Science of the Total Environment 999 (2025) 180309

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Personalised estimates of dosage within a population-based cohort suggest limited evidence that drinking water chemistry modulates health outcomes

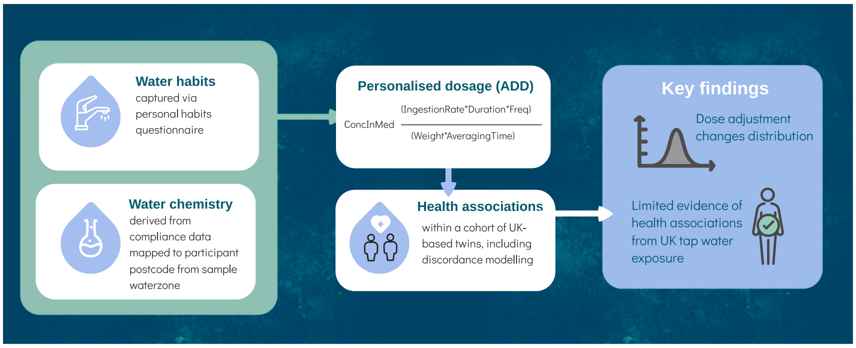
Ruth C.E. Bowyer [a,*], Daniel N. Schillereff [b], Matthew J. Ascott [c], Lauren Giles [d], Maria Paz García [a], Genevieve Lachance [a], Mary Ni Lochlaínn [a], Claire J. Steves [a], Daren C. Gooddy [c,e,f]

[a] *Department of Twin Research and Genetic Epidemiology, King's College London, London SE1 7EH, UK*
[b] *Department of Geography, King's College London, Bush House North East Wing, Aldwych, London WC2B 4 BG, UK*
[c] *British Geological Survey, Maclean Building, Benson Lane, Crowmarsh Gifford, Oxfordshire OX10 8BB, UK*
[d] *Scientific Computing Department, Science and Technology Facilities Council, Rutherford Appleton Laboratory, Harwell, Didcot OX11 0QX, UK*
[e] *Lancaster Environment Centre, Lancaster University, Lancaster LA1 4YQ, UK*
[f] *UK Centre for Ecology and Hydrology, Maclean Building, Crowmarsh, Oxfordshire OX10 8BB, UK*

HIGHLIGHTS

- Drinking water habits differ individually; exposure estimates should consider this.
- Personalised dosage adjustment significantly changes observed solute distributions.
- Limited evidence that UK tap water composition associates with health outcomes.

GRAPHICAL ABSTRACT



ABSTRACT

Access to clean drinking water is crucial for human health, but there are concerns that consumption levels of particular solutes may be linked to negative health outcomes. Many studies use data aggregated to area-level to assess consumption-health associations, but these do not account for differences in behaviour between individuals. Therefore, we combined publicly reported tap water chemistry from compliance data with estimated drinking water consumption within the home calculated from a water habits survey for 1970 UK adults from the TwinsUK cohort. The resulting average daily dose (ADD) estimate of key solutes (including nitrate, hardness, chlorine, selenium), multiple solutes dimensionally reduced to k-means clusters, and ingestion rate (IngR) were used as predictors in nested regression analysis, including stratification for employment status (as a proxy for time spent and home) and adjustment for age. Health outcomes included cardiovascular disease (CVD), CVD risk factors, eczema, sarcopenia, frailty, gastrointestinal disease and cancer. We found estimation of ADD significantly changed the distribution of solutes (ks-tests $p < 0.001$). Overall, we identified few associations with health outcomes, with mixed or inconsistent signals across nested models. There were some exceptions, including increased odds of hardness predicting CVD risk factors in our employment strata (Hardness ADD OR:1.25, 1.09–1.48, $p < 0.002$; age-adjusted OR: 1.22, 1.05–1.4, $p < 0.002$) and eczema negatively associated with IngR in non-stratified models (IngR OR: 0.86, 0.77–0.96, $p < 0.01$). We found no evidence of

---

[*] Corresponding author.
E-mail address: ruth.c.bowyer@kcl.ac.uk (R.C.E. Bowyer).

https://doi.org/10.1016/j.scitotenv.2025.180309
Received 12 June 2025; Received in revised form 29 July 2025; Accepted 19 August 2025

difference in ADD in twins discordant for health outcome. The lack of significant findings in solute-health pairings could be inferred as a positive result that supports UK drinking water as a safe source of hydration and therefore our results represent a positive public health outcome. Our study demonstrates an effective approach to estimate personalised exposure to water solutes that can inform researchers designing similar studies.

1. Introduction

Access to clean drinking water is crucial for human health. Tap water contains many key nutrients (Olivares and Uauy, 2005) but there are concerns that excess consumption may be linked to negative health outcomes (for literature review of water-health associations, please see Table S1). Many studies use data aggregated to area-level to assess findings (e.g. Maheswaran et al., 1999; Richards et al., 2022; Schullehner et al., 2018; Temkin et al., 2019; Theisen et al., 2022), which has the advantage of large numbers, but these are often inconclusive, continue to recommend that more research is needed, and that personalisation of dosage estimate is essential.

Improving the assessment of exposure from drinking water for individual people is frequently highlighted as a vital next step. Knowing the chemical composition of a drinking water sample differs from knowing the intake volumes for individuals in a population and how much of a given water solute each person ingests. Catling et al., 2008 called for concerted efforts to accurately measure individual consumption of minerals. Similarly, Ward et al., 2018 emphasised that estimates of exposure through drinking water in specific locations – in the home, at work – were needed. This is borne out by the water consumption literature that reports daily tap water consumption can vary between 0.5 L and 2.5 L/day (Elmadfa and Meyer, 2015; Schillereff et al., 2024).

We present an innovative study to explore the associations between multiple health outcomes and individual exposure from drinking water. We combined a publicly reported tap water chemistry compliance dataset for England and Wales (Ascott et al., 2019) with estimated drinking water consumption within the home calculated from a water habits survey for 1970 adult UK twins. We integrated detailed, historical health data for each participant to generate personalised dosage estimates. Health outcome – solute pairings were selected based on a comprehensive literature search (see Table S1). Given drinking water solutes are not consumed in isolation, and their concentration is often correlated (e.g. chlorine and Tri Halo Methanes; Brown et al., 2011) we also investigated associations following clustering of drinking water variables. The health outcomes selected were: cardiovascular disease, eczema, sarcopenia, frailty, gastrointestinal disease and cancer. Our study demonstrates a successful approach and key considerations in estimating personalised exposure to water solutes, with discussion of the benefits and limitations for researchers designing similar studies.

2. Materials & methods

2.1. Participants

The Department of Twin Research and Genetic Epidemiology at St. Thomas' Hospital, King's College London (KCL), hosts TwinsUK, the UK's largest adult twin registry. The adult participants consist of 16,000 monozygotic (MZ) and dizygotic (DZ) twins aged between 18 and 100 years. Since 1992, active twins have participated in both questionnaire and clinical visits, where multiple samples and physical measures were obtained, resulting in extensive health and multiomics data. Members of the TwinsUK research team have been focusing extensively on dietary influences on health for several years (Leeming et al., 2022) with growing consideration of drinking water consumption (e.g., Bowyer et al., 2020). We have recently executed the first study to directly quantify water consumption patterns by administering a recall questionnaire amongst the TwinsUK cohort (Schillereff et al., 2024).

2.2. Calculating daily water ingestion using a recall questionnaire

The tap water questionnaire design is adapted from the validated fluid diary of Johnson and colleagues (Johnson et al., 2017; Nyström et al., 2017). Individual water consumption was quantified as follows: respondents were asked to reflect on the previous seven days and tally how many portions of water of pre-set volumes from their household tap they consumed for drinking and cooking in a typical day. Hot and cold drinks were tallied separately. Further detail on ingestion rate derivation, along with detail on the administration, response rates and descriptives of our questionnaire, along with a copy of it, are all available within Schillereff et al. (2024). The questionnaire was sent to 4821 potential participants in the UK via email. This number represents twins from the full cohort who had previously granted permission to be contacted for research questionnaire purposes via email. We linked each respondent's completed survey to their demographic and socioeconomic characteristics and personal health data held within the TwinsUK repository.

