PFOS of 1.27 (95 % CI:1.05, 1.55) and 1.47 (95 % CI: 1.06, 2.04)	1 paper (Darrow et al., 2013)
Blood Lead Levels	The homes of two children with elevated blood lead in Macon County, North Carolina	High water lead levels in private wells	•The BLLs of a 1-year-old child in one home dropped from 5.95 μg/dL to 3.72 μg/dL in three months after trying to avoid stagnant well water for all drinking and cooking purposes, including the preparation of formula and water-diluted juices. •After avoiding well water consumption, the child's BLL dropped to 4.88 μg/dL in 2 months and to 3.37 μg/dL in 6 months.	1 paper (Pieper et al., 2018)
Cardiovascular problems	Residents exposed to PFOA contaminated water for at least a year near a Teflon manufacturing plant located along the Ohio River in Wood County, West Virginia	Any of the public water districts or private water sources which contained >0.05 ppb PFOA	• Among study participants, the exposed subjects reported statistically significant greater prevalence of angina, myocardial infarction, and stroke (SPR = 8.07, 95 % CI = 6.54–9.95; SPR = 1.91, 95 % CI = 1.40–2.62, and SPR = 2.17, 95 % CI =1.47–3.21, respectively).	1 paper (Anderson-Mahoney et al., 2008)
Contaminants in blood serum: PFOA, PFOS	Residents living in a PFOA contaminated water district (any of six public water districts or from private water sources which contained >0.05 ppb PFOA) Worley et al. (2017) Local community near PFAS manufacturer in Decatur, Alabama	Public and private drinking water supplies where PFOA was detected near a manufacturing facility	•Population geometric mean PFOA serum concentrations were elevated compared to the general population and 500 % higher in some cases •PFOA and PFOS serum concentrations were both significantly associated with high cholesterol, disruption of thyroid function, thyroid disease, ulcerative colitis, and pregnancy-induced hypertension •Estimated cumulative serum PFOA concentrations were positively associated with kidney and testicular cancer, and reduced antibody titer rise	11 papers (Bartell et al., 2010; Darrow et al., 2013; Emmett et al., 2006; Frisbee et al., 2009, 2010; Javins et al., 2013; Knox, 2011; Stein et al., 2013; Vaughn et al., 2013; Watkins et al., 2013; Winquist et al., 2013; Worley et al., 2017)
Diarrhea	Households living in water districts contaminated by West Virginia's Elk River "Crude MCHM" spill	Tap water contaminated with "Crude MCHM"	•Patients who drank contaminated water were more likely to report diarrhea ($p < 0.001$) symptoms. •6.3 % of 16 households reported diarrhea symptoms	2 papers (Whelton et al. 2015, Schade et al., 2015)
Heart disease	Populations who drank well water for 20 to 83 years with arsenic water concentrations between 0 and 2389 μg/L. Most users had arsenic concentrations of 10 μg/L or less. Mean age of respondents was 62 years	Arsenic in well water	•Respondents with arsenic levels of 2 μg/L or greater had an adjusted odds ratio of 1.52 for heart disease.	1 paper (Zimeri et al., 2015)
Infections: *Helicobacter pylori*	Households who reported clinical symptoms or concerns regarding microbiological quality of their drinking water	Untreated well water	•The presence of *H. pylori* in the wells correlated with infection in consumers and with the presence of *Escherichia coli*, indicating fecal contamination.	1 paper (Baker and Hegarty, 2001)

(*continued on next page*)

Table 5 (*continued*)

Outcomes	Populations	Exposures	Results	Paper/s
Infections: *Salmonella* Javiana	Patients with laboratory confirmed *S.* Javiana infection identified in Georgia and Tennessee from August–October 2004	Well water consumption	•Consumption of well water [adjusted odds ratio (aOR 2.6, 95 % CI 0.9–7.1) was associated with infection.	1 paper (Clarkson et al., 2010)
Kidney problems: Kidney cancer, Kidney disease, Kidney function	C8 Health Project participants living in PFOA contaminated water district	Prolonged exposure to PFOA in drinking water	•Authors found evidence of increased rates of kidney cancer among PFOA exposed study participants	4 papers (Unrine et al., 2019; Vaughn et al., 2013; Watkins et al., 2013; Winquist et al., 2013)
Thyroid problems: Thyroid function, Thyroid disease	C8 Health Project participants living in PFOA contaminated water district	Prolonged exposure to PFOA in drinking water	• Thyroid problems & diabetes were marginally elevated in this PFOA-exposed group (Standardized prevalence ratio (SPR) = 1.56; 95 % C.I. = 0.22–1.98 and SPR = 1.54; 95 % C.I. = 1.16–2.05, respectively)	3 papers (Anderson-Mahoney et al., 2008; Knox, 2011; Winquist et al., 2013)

Note: Additional paper-specific health outcomes are reported in Table S16.

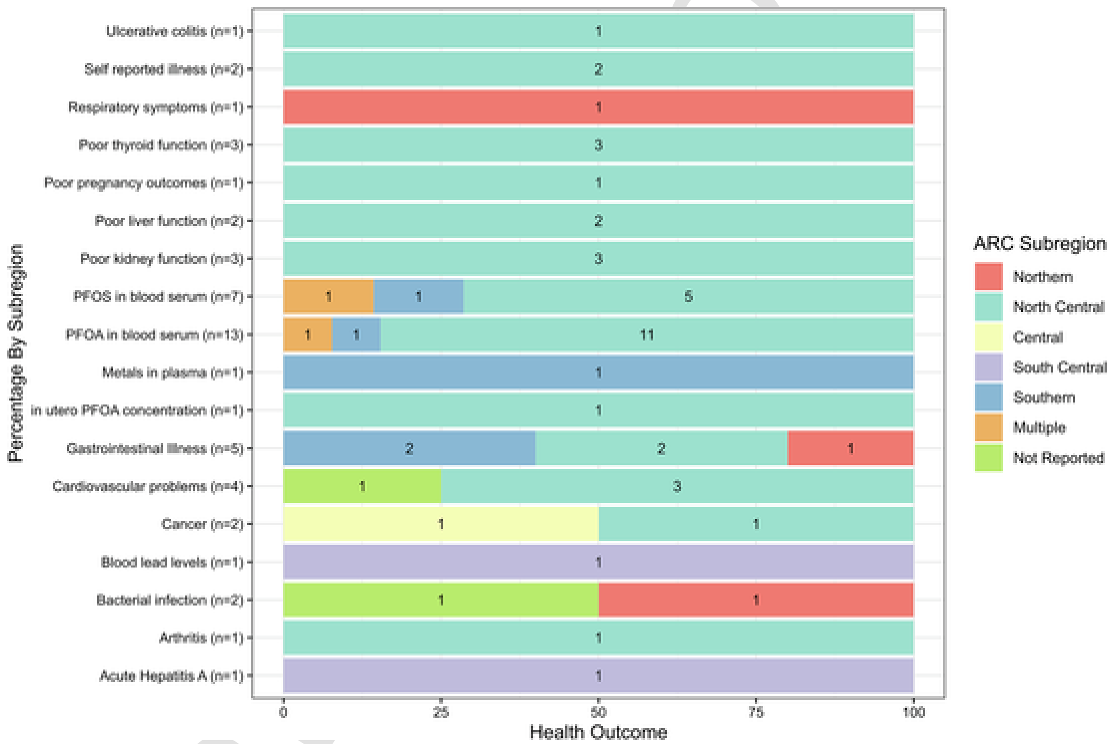

Fig. 5. Health outcome frequency by subregion.
Notes: Numbers in bar plots correspond with number of papers represented.n = Total number of papers for specified outcome.

et al., 2016), and a single paper related to the 2000 Martin County KY dam failure and resultant coal slurry flood (Wigginton et al., 2007) (Table 5). For 52 % (n = 14) of papers that collected health outcome data, the study populations were taken from the larger C8 Health Project cohort, which specifically aimed to examine exposures and health outcomes related to the industrial release of PFAS in Ohio and West Virginia (www.c8sciencepanel.org) (Supplemental Data Excel File) (Anderson-Mahoney et al., 2008; Bartell et al., 2010; Darrow et al., 2013; Darrow et al., 2013; Darrow et al., 2013; Emmett et al., 2006; Frisbee et al., 2009; Frisbee et al., 2010; Javins et al., 2013; Knox, 2011; Looker et al., 2014; Stein et al., 2013; Stein et al., 2014; Vaughn et al., 2013; Watkins et al., 2013; Winquist et al., 2013). These papers measured associations between drinking water exposures and elevated levels of contaminants in blood serum (Darrow et al., 2013; Emmett et al., 2006; Frisbee et al., 2009; Javins et al., 2013; Knox, 2011; Stein et al., 2013; Vaughn et al., 2013; Watkins et al., 2013; Winquist et al., 2013; Worley et al., 2017; Zimeri et al., 2015) (Table 5). The most commonly reported measured outcome in blood serum, PFOA, was reported to have associations with thyroid function, kidney cancer, testicular cancer, and hypertension (Anderson-Mahoney et al., 2008; Knox, 2011; Vaughn et al., 2013; Watkins et al., 2013). When measured in drinking water, the weighted mean for PFOA across papers was 103 ng/L, approximately 1.5 times higher than the EPA's 2016 non-enforceable lifetime health advisory level (US EPA, 2020).

4.2. *Private wells, roadside springs, and bottled water*

Although the data were quite heterogenous across papers and sample sizes from many studies were relatively small (n < 50), some qualitative observations regarding the heightened vulnerability of private wells are worth noting. In general, and as reported above, average observations of various water constituents in water sources from utility supplied systems were less likely to be elevated to levels of concern when compared to values measured in samples from private wells, though samples sizes for utility and spring water sources were considerably lower compared with wells for most parameters (Table S17). This was true for most studies other than those undertaken directly after a contamination event. Across papers not reporting on utility supplied