2.3. Tap water chemistry

To calculate average daily dosage of multiple water solutes for each participant within our study, we combined variables calculated from the water questionnaire with water chemistry data reported by the 27 water utilities that supply drinking water across England and Wales. Drinking water chemistry is actively measured for regulatory compliance. Water companies must submit results to the Drinking Water Inspectorate at regular, pre-set intervals and these data are publicly available online. The Drinking Water Directive covers 55 water parameters. A further group of non-regulated solutes, including several commonly relevant to our study including calcium (Ca) and magnesium (Mg), are measured at certain times and by some water companies, but reporting is inconsistent.

Ascott et al. (2019) performed the first national-scale assessment of drinking water compliance data and identified distinct spatial clustering in water chemistry across England and Wales. Our study re-uses the data and clustering approach from Ascott et al. (2019). Their full methodology is described therein. In brief, they downloaded the 2015 water quality compliance report for every water supply zone from each water company supplying England and Wales. A water supply zone is a defined area comprising up to 100,000 people. Concentrations for each chemical parameter were manually extracted from the reports and collated in a local database.

The water compliance data were obtained for 2015. Although the reporting requirements are set in legislation, the format and availability of these reports differ between water companies. It is therefore hugely laborious to collate reports for all 1539 water supply zones on an annual basis. As our water questionnaire was distributed in 2022, it is possible that water composition had changed over those intervening seven years. We evaluated these effects in two ways. First, a spot comparison between the samples reported in Bowyer et al. (2020) and Ascott et al. (2019) revealed little fluctuation (see supplementary material S2). For this present study, we downloaded new compliance reports for year 2023 for the 100 most populous water supply zones of the UK's five largest water companies where there were ≥ 3 participants located. For these 100 Water Supply Zones, we (1) correlated the concentrations in 2015 and 2023 for the 16 water quality parameters reported by Ascott et al., (2) compared the means and (3) compared the distributions.

2.4. *Estimating individual ingestion dosages from water compliance data*

To maximise data for cluster input, in addition to our hypothesised pathways (Table 1), we further selected a wider range of solutes. We chose solutes based on three criteria: (i) reported by the five largest water companies; (ii) were used in the original analysis by Ascott et al., 2019 and/or (iii) solutes we highlighted specifically for their hypothesised associations with health outcomes (see Table 1): aluminium, ammonium, antimony, arsenic, benzene, boron, cadmium, chloride, chromium, copper, cyanide, fluoride, free chlorine, magnesium, manganese, mercury, nickel, nitrate, phosphorus, selenium, simazine, sodium, sulphate, Tri-halo methanes (combined, THMs) and total organic carbon (TOC). We additionally considered conductivity, hardness (converted where otherwise reported to Ca), turbidity and pH. We assigned estimated values of exposure to each individual based on the water supply zone(s) they had reported their home address as being in during the 20 years preceding the survey. We demonstrated in earlier work (Bowyer et al., 2020) good agreement between water chemistry reported within compliance data and water measured directly from individuals' household tap.

We calculated the average daily dose (ADD, mg/kg-day) for the water solutes of interest for each respondent using the US Environmental Protection Agency protocol (U.S. EPA. Guidelines for Exposure Assessment, 1992), using the following formula:

$$\mathrm{ADD} = \mathrm{Cmed}^{*}\ \left((\mathrm{IngR}^{*}\ \mathrm{ED}^{*}\ \mathrm{EF})/(\mathrm{BW}^{*}\ \mathrm{AT})\right) \qquad (1)$$

where Cmed is the concentration of the contaminants in medium (mg/L), IngR (L/day) is the ingestion rate, estimated from response to tap water questionnaire habits survey (see Schillereff et al., 2024), ED is the exposure duration (years) and EF is the exposure frequency (days/year), BW is body weight in kilograms, and AT is the averaging time (days).

Table 1
Summary of health outcomes captured and their hypothesised association with tap water exposures based on literature review (please refer to Table S1).

Health outcome	Phenotypes captured	Hypothesised association with tap water exposure
Cancer	Bladder, brain, breast, cervical, colonic, kidney, lung, oesophageal, ovarian, prostate, uterine and other cancer, lymphoma, leukaemia and skin melanoma	Increased likelihood associated with high exposure to THMs and nitrate
Cardiovascular disease (CVD)	Congestive heart failure, angina, atrial fibrillation, coronary heart disease, congenital heart disease	Increased likelihood associated with high exposure to nitrate Decreased likelihood associated with high exposure to hard water
Cardiovascular risk factor	Hypertension, high cholesterol, heart murmur	Increased likelihood associated with high exposure to nitrate Decreased likelihood associated with high exposure to hard water
Eczema	Eczema	Increased likelihood associated with presence of high exposure to hard water
Gastrointestinal disease	Ulcer, polyps, diverticular disease, gall stones	Nitrate is positively associated with health unless converted to nitrite; chlorine exposure disrupts the gut microbiota
Frailty	38 domains of health and disease relating to ageing resilience	Frailty is associated with environmental exposures over genetic
Sarcopenia	Age-related loss of muscle	Decreased likelihood associated with presence of high exposure to hard water and selenium

To calculate ED, we considered all individuals who had reported their living addresses for the last 20 years (as captured by our water questionnaire) and mapped this to the corresponding water supply zone. ED was therefore the corresponding number of years they lived in that particular water supply zone, with all individuals having the cumulative exposure calculated for the last 20 years. EF was set to 365 for all participants, and AT was 7300 (20 years of 365 days). As our questionnaire only captured drinking habits within the home, we did not include adjustment here for time spent within or without the home, which does consequently limit the accuracy of this estimate. We partially address this by stratification; see statistical methods for further detail.

To handle missingness within the water solutes data, we used nonparametric missing value imputation using random forest via the missForest package (Stekhoven and Bühlmann, 2012), considering all data available, with 50 iterations and 500 trees. Simazine, phosphorus and magnesium were removed at this stage as they were $> 50\ \%$ missing in our dataset. Individuals with reported quantities $>$4SD of the mean for ingestion rate were considered as reporting-errors or spurious and removed from analysis. Correlations of ADD-adjusted solutes and estimates unadjusted for consumption (i.e., from compliance data, ‘Cmed’) were assessed using ‘complete linkage’ hierarchical clustering via the ‘corrplot’ package (v. 0.92, Wei and Simko, 2024) and for the selected solutes (free chlorine, hardness, nitrate, selenium, THMs).

2.5. *Health outcomes*

We used existing, historically collected, self-reported and clinic data to derive targeted health outcomes where available for each respondent (Table 1). Cardiovascular disease (CVD), CVD risk factors, eczema, cancer and gastrointestinal (GI) disease were all derived from answers to the question: ‘Has a doctor ever told you that you have/had any of the following conditions?’. Composite variables capturing similar conditions as a data reduction strategy were scored 1 for the presence of the disease and 0 for the absence. Frailty represents a measure of susceptibility to stressor events and is the age-associated accumulation of health deficit. We use a Rockwood derivation (Searle et al., 2008) of the Frailty Index, capturing 38 self-reported domains of health and disease. The latest available data were used (to 2020). Sarcopenia is the age-related loss of muscle and was captured at clinic visit, and defined as a binary variable (sarcopenia or no sarcopenia) based on EWGSOP2 cut-off values (Cruz-Jentoft et al., 2019). The muscle mass component was measured using DXA (Hologic Bone Densitometer QDR Horizon W, Serial Number 200884),

2.6. *Statistical analysis*

In addition to directly using the ADD-adjusted solutes as indicated in Table 1, we hypothesised that a composite measure of water consumption would provide a useful exposure measure for health outcomes. We replicated the clustering approach of Ascott et al. (2019) for our dataset of solutes from compliance data mapped to individuals, for both the unadjusted and adjusted measures. All variables were scaled prior to clustering via k-means with 10,000 starts. Centre numbers were estimated from scrutiny of elbow and silhouette plots via the ‘factoextra’ package (Kassambara and Mundt, 2020).

To understand associations with health outcomes, we used a stepwise approach. Binary health outcomes were analysed using poisson logistic regression, whereas frailty was analysed via linear regression, with frailty root-normalised prior to inclusion. Our tap water intake questionnaire focused on water consumed *within the home,* to be able to accurately map it to water supply zones. For this reason, we applied a crude stratification for individuals who were employed (and those more likely to spend time within the home. We therefore: 1. Analysed each health outcome in univariate models with the following predictors: ADD cluster membership, Cmed cluster membership, consumption of water

(IngR) and the individual ADD-adjusted solutes hypothesised as predictors (see Table 1); 2. Each health outcome in models of Cmed cluster membership adjusted for IngR (ADD solutes already consider this implicitly); 3. Models in 1 and 2 repeated, but stratified by employment status (Retired, fulltime caregiver, unemployed, homemaker vs employed and self-employed; hereafter referred to as 'retired' and 'employed' strata), as a crude reflection of the time likely to be spent within the home; 4. Repeating the stratification in 3, but age adjusted. Where ADD or Cmed cluster were used as the predictor, the cluster with the largest membership was taken as the reference. We considered the number of independent tests to be twenty-five (stratified and adjusted models are not considered in this count) and therefore set an a priori significance threshold of $0.05/25 = 0.002$.

3. Results

3.1. Evaluating temporal stability of UK drinking water

We evaluated compliance data mapped to our participants (sample year 2015) with more recent data. For each water quality parameter, the concentrations in 2023 were significantly correlated with the concentrations in 2015 ($p < 0.01$ for all parameters, median correlation coefficient $r = 0.80$, see Fig. 1). Concentrations in 2023 were slightly higher than in 2015, although the relationship between 2015 and 2023 concentrations was still relatively close to 1:1 (for all parameters, median gradient of linear regression slope between 2015 and 2023 concentrations = 0.78). The data for all parameters were non-normal in both 2015 and 2022 ($p < 0.01$, Shapiro-Wilk test). For each water quality parameter, variances were not significantly different between 2015 and 2022 ($p > 0.01$, F test) with the exception of nickel, ammonium, antimony and selenium ($p < 0.01$, F test). There were no significant differences in mean concentrations of 7 (Total trihalomethanes, pH, total organic carbon, chloride, chlorine, nickel, nitrate) of the water quality parameters between 2015 and 2022 ($p > 0.01$, Wilcoxon rank sum test with continuity correction). Except for nitrate ($p = 0.05$) and pH ($p = 0.19$), there were significant differences in the distributions of concentrations of the 14 water quality parameters between 2015 and 2022 ($p < 0.01$, ks-test).

This analysis suggests that whilst there may be differences in the means and distributions of individual water quality parameters between 2015 and 2023, the overall spatial variability in concentrations between water supply zones (as indicated by the correlation analysis) remains broadly the same between 2015 and 2023.

3.2. Mapped compliance data

Compliance data was mapped to 1970 participants who responded to the water questionnaire, whose postcodes could be mapped within England and Wales for the last 20 years and who had response data for at least one of the desired health outcomes (Table 2). Of these, 1865 individuals had data available on their likely employment status for inclusion in stratified analysis (see methodology). Included participants were located across the study area, including pairs of twins living in different Water Supply Areas (Fig. 2).

3.3. Differences in exposure estimated by concentration and by ADD

Fig. 3a demonstrates the correlation between solute concentrations extracted from the compliance sampling data and adjusted for consumption (ADD). As would be expected given the former feeds into the latter, there is high correlation between the different variables (Fig. 3a). However, paired non-adjusted and adjusted solutes were not 1:1 (e.g.

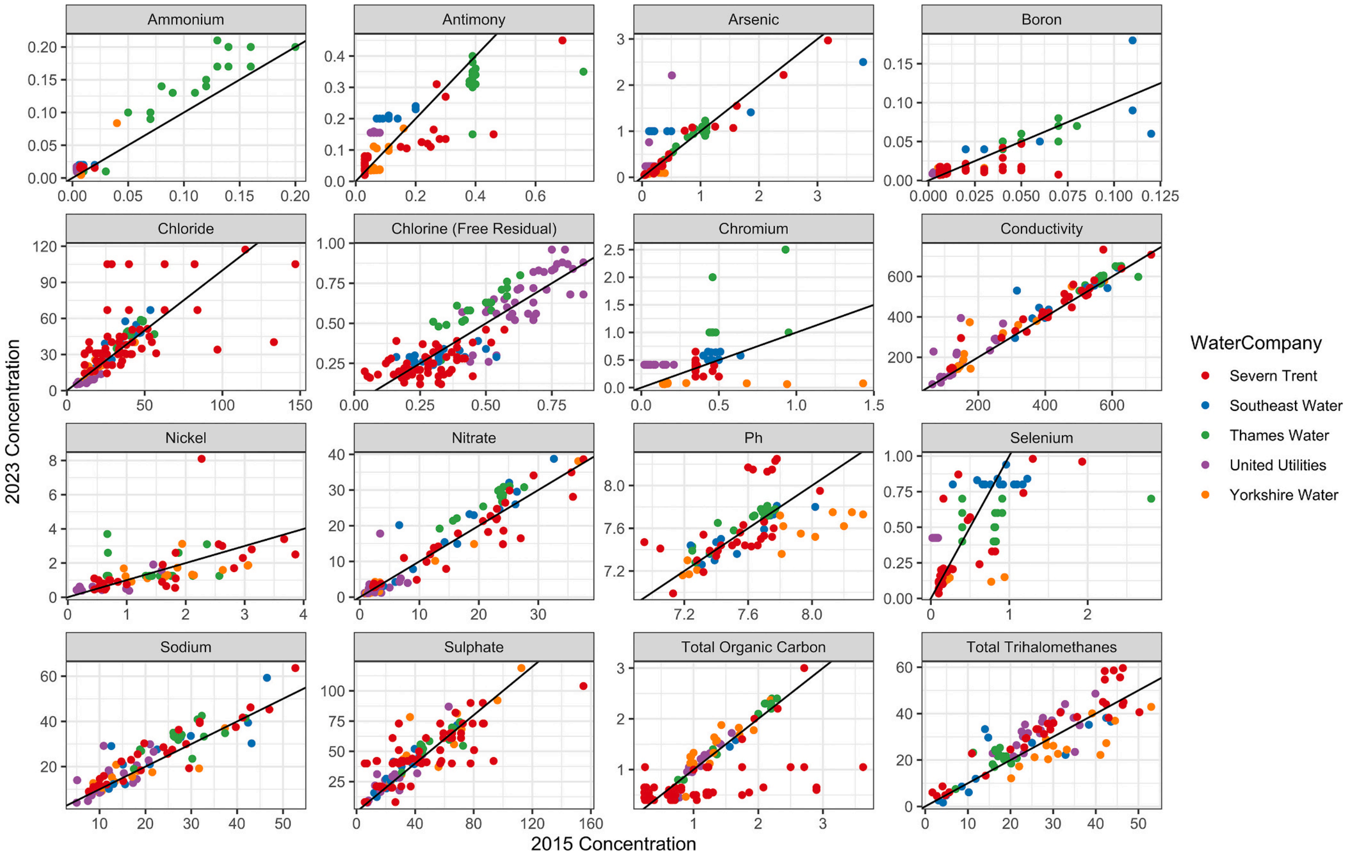


Fig. 1. Concentrations of water quality parameters from 2015 and 2023 for 100 most populous WSZs in the five largest UK water companies with ≥ 3 participants used in this research.

Table 2
Descriptive statistics of a. all participants ($n = 1970$), and by employment strata, and b. by health outcome.