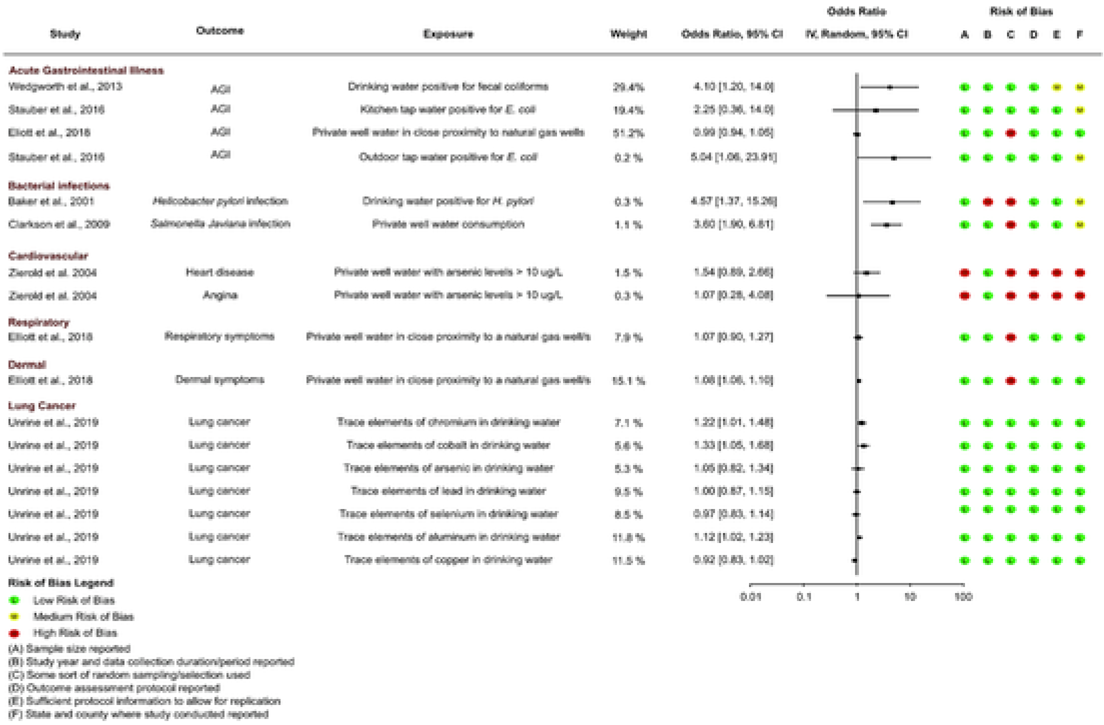

Fig. 6. Forest plot for drinking water associated health outcomes.

Table 6
Meta-regression results.

	Chemical Outcomes: Mean Above EPA MCL														
	Model 1			Model 2			Model 3			Model 4			Model 5		
Variable	OR	95 % CI	p-value	OR	95 % CI	p-value	OR	95 % CI	p-value	OR	95 % CI	p-value	OR	95 % CI	p-value
Study Initiation Year	0.857	0.745–0.985	0.030										0.876	0.710–1.080	0.214
Number of sampling points[a]				0.742	0.368–1.495	0.404							0.520	0.120–2.251	0.382
ARC Subregion															
Northern (vs Southern)							0.188	0.024–1.504	0.115				0.145	0.006–3.388	0.230
North Central (vs Southern)							1.167	0.208–6.535	0.861				5.945	0.218–161.905	0.290
Central (vs Southern)							1.000	0.156–6.425	1.00				1.948	0.139–27.377	0.621
South Central (vs Southern)							0.500	0.077–3.240	0.467				2.504	0.132–47.417	0.541
Source water															
Private well (vs Utility)										1.157	0.222–6.019	0.862	0.183	0.013–2.579	0.208
Other (vs Utility)										0.973	0.101–9.399	0.981	0.210	0.020–2.198	0.193
Model: number of observations	132			140			107			140			101		

Notes.
[a] log-10 transformed.

water, the most commonly elevated contaminants were inorganic constituents including arsenic, nitrate, barium, lead, and strontium, as well as fecal indicator bacteria such as total coliform and *E. coli*.

There were a number of papers reporting NPDWR violations for inorganic contaminants in groundwater in areas affected by shale gas extraction. The sample mean for arsenic, for instance, was equal to the EPA MCL for one paper reporting on groundwater quality prior to shale gas drilling in the Appalachian basin (Siegel et al., 2015). In this study, 4.2 % of the 11,034 samples analyzed from Northeastern Pennsylvania were above the EPA limit of 0.010 mg/L. Similar EPA MCL exceedances existed for lead (3.6 %) and barium (3.3 %) (Siegel et al., 2015). Comparatively, in another study evaluating groundwater quality in an area of shale gas development in West Virginia, 25 well samples were above the EPA MCL for arsenic (Harkness et al., 2017). Though these studies' findings were both motivated and influenced by shale gas development, these levels arguably justify the need for more research on inorganic contaminants in private well water in the area.

Corrosion of plumbing in private wells was evidenced by high concentrations of lead in well water. Pieper et al., 2018 found a mean concentration of 0.249 mg/L for lead, greater than 15 times the EPA MCL, in first draw samples across 15 household private well systems in North Carolina, and the mean after flushing was 0.0434 mg/L. Though we did not include first draw samples in our aggregate mean for lead if samples taken after flushing were available, these instances suggest higher than average lead exposure risks for private well users potentially due to lack of corrosion control which has been reflective of previous sampling campaigns (Swistock et al., 2013; Pieper et al., 2018; Swistock et al., 1993).