2a.	N	Complete twin pair (n, % MZ)	Age, years ($\bar{x}$, σ)	Sex (F, %)	IngR L/d ($\bar{x}$, σ)
Full sample	1970	512 (67.6)	60.4 (14.1)	1764 (89.3)	2.5 (1.1)
Employed	854	155 (75.2)	50.5 (13)	775 (90.8)	2.4 (1.1)
Retired	1011	222 (65.3)	69.3 (7.6)	903 (89.3)	2.6 (1.1)

2b.	n	Complete twin pair (n, % MZ)		Age, years ($\bar{x}$, σ)		Sex (F, %)		IngR L/d ($\bar{x}$, σ)		Employed (n)	Retired (n)
Cancer Controls	1644	361	68.4	59.1	14.4	1465	89.1	2.4	1.2	766	782
Cases	295	23	73.9	67.6	9.2	270	91.5	2.5	1.1	74	212
CVD Controls	1530	328	68.3	58.4	14.3	1371	89.6	2.5	1.2	739	709
Cases	128	8	87.5	71	9.2	112	87.5	2.5	1.1	25	99
CVD RF Controls	1785	418	68.7	59.7	14.3	1597	89.5	2.4	1.1	806	893
Cases	82	4	75	68.7	8.2	71	86.6	2.6	1.2	19	53
Eczema Controls	483	49	71.4	61.9	12.8	452	93.6	2.6	1.1	204	257
Cases	252	21	76.2	55.6	15.8	230	91.3	2.3	1.1	137	103
Frailty FI < 0.25	1288	264	70.8	57.4	14.5	1132	87.9	2.4	1.1	655	570
FI > 0.25	671	91	65.9	66.4	11.1	621	92.5	2.5	1.2	191	438
GID Controls	1321	254	71.3	58.3	14.8	1173	88.8	2.5	1.1	642	608
Cases	406	40	75	66.1	10.1	366	90.1	2.5	1.2	117	271
Sarcopenia Controls	1039	279	64.2	69.2	6.1	925	89	2.5	1.1	208	791
Cases	73	6	66.7	72.5	6.9	66	90.4	2.5	1.2	11	59

hardness Pearson's correlation = 0.68, $p < 0.01$), suggesting (as observed in Schillereff et al., 2024) that behaviourally driven differences in tap water consumption are likely influenced by the composition of that tap water. This changes the distribution of many of the variables observed within our sampling, such as water hardness (Fig. 3b). When clustering our variables via k-means, we found a two-cluster solution to best fit the ADD variables, and a five-cluster solution to best fit the concentration data (see supplementary Figs. S1 & S2); cluster 2 represented the greatest number of individuals ($n = 713$) and so was releveled as the reference category in regression analysis. Two-sample Kolmogorov-Smirnov tests of key solutes adjusted and unadjusted (Fig. 3b) were all significant ($p < 0.0001$).

3.4. Associations with tap water composition and health are limited within our cohort

We found limited associations with health outcomes in our sample, with results inconsistent across stratified models, and few of our results passed multiple-testing correction ($p = 0.002$). Here, we report the modest results we did observe, without multiple-testing threshold applied. These results are summarised in Fig. 4. Cluster 3 of the Cmed solutes, characterised by increased levels of THMs, manganese, aluminium and chlorine compared to other cluster (Supplementary Fig. S2), and cluster 5, characterised by lower amounts of dissolved solutes, predicted a significant, increased odds ratio for CVD compared with other clusters in the employed strata in adjusted and unadjusted models (Employed strata, Cmed-3, OR: 5.52, 0.76–28.29, $p = 0.049$; Cmed-5, OR: 3.27, 1.17–11.52, $p = 0.037$; employed strata, age-adjusted, Cmed-3, OR: 5.69, 0.79–29.19, $p = 0.045$, Cmed-5 OR: 1.09, 1.05–1.13, p = 0.03). However, this association demonstrate very wide confidence intervals was not replicated in unstratified models, or within the retired strata (see Fig. 4).

Within the employed strata, both ADD-adjusted Nitrate and ADD-adjusted hardness predicted greater odds for cardiovascular risk factors (Nitrate ADD: OR: 2.19, 1.04–4.32, p = 0.03; Hardness ADD OR:1.25, 1.08–1.41, $p < 0.002$) but not the retired strata. Inclusion of age within these stratified models moderately modified the significance of these variables (Employed strata, Nitrate ADD: OR: 2.23, 1.04–4.5, p = 0.03; Employed strata, hardness ADD: OR: 1.28, 1.09–1.48, p < 0.002). The modest trend was reflected in the non-stratified models but were not significant (nitrate ADD OR: 1.02, 1–1.03, $p = 0.07$; hardness ADD OR:1.0, 1–1.01, $p = 0.1$). The observed association with hardness is the opposite direction to that hypothesised. We found ingestion rate (IngR) to be negatively associated with eczema in the non-stratified models (IngR OR: 0.86, 0.77–0.96, $p < 0.01$), although this was only tentatively replicated within the employed strata (Employed OR: 0.86, 0.77–0.96, $p = 0.055$), with this association further modified with age-inclusion (Employed, age adjusted IngR, OR: 0.88, 0.75–1.018, $p = 0.08$). Odds of sarcopenia were reduced in association with ADD-cluster 2 in unadjusted models (ADD-2, OR: 0.5, 0.27–0.86, $p = 0.019$) but there was only a moderate suggestion of association within the retired strata (ADD-2, retired, OR: 0.54, 0.27–0.98, $p = 0.054$) with age-adjusted results suggesting this was partly due to age (ADD-2, age-adjusted, retired, OR: 0.57, 0.29–1.04, p = 0.08). Similarly, there was a trend of Cmed-3 predicting greater odds of sarcopenia in retired individuals. There were too few individuals within the employed strata who had sarcopenia when split across the five clusters of unadjusted solutes for these odds to be estimated. Finally, there was a non-significant suggestion of ingestion rate positively predicting frailty in linear regression (Unadj, beta = 0.042, $p = 0.065$), and across the retired strata (Retired, beta = 0.056, $p = 0.074$; age-adjusted, beta = 0.059, p = 0.055).

3.5. Twin pair results

We used paired Wilcoxon rank sum tests to understand the difference of ingestion rate and hypothesised ADD solutes between twins discordant for each health outcome (Table 3). There was no significant difference between twin pairs.

4. Discussion

We have successfully demonstrated an approach to adjust national compliance sampling data to account for intra-individual differences in exposure from tap water consumption. By combining data from a self-reported drinking questionnaire and publicly reported water chemistry, our protocol provides a means to estimate individual daily dosage, as called for by recent reviews (Ward et al., 2018). Overall, we found limited evidence of significant associations between solute intake via tap water within the home and the investigated health outcomes. Many of our results show wide confidence intervals and this exploratory analysis should be interpreted with caution as a result. This could be inferred as a positive finding for UK public health on the basis that drinking water from household taps is safe regardless of consumption rate and solute composition, although more research is required.

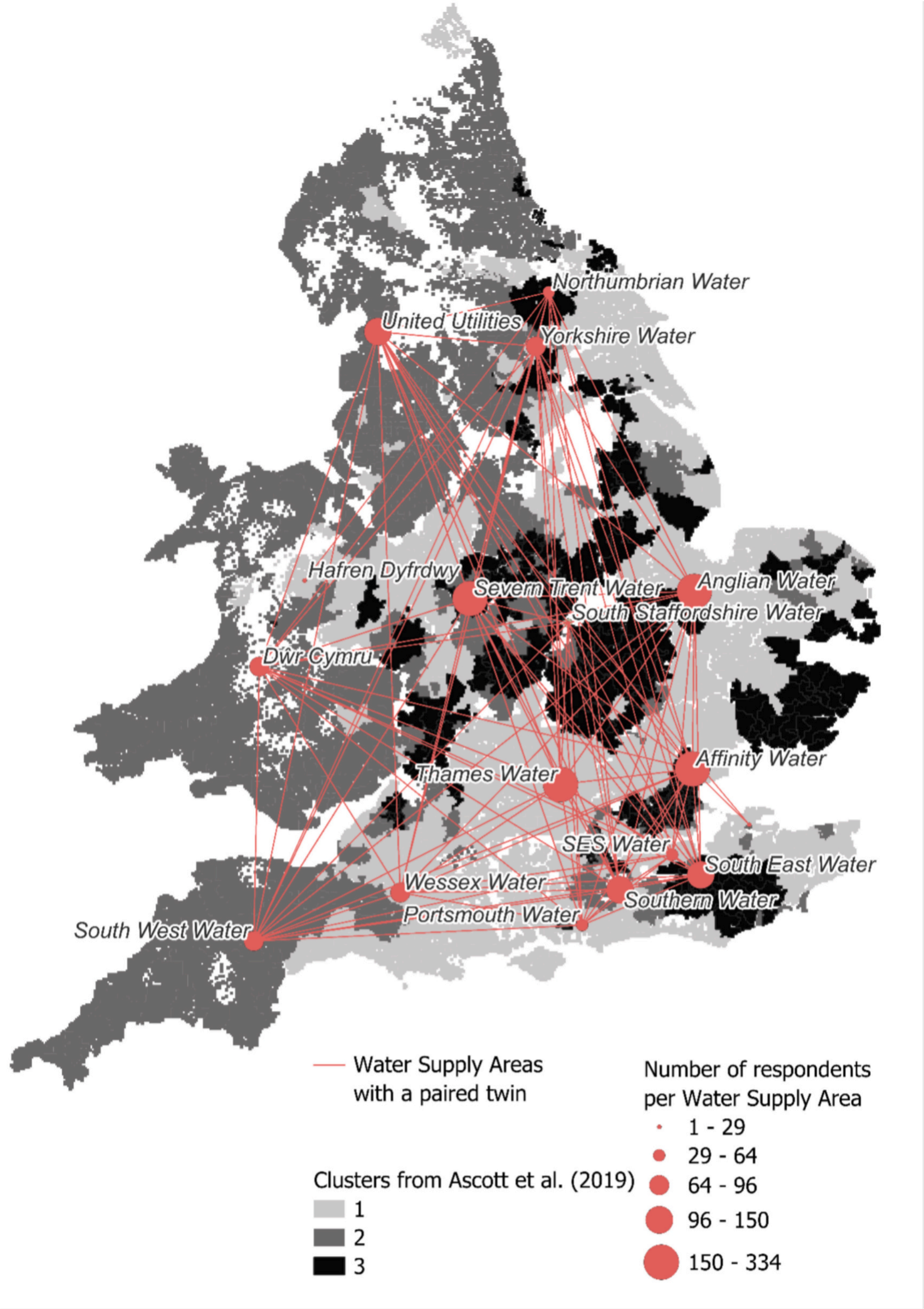


Fig. 2. A map of individuals in this subset overlaid with clusters of water composition defined in Ascott et al. (2019). The centroid for each major water supply area is labelled.

4.1. Dosage adjustment significantly affects solute distributions

We found that dosage adjustments have a significant effect on solute concentration distributions and individual estimated exposures (Fig. 2a). Our finding that ADD estimates for individual solutes in some cases correlate only moderately well with raw compliance sampling concentrations (see Fig. 2b) illustrates that dosage adjustment ought to be a key consideration in tap water - health research. Clusters also differed between ADD and non-adjusted solutes. Clusters for ADD-solutes were distinguished along a low-high dose estimate, whereas the non-adjusted subset generated five solutions (supplementary Fig. S2). Both differ from the three clusters found in Ascott et al. (2019)

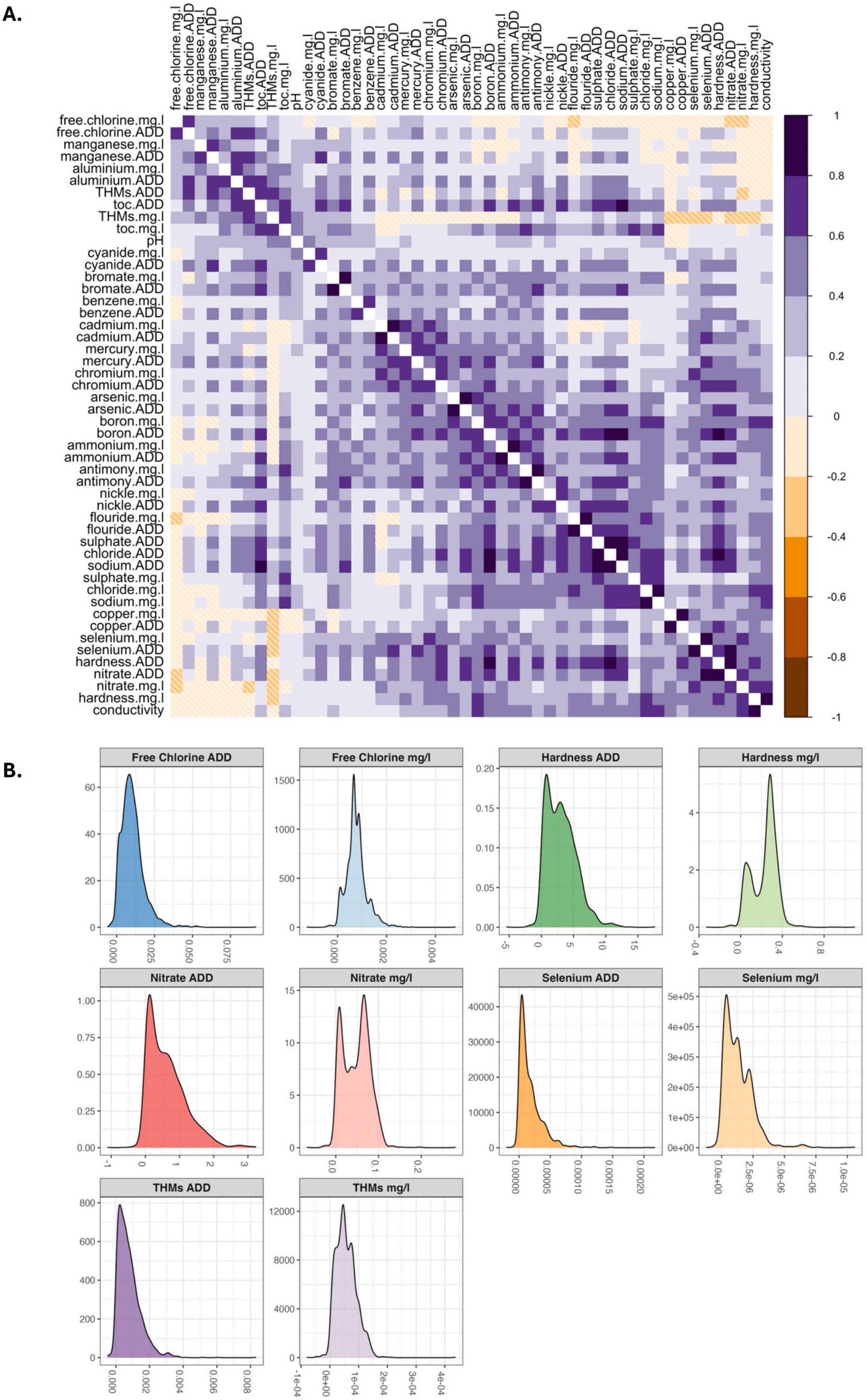


Fig. 3. a. Correlation and b. distributions of non-adjusted and adjusted (ADD) solutes.