We observed higher levels of barium and sodium reported in well water samples compared to utility water samples (Table S17; Supplementary Data Excel File). The maximum mean reported for barium was 2.4 mg/L, 1.2 times higher than the barium EPA MCL of 2 mg/L. Barium is regulated as a health-based MCL by the EPA because it can increase blood pressure (US EPA, 2022). High levels of barium in drinking water in the Appalachian region are of concern because, compared to non-Appalachian counties, counties in Appalachia have an 18 % higher heart disease mortality rate (ARC, 2019). This is of additional concern when contextualized with high levels of sodium in private well water, since 20 mg/L is the recommended level of sodium intake for populations with high blood pressure and/or at higher risk for heart disease (Farquhar et al., 2015; Grillo et al., 2019). While the average sodium level across papers was 48.2 mg/L (Table S10), the maximum reported sodium level from private well water was 4610 mg/L (Siegel et al., 2015).

Though there is no current regulatory limit for strontium in drinking water, levels above 1.5 mg/L may be of concern when contextualized with some morbidities known to be common in the region. The maximum mean reported for strontium was 1.24 mg/L and the overall maximum across papers was 64.4 mg/L (Table 3). The US EPA has provided a health reference level (HRL) of 1.5 mg/L for strontium for children under 18, as a high level of strontium in drinking water is thought to contribute to rickets (US EPA, 2014; Peng et al., 2021), particularly when paired with poor nutrition. As the Appalachian region is known to have a significant number of food deserts (Miller et al., 2016), the presence of strontium in drinking water in the region is therefore of potential concern.

Even more common than chemical contamination in private wells, is the presence of microbial pathogens due to higher amounts of fecal related point sources of contaminants compared to utility supplied water in addition to poor disinfection practices. Though the majority of papers identified in our review studied chemical outcomes in private wells, those which reported levels of microbial contaminants often had relatively more consistent NPDWR violations. For 828 household well water samples tested across Virginia, 42 % (n = 349) were positive for total coliform and 6.6 % (n = 55) were positive for *E. coli (*Smith et al., *2014)*. Similar results were presented in Allevi et al., 2013 which found total coliform in 41 % (n = 221) and *E. coli* in 10 % (n = 53) of sampled private wells in Virginia. In Won et al., 2013, private wells in a region with a high concentration of dairy farms was assessed, detecting *E. coli* in 9 % (16/180) and *E. coli* O157: H7 in 4 % (7/180) of samples, though *Campylobacter* spp. was not detected. Comparable levels of *E. coli* and total coliform were detected in Law et al., 2017, Swistock et al., 2013, and Pieper et al., 2015b. Though fecal indicator bacteria provide a standardized monitoring tool for microbial contamination of private wells, further assessment of the specific pathogens that persist in private well plumbing is needed to provide a more direct exposure assessment.

Naturally occurring geologic contaminants, including radium, radon, and uranium, were often detected in studies which reported data from private wells (Aelion and Conte, 2004; Christian et al., 2016; Darrah et al., 2015; Harkness et al., 2017; Johnson et al., 2015; Kreuzer et al., 2018; Llewellyn et al., 2015; McMahon et al., 2019; Pehrsson et al., 2006; Penningroth et al., 2013; Reilly et al., 2015; Rhodes and Horton, 2015; Shiber, 2005; Siegel et al., 2015; Tomlinson et al., 2019; Woda et al., 2018; Alawattegama et al., 2015; Law et al., 2017; Pieper et al., 2015b; Pieper et al., 2015b; Smith et al., 2014; Swistock et al., 2013; Pieper et al., 2018; Zierold et al., 2004). This is perhaps not surprising given that most private systems do not employ any treatment prior to consumption, and anomalous levels of geological contaminants in groundwater are commonplace for some subareas in Appalachia (Chapman et al., 2013). For example, consistent detection of arsenic and radon in private wells at levels higher than EPA MCLs was observed in counties of West Virginia with significant natural deposits (Law et al., 2017). Similarly, an examination of uranium in drinking water by L. D. Hughes et al. (2005b) focused on a region of South Carolina with anomalously high levels of radionuclides in groundwater. The reported levels of uranium in this paper heavily biased our results for average concentrations in the region, since their sample mean was >30 times the EPA MCL (Hughes et al., 2005b).

Evidence of potential distrust of private well water sources, and utility supplied water, in Appalachia is also supported by the reliance on alternative sources of drinking water such as roadside spring and bottled water use (Krometis et al., 2019; Cohen et al., 2022b; Patton et al., 2020). Despite its utility as an alternative drinking water source, roadside springs are typically unprotected from sources of fecal contamination (Patton et al., 2020). Of the eligible papers that presented results from roadside springs (n = 2), authors reported consistent detection of *E. coli* and total coliform levels well above EPA MCLs (Krometis et al., 2019; Swistock et al., 2015). Protozoa including *Giardia spp.* and *Cryptosporidium spp.,* which have 99 % and 99.9 % removal requirements respectively for EPA's NPDWRs, were also detected in 50 % of roadside spring samples collected in Pennsylvania with average concentrations of 2.99 cysts/L and 2.57 oocysts/L for *Giardia* and *Cryptosporidium* respectively (Swistock et al., 2015) (Supplementary Data Excel File). In addition to well and spring water sources, as part of our review we also collected data on the use of bottled water as a primary source of drinking water. Limited data indicate potentially high rates of bottled water use as a primary source of drinking water in areas of rural Appalachia (Cohen et al., 2022b; McSpirit and Reid, 2011), and there is clear evidence of rapidly growing bottled water use in the USA more broadly, as well as in LMICs, over the past few decades (Cohen and Ray, 2018). It is noteworthy, therefore, that only one paper in our review (Shiber, 2005) collected and analyzed bottled water samples (detecting arsenic in two of three bottled water samples, but at concentrations well below the MCL).