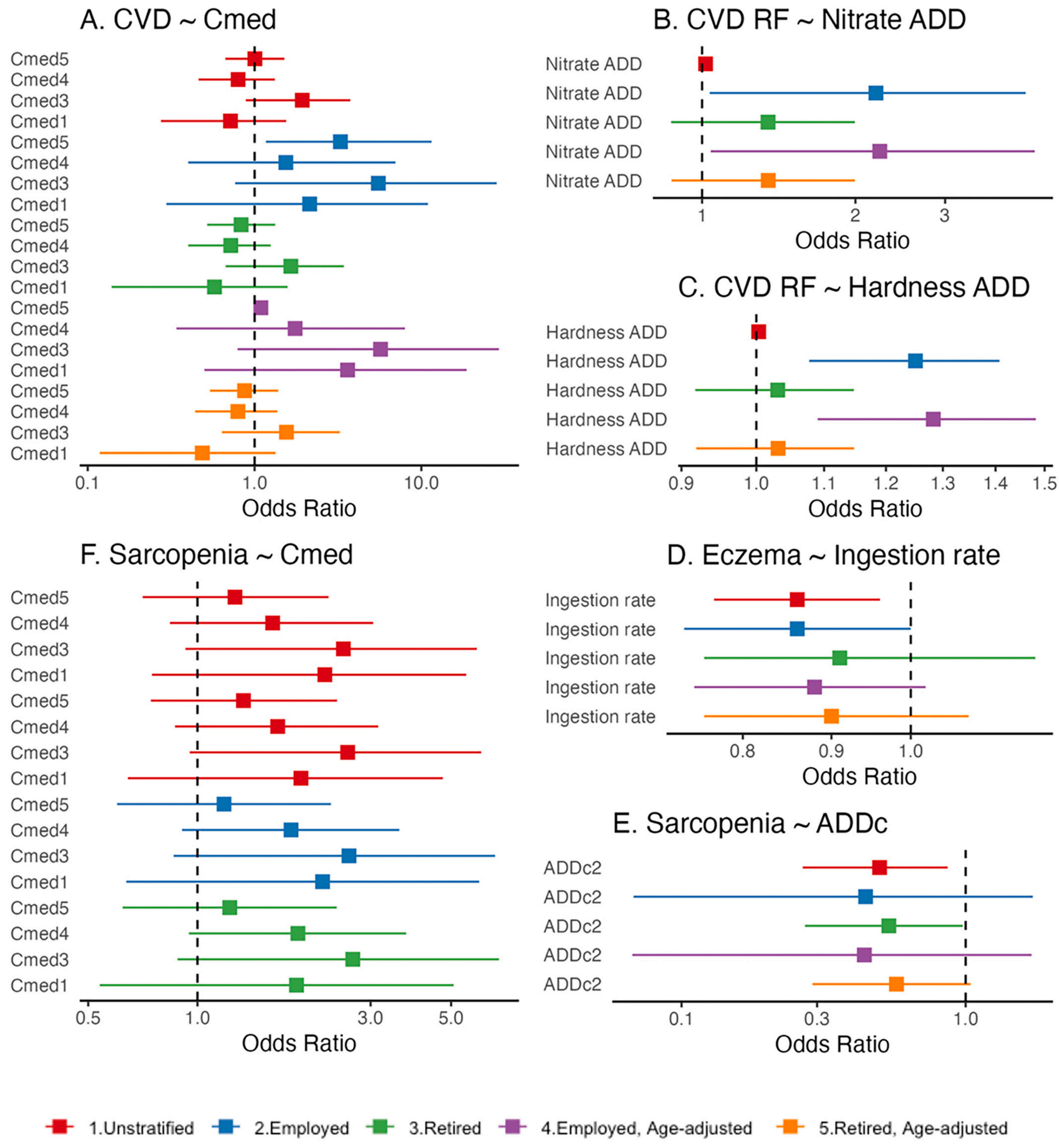


Fig. 4. Modest results of logistic regression models within outcome-exposure analysis, for a. cardiovascular disease ~ unadjusted solute cluster (Cmed), b. cardiovascular disease ~ nitrate, ADD-adjusted, c. cardiovascular risk factors ~ hardness, ADD-adjusted, d. eczema ~ ingestion rate (L/d) e. sarcopenia ~ adjusted (ADD) solute cluster, e. sarcopenia ~ unadjusted solute cluster (Cmed). For clusters of unadjusted solutes (Cmed) cluster 2 had the most participants assigned, this was taken as the reference. There were too few individuals within the employed strata who had sarcopenia when split across the five clusters of unadjusted solutes for these odds to be estimated.

as we subset to the water supply zones as mapped to our participants.

4.2. Heath associations with personalised estimates of dose

Allocating risk to specific concentrations is non-trivial. For example, studies of nitrate and health outcomes use a wide range of percentile bands for nitrate concentrations in drinking water (e.g Picetti et al., 2022; Schullehner et al., 2018; Stayner et al., 2021). Essien et al. (2022) called for more consistent dosages to be analysed. Similarly, international guidelines on risk levels of a particular solute in drinking water do differ. For example, Kozisek (2020) highlights that countries in the EU take different approaches to regulating hardness in drinking water.

Table 3
Results of paired tests for twins discordant for health outcome and drinking water related predictor. IngR = Ingestion rate, ADD = Average Daily Dose.

	N pair discordant	Predictor	Result (*p*-value)
CVD	34 of 376	IngR	0.97
		Nitrate.ADD	0.6
		Hardness ADD	0.82
CVD RF	33 of 463	IngR	0.56
		Nitrate.ADD	0.4
		Hardness ADD	0.34
Eczema	33 of 103	IngR	0.07
		Selenium ADD	0.76
		Hardness ADD	0.48
Sarcopenia	20 of 305	IngR	0.95
		Hardness ADD	0.7
		Selenium ADD	0.14
		Turbidity	0.55
Gastrointestinal disease	109 of 410	IngR	0.74
		pH	0.28
		Nitrate	0.41
		Free chlorine	0.78
Cancer	114 of 505	IngR	0.55
		Nitrate	0.71
		THMs	0.34
Frailty	28 of 516 (strict discordance)	IngR	0.58

Furthermore, baseline concentrations vary enormously between and indeed within countries due to environmental factors such as geology and historical water treatment policies. For example, nitrate concentrations in drinking water in New Zealand ranged from below detection limits (< 0.01 mg/L) to 41.8 mg/L (Lin et al., 2023).

We observed some moderate health associations with ingestion rate. This raises the important consideration that the hydrating properties of water, and the act of drinking water, simultaneously influence health outcomes and reflect health behaviour. These effects are likely to be greater than those arising purely from ingesting the UK's regulated tap water. Similarly, our finding of a lower likelihood of eczema in association with higher ingestion rate could reflect the general preference of drinking softer water (Lanz and Provins, 2016) and therefore, eczema, which is exacerbated by dermal hardwater exposure (Lopez et al., 2022), is associated with lower dietary consumption in these areas and could therefore be confounding the association. Consequently, the ADD adjustment of hardness in the corresponding model may not have been appropriate in this instance. Furthermore, the suggestion of higher ingestion rate predicting frailty (in the absence of similar associations observed with clusters/solutes) could reflect the greater amounts of time frailer older adults spend indoors.

Indeed, there are many considerations to contemplate in effectively estimating water consumption in large numbers of individuals without direct measurement. Our questionnaire purposefully considers tap water *within the home* and therefore we included a crude stratification to account for the assumed differences in time spent at home versus outside the home. Future questionnaires should capture volumes drunk outside the home and daily time diaries. Our need to stratify in this manner lowered the number of cases (individuals with a disease) within each strata and thus limited statistical power. We did not specifically recruit twins discordant for outcome, which provides a powerful case-control. We undertook a post-hoc power analysis (using G*Power) to estimate the optimum number of participants required for the modest effect sizes we observed. For ADD-adjusted hardness in the CVD risk factor paired analysis, we used the mean, standard deviation, and correlation of the discordant twin groups, along with our sample size of 66 individuals (33 discordant twin pairs), and only achieved a power of 0.48. Achieving a power > 0.80 for this variable would have required 160 individuals, or 80 matched pairs. Relatedly, our significant observations of Hardness ADD and CVD risk factor within the employed strata are likely due to the low number of individuals within this group (19 of 832). Given our need to stratify (see Methods), and assuming similar differences in means, we were likely underpowered in the cross-sectional analysis for CVD, CVD risk factors, eczema, and sarcopenia.

4.3. Strengths and limitations

There are some strengths to our approach. Firstly, we computed individual exposure levels to multiple solutes for 1970 participants. Very few papers amongst the vast drinking water - health literature have been able to conduct such granular analysis (e.g., Ward et al., 2018). Leurs et al., 2010 is one of the few to calculate individual exposure from a dietary questionnaire and found no evidence of a significant association between tap water Ca, Mg or total hardness and IHD / stroke mortality. For outcomes where some sort of risk or protective threshold exists (e.g. magnesium concentrations), knowing the percentage of the population who consume above or below said threshold is crucial but rarely known. Gillies and Paulin (1983) were amongst the first to point out that large differences in individual tap water consumption could explain the mixed results in drinking water epidemiological studies. Temkin et al. (2019) developed an exposure metric for the US population but this was model derived rather than a survey of individuals. The wide variance in tap water consumption within and between countries (Guelinckx et al., 2015; Schillereff et al., 2024) makes generalisations problematic.

Second, we were able to investigate multiple solutes and health outcomes within the same analytical framework. Many epidemiological studies involving drinking water focus on single solute – outcome pairs. That is understandable given the scale of data collection and complexity of disentangling causal mechanisms. Whilst we don't explicitly test for interactive effects of one contaminant on another, our approach will enable such investigations. Our approach addresses the requirements for adequate exposure assessment set out by Schullehner et al. (2018).

There are also some important limitations. Cohort studies such as ours are subject to selection biases and rarely representative of a population (in our case, England and Wales). Equally, the means to estimate personalised exposures, draw direct linkage of individual data to spatial datasets and access to more detailed health data (e.g. omics) are advantages over ecological studies using area-level data. Furthermore, other factors contributing to the health outcome may be spatially correlated with our measured environmental variable – water composition. This could explain our CVD risk factor associations with ADD-adjusted variables within the employed strata. This was by far the strongest signal in our analysis yet is particularly intriguing and tricky to explain because the association is opposite to previous studies. Previous work on CVD (such as heart failure, heart attack) and CVD risk factors (such as hypertension, high cholesterol and heart murmur) tends to observe hardness as protective. For example, some observed effects at high Ca and Mg concentrations or increased mortality risk under particularly low concentrations (Gianfredi et al., 2016). Results are mixed, however. Other work found no significant relation (Leurs et al., 2010), including a study of nearly 1,500,000 residents in northwest England (Maheswaran et al., 1999).