4.3. Utility-supplied drinking water

Though instances of contamination are more widely associated with private wells and alternative sources of drinking water, there are also health risks that correspond with utility supplied water including those that serve rural Appalachian counties (Marcillo and Krometis, 2019). Due to their smaller size compared to urban areas and higher reliance on surface water, utilities in Appalachia tend to face higher operating and capital costs than the national average, which are exacerbated by many of their shrinking customer bases, leading to contamination and shortage issues (Hughes et al., 2005a). Based on data from the EPAs Enforcement and Compliance History Online (ECHO) database, isolated, rural counties have 28 % more violation points than metropolitan ones (EPA, 2022). Spatial patterns of SDWA violations are also known to cluster in specific regions of the United States, including rural Appalachia (Marcillo and Krometis, 2019; Mueller and Gasteyer, 2021). These clusters were maintained by evidence in our review, seeing as a number of utility supplied water sources had reportedly higher than regulatorily acceptable concentrations of total coliform and *E. coli (*Wedgworth et al., *2014;* Wedgworth et al., *2015;* Stauber et al., *2016)*; radionuclides (Kitto and Kim, 2005), disinfection byproducts (Wang et al., 2017), lead (Whelton et al., 2015), 4-Methylcyclohexanemethanol (MCHM) (Whelton et al., 2015), and PFOA (Dasu et al., 2017; Lindstrom et al., 2011). Considering the higher instances of boil water advisories and news coverage on drinking water issues in rural parts of the Appalachian region, the levels of utility supplied water contamination we report herein likely do not reflect the region as a whole, especially considering the lack of data collected from Central Appalachia which is anecdotally known to be impacted disproportionately by issues of this nature (Mueller and Gasteyer, 2021; Krometis et al., 2017).

4.4. Author provided hypothesis for observed contamination

In accordance with our pre-specified protocols, we extracted data on the suspected reasons for observed contamination provided by study authors to contextualize results from our meta-analysis. Suspected reasons generally differed for observations of chemical versus microbial contamination (Figs. 7 & 8). Of the 57 papers documenting chemical contamination, authors most commonly suggested shale gas extraction (37 %, n = 21/57) and surrounding geological conditions (39 %, n = 22/57) as potential drivers, while authors collecting data on microbial contamination pointed primarily to fecal pollution (52 %, n = 11/21) and poor maintenance and treatment practices across all water source types (48 %, n = 10/21) as likely responsible for observed poor water quality (Figs. 7 & 8).

Though there were observed differences by subregion, the primary stated drivers of research on chemical contaminants included surrounding geology, shale gas development, infrastructure and treatment issues, and impacts from industry. Across papers, 26 % (n = 22/85) identified surrounding geology as a primary reason for suspected chemical contamination (Aelion and Conte, 2004; Harkness et al., 2017; Hughes et al., 2005b; Impellitteri et al., 2011; Johnson et al., 2015; Kitto and Kim, 2005; McMahon et al., 2019; Osborn et al., 2011; Penningroth et al., 2013; Pieper et al., 2015a; Shiber, 2005; Szabo et al., 2012; Vengosh et al., 2016; Vinson et al., 2008; Woda et al., 2018; Zhu et al., 2018; Law et al., 2017; Pieper et al., 2015b; Smith et al., 2014; Swistock et al., 2013; Zierold et al., 2004; Zimeri et al., 2015) (Supplementary Data Excel File). Shale gas extraction and downstream effects from industry were also often primary motivators for research on chemical drinking water outcomes in the area, especially in Northern Appalachia, where development of the Marcellus shale fields began in the early 2000s (Vidic et al., 2013) (Fig. 7). Primarily, authors of these studies sought to determine alterations in groundwater chemistry resulting from hydraulic fracturing. This contributed to the higher representation of data from private wells across papers as well as the large number of papers with water quality data for inorganic contaminants such as arsenic, barium, and strontium. Though the majority of shale gas extraction papers primarily studied methane in groundwater, ingestion of methane has not been linked to any reported human health effects of concern, though can cause operational issues for well systems and create explosion and fire hazards (Osborn et al., 2011). Industrial activity as a whole was frequently mentioned as a likely causal factor for chemical contamination, reinforcing the notion that higher than average environmental health risks exist for rural Appalachian populations. As discussed previously, some authors reporting chemical outcomes also cited significant contamination events as a primary motivator for their primary data collection (n = 5) (Dasu et al., 2017; Foreman et al., 2015; Vengosh et al., 2016; Wigginton et al., 2007; Whelton et al., 2015).

Insufficient or lacking drinking water treatment and infrastructure maintenance challenges were also highlighted by many study authors as primary drivers of observed chemical contaminant levels (Fig. 7). Notable issues in this domain included corrosion and leaching of lead into centralized distribution systems and premise plumbing, in addition to general issues associated with private well use (Pieper et al., 2015b; Pieper et al., 2018). Considering the majority of the 85 eligible papers focused on data collection from private wells, which are known to be more vulnerable to contamination when compared to utility supplied water, the observed high frequency of references to infrastructure and treatment issues associated with private well use is not unexpected.

Author hypothesized reasons for microbial contamination primarily involved aging infrastructure and poor maintenance and treatment

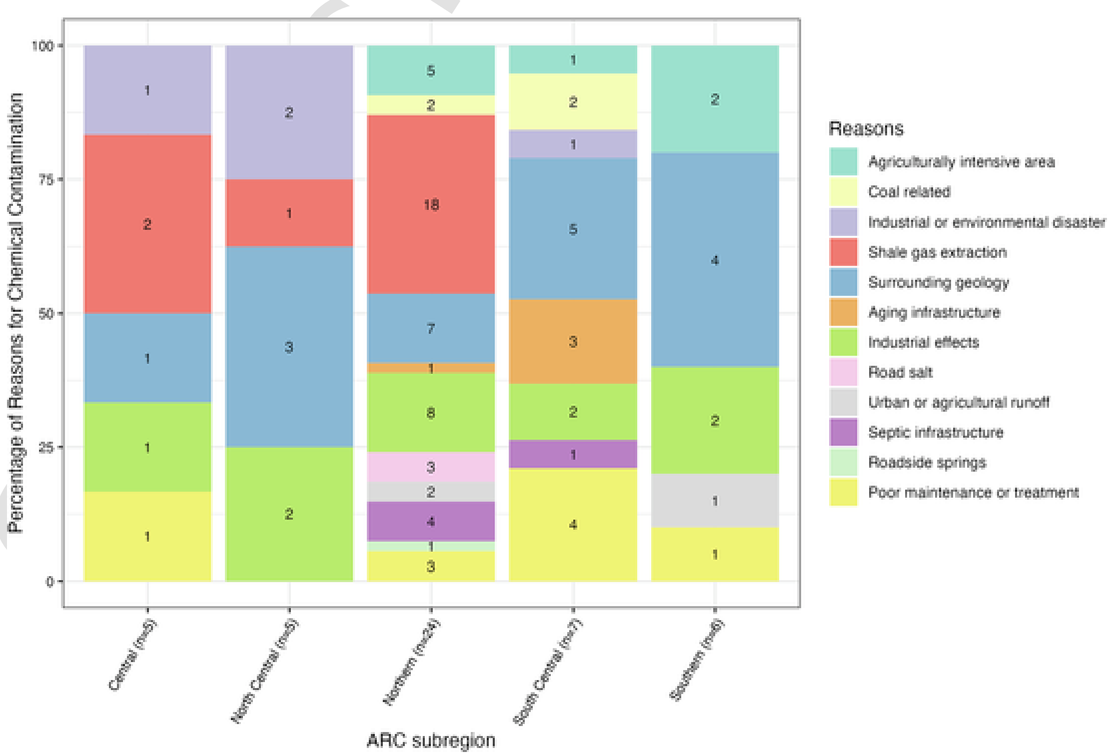

Fig. 7. Author provided reason for observed chemical contamination by subregion.
Notes: n = total number of papers per subregion.Numbers in stacked plot indicate the number of papers with recorded author provided reasons for observed contamination. Papers which did not have a distinct subregion were omitted from this figure.