Age is likely to be key contextual factor. Whilst our previous work (Schillereff et al., 2024) showed that age is not predictive of consumption rate in stratified models, age is of course an important inclusion given that the health outcomes explored in our study are generally associated with increasing years. The opt-in nature of our cohort means that age could also confound associations. For instance, differences in age demographics by water area were not part of our spatial sampling design (supplementary figure). Whilst many within-strata observations were only moderately attenuated by the inclusion of age, it ought to be a key consideration for researchers adapting similar sampling strategies.

Some of our health outcomes could reflect small, chronic effects that are hard to detect. For example, Schullehner et al., 2018 flag the need for long-term studies with large populations to assess links between nitrate and colorectal cancers. Whilst our study advantageously made use of detailed historical health data and changing estimates of exposure from postcode histories, we did not have historical data on either water compliance sampling nor drinking habits. Collecting an intra-individual measure of changes in ingestion rate with age could be a powerful addition to this work. Furthermore, we used aggregated, binarized health measures. In future, using health outcomes that reflect more variance in health (e.g. continuous biomarkers) could reveal associations not captured here, and permit a more detailed study of the underlying biological mechanisms.

Our calculations of individual consumption are still dependent on spatial accuracy. Compliance data are reported for each water supply zone, which encompass up to 100,000 people. We have not, however, measured water composition that comes out of the tap at each household. Modification by household pipes and/or beyond the final compliance monitoring point is a possibility. Pipes in the UK still contain lead, for example, and phosphorus is added to mitigate these effects (Gooddy et al., 2015). Reassuringly, a study in Sweden found a strong correlation between the chemistry at water supply works and samples measured from household taps (Rosenlund et al., 2005). Leurs et al., 2010 also highlight this concern, but point out that Mg concentrations in water is unlikely to be affected within the distribution network.

5. Conclusion

We have developed and successfully applied a method to estimate individualised daily dosage of solutes from drinking tap water for studying consumption - health outcome linkages. Adjusting for personal intake overcomes a frequent concern in the drinking water exposure literature that area-level studies do not account for differences in individuals' behaviour. Our approach integrates publicly reported tap water chemistry data for England, volumes of drinking water consumption for 1970 twins and their individual historical health records. We found, after dosage adjustment, limited evidence of significant associations to UK drinking water composition. We also found no statistical differences between twin pairs discordant for each health outcome. Considered together, these generally null results could reflect a public health success of the relative safety of drinking water in the UK, although further studies on chronic exposures and more sensitive biomarkers as health outcomes in larger, more generalisable populations are needed to confirm this. Importantly, our data do show that dosage adjustments significantly change the distribution of solute consumption. This strongly implies that future studies should take steps to account for differences in dietary exposure between individuals and across the life course.

Abbreviations and acronyms

ADD	Average Daily Dose
AT	averaging time (days)
BW	body weight (kilograms)
Cmed	the concentration of the contaminants in medium (mg/L)
CVD	Cardiovascular disease
CVD RF	Cardiovascular disease risk factor
ED	Exposure Duration (years)
EF	Exposure Frequency (days/year)
IngR	Ingestion Rate (L/day)

CRediT authorship contribution statement

Ruth C.E. Bowyer: Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Daniel N. Schillereff:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Matthew J. Ascott:** Writing – review & editing, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Lauren Giles:** Writing – review & editing, Formal analysis. **Maria Paz García:** Writing – review & editing, Resources, Project administration. **Genevieve Lachance:** Writing – review & editing, Project administration, Data curation. **Mary Ni Lochlaínn:** Writing – review & editing, Data curation. **Claire J. Steves:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Daren C. Gooddy:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Ethics statement

This study was carried out under TwinsUK BioBank ethics, approved by North West – Liverpool Central Research Ethics Committee (REC reference 19/NW/0187), IRAS ID 258513. This approval supersedes earlier approvals granted to TwinsUK by the St Thomas' Hospital Research Ethics Committee, later London – Westminster Research Ethics Committee (REC reference EC04/015), which have now been subsumed within the TwinsUK BioBank.

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.

Acknowledgements

We are very grateful to all the members of TwinsUK who participated in this study, and the supporting TwinsUK admin, clinic and laboratory staff without whom our work would not be possible. We would particularly like to thank Rajan Wignarahjah and Darioush Yarand for their values assistance in implementing the questionnaire online. We thank Katie Meehan for helpful advice on designing water surveys and for pointers to relevant literature. This study was funded in part by Natural Environment Research Council award NE/X018474/1 to DNS and RCEB. MJA and DCG were supported by the British Geological Survey via NERC national capability and publish with the permission of the Director, British Geological Survey. TwinsUK is funded by the Medical Research Council (MRC), Wellcome Leap Dynamic resilience program (co-funded by Temasek Trust), Wellcome Trust, EPSRC, BBSRC, Versus Arthritis, European Commission, Chronic Disease Research Foundation (CDRF), Zoe Ltd., the National Institute for Health and Care Research (NIHR) Clinical Research Network (CRN) and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London. For the purposes of open access, the author has applied a Creative Commons Attribution (CC BY) licence to any Accepted Author Manuscript version arising from this submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2025.180309.

Data availability

Our study makes use of personal health behaviour data and demographic characteristics for individuals. Therefore, under UK data governance laws and the data governance protocols by which ethical approval for this study was granted, our questionnaire and demographic data is only available following reasonable request to the TwinsUK Data

Access Committee. Information on data access and how to apply is available at https://twinsuk.ac.uk/resources-for-researchers/data-samples/.

References

Ascott, M.J., Stuart, M.E., Gooddy, D.C., Marchant, B.P., Talbot, J.C., Surridge, B.W.J., Polya, D.A., 2019. Provenance of drinking water revealed through compliance sampling. Environ Sci Process Impacts 21, 1052–1064. https://doi.org/10.1039/C8EM00437D.

Bowyer, R.C.E., Schillereff, D.N., Jackson, M.A., Le Roy, C., Wells, P.M., Spector, T.D., Steves, C.J., 2020. Associations between UK tap water and gut microbiota composition suggest the gut microbiome as a potential mediator of health differences linked to water quality. Sci. Total Environ. 739, 139697. https://doi.org/10.1016/j.scitotenv.2020.139697.

Brown, D., Bridgeman, J., West, J.R., 2011. Predicting chlorine decay and THM formation in water supply systems. Rev. Environ. Sci. Biotechnol. 10, 79–99. https://doi.org/10.1007/s11157-011-9229-8.

Catling, L.A., Abubakar, I., Lake, I.R., Swift, L., Hunter, P.R., 2008. A systematic review of analytical observational studies investigating the association between cardiovascular disease and drinking water hardness. J. Water Health 6, 433–442. https://doi.org/10.2166/wh.2008.054.

Cruz-Jentoft, A.J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., Sayer, A.A., Schneider, S.M., Sieber, C.C., Topinkova, E., Vandewoude, M., Visser, M., Zamboni, M., Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), the Extended Group for EWGSOP2, 2019. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48, 16–31. https://doi.org/10.1093/ageing/afy169.

Elmadfa, I., Meyer, A.L., 2015. Patterns of drinking and eating across the European Union: implications for hydration status. Nutr. Rev. 73 (Suppl. 2), 141–147. https://doi.org/10.1093/nutrit/nuv034.

Essien, E.E., Said Abasse, K., Côté, A., Mohamed, K.S., Baig, M.M.F.A., Habib, M., Naveed, M., Yu, X., Xie, W., Jinfang, S., Abbas, M., 2022. Drinking-water nitrate and cancer risk: A systematic review and meta-analysis. Arch. Environ. Occup. Health 77 (1), 51–67. https://doi.org/10.1080/19338244.2020.1842313. Epub 2020 Nov 3. PMID: 33138742.