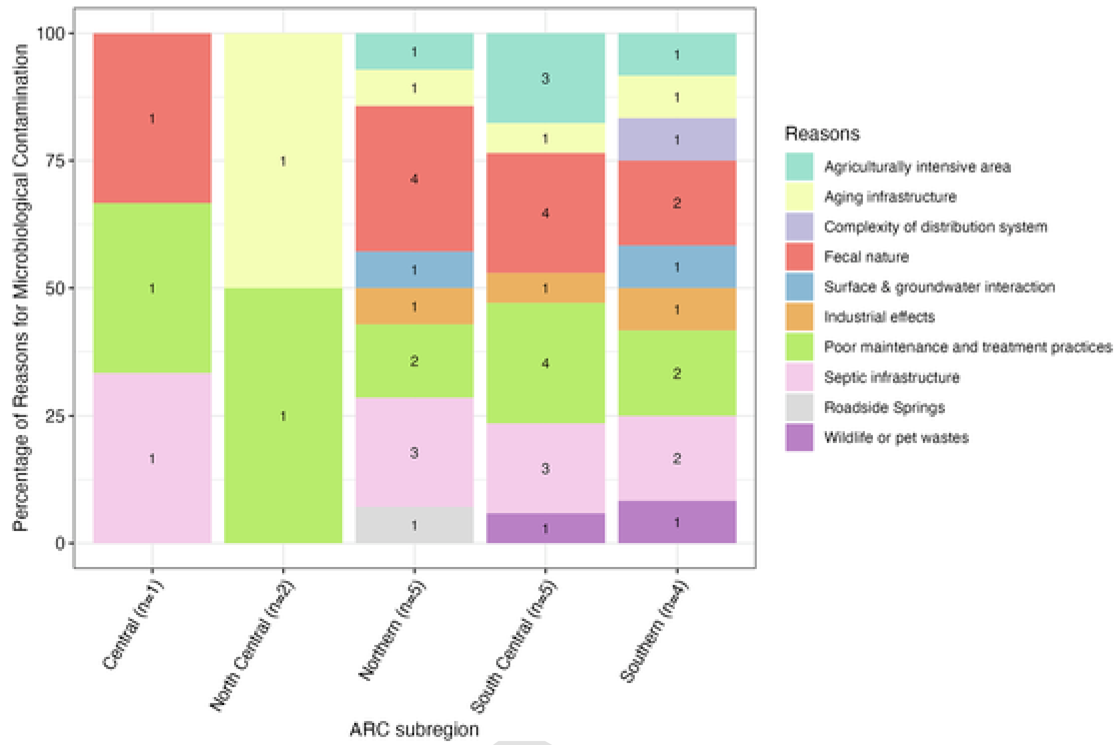

Fig. 8. Author-provided reason for observed microbiological contamination by Subregion.
Notes: n = total number of papers per subregion.Numbers in stacked plot indicate the number of papers with recorded author provided reasons for observed contamination. Papers which did not have a distinct subregion were omitted from this figure.

practices (Fig. 8). Similar to trends observed for chemical papers, private well use was a common focus for microbial papers examining issues related to treatement (Allevi et al., 2013; Pieper et al., 2015b; Smith et al., 2014), with some exceptions including those that studied intermittent supplied utility water in rural Alabama (Stauber et al., 2016; Wedgworth and Brown, 2013) and roadside spring use (Krometis et al., 2019; Swistock et al., 2015). Out of all 21 eligible papers reporting on microbial contaminants, 11 cited fecal contamination as a suspected reason for quality issues (Allevi et al., 2013; Arcipowski et al., 2017; Krometis et al., 2019; Smith et al., 2014; Swistock et al., 2015; Swistock et al., 2013; Won et al., 2013; Baker and Hegarty, 2001; Stauber et al., 2016; Tallon et al., 2008; Wedgworth and Brown, 2013). Impacts from improperly maintained on site wastewater treatment systems (e.g. septics) were repeatedly (n = 9) mentioned as likely responsible for fecal contamination (Allevi et al., 2013; Arcipowski et al., 2017; Smith et al., 2014; Swistock et al., 2013; Won et al., 2013; Baker and Hegarty, 2001; Stauber et al., 2016; Tallon et al., 2008; Wedgworth and Brown, 2013). Other sources were attributed to agriculture such as proximity to grazing animals, swine manure storage pits, and runoff from land used for livestock (Allevi et al., 2013; Smith et al., 2014; Okeke et al., 2011; Won et al., 2013; Tallon et al., 2008).

4.5. Geographic variation in water and health research

Overall, we found that public health related drinking water quality issues were under-represented for less populated and more rural parts of the Appalachian region. Central Appalachia, in particular, which has consistently performed worse in standard health metrics compared to national averages (Marshall and Alcalde, 2017; White et al., 2021) was largely unrepresented in our review, with only 5 papers (6 %) exclusively set in the subregion (StTM et al., 2016; Wigginton et al., 2007; Zhu et al., 2018; Arcipowski et al., 2017; Unrine et al., 2019), as well as another three partially conducted in Central Appalachia (Krometis et al., 2019; Shiber, 2005; Stanish et al., 2016). That said, the disproportionate number of North and North Central Appalachia focused studies appear to be the direct result of the C8 Health Project, a series of exposure and health studies arising from Dupont's PFOA contamination of the Ohio River from the 1950s to the early 2000s (http://www.c8sciencepanel.org/). The C8 Health Project resulted in ~66 peer reviewed publications, not all of which aligned with our review's eligibility criteria (Bartell et al., 2010; Frisbee et al., 2009; Frisbee et al., 2010; Andersson et al., 2019; Avanasi et al., 2016; Ballesteros et al., 2017; Barry et al., 2014; Blum et al., 2015; Cousins et al., 2015; Darrow et al., 2014; Darrow et al., 2016; Dhingra et al., 2016; Fletcher et al., 2013; Gallo et al., 2012; Guelfo et al., 2018; Hoffman et al., 2011; Karnes et al., 2014; Lopez-Espinosa et al., 2011; Lopez-Espinosa et al., 2016; Lopez-Espinosa et al., 2012a; Lopez-Espinosa et al., 2012b; MacNeil et al., 2009; Mondal et al., 2012; Ritscher et al., 2018; Savitz, 2018; Savitz et al., 2012a; Savitz et al., 2012b; Shin et al., 2014; Shin et al., 2011a; Shin et al., 2011b; Steenland et al., 2018a; Steenland et al., 2015; Steenland et al., 2010a; Steenland et al., 2009a; Steenland et al., 2018b; Steenland et al., 2009b; Steenland et al., 2010b; Stein and Savitz, 2011; Watkins et al., 2014; Winquist and Steenland, 2014a; Winquist and Steenland, 2014b; Xu et al., 2020). Those subregions with more papers in our review also have comparatively more research-intensive "R1" universities in their geographical boundaries (Carnegie Foundation for the Advancement of Teaching, 2022). By subregion, Northern Appalachia has five (27 % of the papers in our review, n = 32), North Central has one, Central has zero (6 % of the papers in our review, n = 5), South Central has two, and the Southern region has four R1 universities.