Gianfredi, V., Bragazzi, N.L., Nucci, D., Villarini, M., Moretti, M., 2016. Cardiovascular diseases and hard drinking waters: implications from a systematic review with meta-analysis of case-control studies. J. Water Health 15, 31–40. https://doi.org/10.2166/wh.2016.131.

Gillies, M.E., Paulin, H.V., 1983. Variability of mineral intakes from drinking water: a possible explanation for the controversy over the relationship of water quality to cardiovascular disease. Int. J. Epidemiol. 12, 45–50. https://doi.org/10.1093/ije/12.1.45.

Gooddy, D.C., Lapworth, D.J., Ascott, M.J., Bennett, S.A., Heaton, T.H.E., Surridge, B.W.J., 2015. Isotopic Fingerprint for Phosphorus in Drinking Water Supplies. Environ. Sci. Technol. 49, 9020–9028. https://doi.org/10.1021/acs.est.5b01137.

Guelinckx, I., Ferreira-Pêgo, C., Moreno, L.A., Kavouras, S.A., Gandy, J., Martinez, H., Bardosono, S., Abdollahi, M., Nasseri, E., Jarosz, A., Ma, G., Carmuega, E., Babio, N., Salas-Salvadó, J., 2015. Intake of water and different beverages in adults across 13 countries. Eur. J. Nutr. 54, 45–55. https://doi.org/10.1007/s00394-015-0952-8.

Johnson, E.C., Péronnet, F., Jansen, L.T., Capitan-Jiménez, C., Adams, J.D., Guelinckx, I., Jiménez, L., Mauromoustakos, A., Kavouras, S.A., 2017. Validation Testing Demonstrates Efficacy of a 7-Day Fluid Record to Estimate Daily Water Intake in Adult Men and Women When Compared with Total Body Water Turnover Measurement. J. Nutr. 147, 2001–2007. https://doi.org/10.3945/jn.117.253377.

Kassambara, A., Mundt, F., 2020. factoextra: Extract and Visualize the Results of Multivariate Data Analyse.

Kozisek, F., 2020. Regulations for calcium, magnesium or hardness in drinking water in the European Union member states. Regul. Toxicol. Pharmacol. 112, 104589. https://doi.org/10.1016/j.yrtph.2020.104589.

Lanz, B., Provins, A., 2016. The demand for tap water quality: survey evidence on water hardness and aesthetic quality. Water Resour. Econ. 16, 52–63. https://doi.org/10.1016/j.wre.2016.10.001.

Leeming, E.R., Mompeo, O., Turk, P., Bowyer, R.C.E., Louca, P., Johnson, A.J., Spector, T.D., Le Roy, C., Gibson, R., 2022. Characterisation, procedures and heritability of acute dietary intake in the Twins UK cohort: an observational study. Nutr. J. 21, 13. https://doi.org/10.1186/s12937-022-00763-3.

Leurs, L.J., Schouten, Leo J., Mons, Margreet N., Goldbohm, R. Alexandra, van den Brandt, Piet A., 2010. Relationship between tap water hardness, magnesium, and calcium concentration and mortality due to ischemic heart disease or stroke in the Netherlands. Environ. Health Perspect. 118, 414–420. https://doi.org/10.1289/ehp.0900782.

Lin, L., St Clair, S., Gamble, G.D., Crowther, C.A., Dixon, L., Bloomfield, F.H., Harding, JE., 2023. Nitrate contamination in drinking water and adverse reproductive and birth outcomes: a systematic review and meta-analysis. Sci. Rep. 13 (1), 563. https://doi.org/10.1038/s41598-022-27345-x. PMID: 36631499; PMCID: PMC9834225.

Lopez, D.J., Singh, A., Waidyatillake, N.T., Su, J.C., Bui, D.S., Dharmage, S.C., Lodge, C. J., Lowe, A.J., 2022. The association between domestic hard water and eczema in adults from the UK Biobank cohort study*. Br. J. Dermatol. 187, 704–712. https://doi.org/10.1111/bjd.21771.

Maheswaran, R., Morris, S., Falconer, S., Grossinho, A., Perry, I., Wakefield, J., Elliott, P., 1999. Magnesium in drinking water supplies and mortality from acute myocardial infarction in north west England. Heart 82, 455–460. https://doi.org/10.1136/hrt.82.4.455.

Nyström, C.D., Henriksson, H., Alexandrou, C., Bergström, A., Bonn, S., Bälter, K., Löf, M., 2017. Validation of an online food frequency questionnaire against doubly labelled water and 24 h dietary recalls in pre-school children. Nutrients 9, 66. https://doi.org/10.3390/nu9010066.

Olivares, M., Uauy, R., 2005. In: World Health Organization (Ed.), Nutrients in drinking water: Section 4. Essential nutrients in drinking water.

Picetti, R., Deeney, M., Pastorino, S., Miller, M.R., Shah, A., Leon, D.A., Dangour, A.D., Green, R., 2022. Nitrate and nitrite contamination in drinking water and cancer risk: A systematic review with meta-analysis. Environ. Res. 210, 112988. https://doi.org/10.1016/j.envres.2022.112988.

Richards, J., Chambers, T., Hales, S., Joy, M., Radu, T., Woodward, A., Humphrey, A., Randal, E., Baker, M.G., 2022. Nitrate contamination in drinking water and colorectal cancer: Exposure assessment and estimated health burden in New Zealand. Environ. Res. 204, 112322. https://doi.org/10.1016/j.envres.2021.112322.

Rosenlund, M., Berglind, N., Hallqvist, J., Bellander, T., Bluhm, G., 2005. Daily intake of magnesium and calcium from drinking water in relation to myocardial infarction. Epidemiology 16, 570. https://doi.org/10.1097/01.ede.0000165390.18798.62.

Schillereff, Daniel, Bowyer, Ruth C., Ascott, Matthew, et al., 2024. Tap water consumption amongst a cohort of UK twins is linked to perceptions of taste and health benefits. ESS Open Archive. https://doi.org/10.22541/essoar.172070562.21295575/v1. July 11.

Schullehner, J., Hansen, B., Thygesen, M., Pedersen, C.B., Sigsgaard, T., 2018. Nitrate in drinking water and colorectal cancer risk: A nationwide population-based cohort study. Int. J. Cancer 143, 73–79. https://doi.org/10.1002/ijc.31306.

Searle, S.D., Mitnitski, A., Gahbauer, E.A., Gill, T.M., Rockwood, K., 2008. A standard procedure for creating a frailty index. BMC Geriatr. 8, 24. https://doi.org/10.1186/1471-2318-8-24.

Stayner, L.T., Schullehner, J., Semark, B.D., Jensen, A.S., Trabjerg, B.B., Pedersen, M., Olsen, J., Hansen, B., Ward, M.H., Jones, R.R., Coffman, V.R., Pedersen, C.B., Sigsgaard, T., 2021. Exposure to nitrate from drinking water and the risk of childhood cancer in Denmark. Environ. Int. 155, 106613. https://doi.org/10.1016/j.envint.2021.106613.

Stekhoven, D.J., Bühlmann, P., 2012. Missforest–non-parametric missing value imputation for mixed-type data. Bioinformatics 28, 112–118. https://doi.org/10.1093/bioinformatics/btr597.

Temkin, A., Evans, S., Manidis, T., Campbell, C., Naidenko, O.V., 2019. Exposure-based assessment and economic valuation of adverse birth outcomes and cancer risk due to nitrate in United States drinking water. Environ. Res. 176, 108442. https://doi.org/10.1016/j.envres.2019.04.009.

Theisen, C.F., Wodschow, K., Hansen, B., Schullehner, J., Gislason, G., Ersbøll, B.K., Ersbøll, A.K., 2022. Drinking water magnesium and cardiovascular mortality: A cohort study in Denmark, 2005–2016. Environ. Int. 164, 107277. https://doi.org/10.1016/j.envint.2022.107277.

U.S. EPA. Guidelines for Exposure Assessment, 1992. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, EPA/600/Z-92/001.

Ward, M.H., Jones, R.R., Brender, J.D., De Kok, T.M., Weyer, P.J., Nolan, B.T., Villanueva, C.M., Van Breda, S.G., 2018. Drinking Water Nitrate and Human Health: An Updated Review. Int. J. Environ. Res. Public Health 15, 1557. https://doi.org/10.3390/ijerph15071557.

Wei, T., Simko, V., 2024. R package "corrplot": Visualization of a Correlation Matrix.