4.6. Study limitations

Publications included in our review represent drinking water quality and related health data that has been published in the region in peer reviewed journals for the 20-year period between January 1, 2000 to December 31, 2019. Specific subregions, source water types, and contaminants were disproportionately represented, e.g., lead, arsenic, barium, nitrate, and *E. coli*; chemical contaminants in the Northern region likely related to Marcellus shale gas extraction (Alawattegama et al., 2015); PFAS levels subsequent to the discovery of the Ohio DuPont industrial release. Conversely, none of the studies in our review reported measuring water samples for viral pathogens (e.g., norovirus, adenovirus).

Despite some extensive data collection and reporting measures across papers, most data types, reporting methods and outcomes were not homogenous. Consequently, meta-analysis and meta-regression on contaminant concentrations had to be limited, restricting our ability to summarize data by factors such as source water type, study design, sampling time, or month or season of data collection. Our meta-regression analysis, for example had low sample sizes in our models due to limited availability of data on output and control variables. For instance, only one paper discussed the differences between dug/bored wells and drilled wells (Pieper et al., 2015b). Therefore, we did not evaluate the effects of well type and similar categorical data in our meta-analysis. Though we prespecified comparing reported drinking water quality outcomes across seasons, in our data extraction phase we observed that too few papers reported the month or time of year when data collection occurred, so we were unable incorporate seasonality into our meta-analyses or meta-regression.

Similarly, though our review primarily sought to understand the existing body of public health research on drinking water related outcomes, there were too few papers reporting this type of data sufficiently for meaningful interpretation. Despite some reported measures of association for health outcomes in some studies, the exposures, outcomes, and reporting methods were too disparate to summarize succinctly. Given the relatively small number of studies with sufficiently similar health outcomes we did not attempt to assess publication bias or small study effects.

With regard to revised SDWA guidelines, although we were able to contextualize changing EPA MCLs with regard to current and expected limits for PFAS, there were not enough eligible papers which reported on contaminants associated with notable revisions to EPA MCLs during the study period (e.g., arsenic) to attempt to assess SDWA changes and associated concentrations over time.

In addition, it is worth noting that in several studies specific populations were targeted for sampling recruitment due to higher susceptibility to contamination caused by close proximity to known pollutant point sources (Hughes et al., 2005b; Kitto and Kim, 2005; Wigginton et al., 2007; Pieper et al., 2015b; Pieper et al., 2018). Kitto et al., for example only studied groundwater wells located in an area with anomalously high levels of uranium and ^{210}Pb (Hughes et al., 2005b). The drinking water concentrations for uranium extracted from this paper heavily influenced our results for this contaminant, since the sample mean from this paper was >3 times above the EPA MCL (Hughes et al., 2005b). Similar biases for lead and MCHM concentrations may have been present in sampling campaigns whose households were willing to enroll due to past histories with drinking water issues or exposures to contamination events (Pieper et al., 2018; Whelton et al., 2015). Targeting suspected “problem areas”, though it renders the information less generalizable, does potentially highlight sub-regions or populations that would benefit from further water treatment and/or targeted examinations of health outcomes.

Due to the heterogeneity of the outcomes of interest for our meta-analysis, we used a modified risk of bias approach by developing our own criteria index. User created indexes present their own limitations however, since they are not validated against well-established methods similar to other risk of bias evaluation tools. Altering the indexes could easily result in overestimations or under estimations for risk of bias across studies. For a list of additional, publication-specific, issues and limitations see SI Text S3.

5. Conclusion

Overall, after conducting a comprehensive systematic review, based on the number and quality of eligible studies identified, we could not reach clear conclusions about the state of water quality, or its impacts on health, in any of Appalachia's subregions. Given increasing national interest in understanding and addressing persistent regional water-related inequities, our review demonstrates that more research on environmental health disparities in rural Appalachia is needed generally, and particularly with regard to drinking water source quality under typical baseline conditions (i.e., rather than post-industrial release or emergency), perceptions of drinking water safety (including trust and distrust of utility-supplied water where available), and associated use of, or reliance on, bottled water as a primary of drinking water source. The relatively limited number of epidemiologic-based research studies identified in our review was both notable and surprising given existing regional health disparities suspected to at least partly be attributable to environmental exposures. Systematic identification of key adverse waterborne exposures and subsequent health risks are therefore critical for the development of regional strategies to reduce water related health disparities within Appalachia. Consequently, we believe more epidemiologic research is needed to understand contaminated water sources, exposures, and potentially associated health outcomes in Appalachia, and in Central Appalachia especially.

CRediT authorship contribution statement

Amanda Darling : Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Hannah Patton :** Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Md Rasheduzzaman :** Formal analysis, Investigation, Methodology, Writing – review & editing. **Rachel Guevara :** Data curation, Investigation, Validation. **Joshua McCray :** Data curation, Investigation, Validation. **Leigh-Anne Krometis :** Methodology, Writing – original draft, Writing – review & editing. **Alasdair Cohen :** Conceptualization, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data used and reported in this paper are provided in the Supplementary Data excel file.

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Appendix A. Supplementary data

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