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Full length article

Assessment of drinking water safety in the Netherlands using nationwide exposure and mortality data

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A B S T R A C T

Background: Although drinking water in the Netherlands is generally accepted as safe, public concern about health risks of long-term intake still exist.
Objective: The aim was to explore associations between drinking water quality for nitrate, water hardness, calcium and magnesium and causes-of-death as related to cardiovascular diseases amongst which coronary heart disease and colorectal cancer.
Methods: We used national administrative databases on cause-specific mortality, personal characteristics, residential history, social economic indicators, air quality and drinking water quality for parameters specified by the EU Drinking Water Directive. We put together a cohort of 6,998,623 persons who were at least 30 years old on January 1, 2008 and lived for at least five years on the same address. The average drinking water concentration over 2000–2010 at the production stations were used as exposure indicators. We applied age stratified Cox proportional hazards models.
Results: Magnesium was associated with a reduced risk for mortality due to coronary heart diseases: HR of 0.95 (95% CI: 0.90, 0.99) per 10 mg/L increase. For mortality due to cardiovascular diseases, a 100 mg/L increase in calcium was associated with a HR of 1.08 (95% CI: 1.03, 1.13) and an increase of 2.5 mmol/L of water hardness with a HR of 1.06 (95% CI: 1.01, 1.10). The results show an elevated risk for coronary heart disease mortality at calcium concentrations below 30 mg/L, but over the whole exposure range no exposure response relation was observed. For other combinations of drinking water quality parameters and cause-specific mortality studied, no statistical significant associations were identified.
Conclusion: We identified in this explorative study a protective effect of magnesium for the risk of mortality to coronary heart disease. Also we found an increased risk of mortality due to cardiovascular disease associated with the concentration of calcium and the water hardness in drinking water.

1. Introduction

Although risk assessments for individual chemicals in drinking water or its sources repeatedly point to large margins of safety between exposure concentrations and (preliminary) health-based guideline values (Baken et al., 2018; Bruce et al., 2010; Houtman et al., 2014; Schriks et al., 2010), public concern about potential health consequences of long-term intake still exists. The concern partly relates to the methods used for the risk assessment, often based on standardized toxicological studies. In addition, there is concern with regard to chronic exposure to complex mixtures at low concentrations (Villanueva et al., 2014).

As alternative to risk assessment based on *in vivo* toxicity data for individual chemicals, the use of *in vitro* bioassays is proposed, which

integrate exposure to multiple chemicals in a measured effect (Escher et al., 2015). When bioassays are applied for risk assessment, questions remain on *in vitro* to *in vivo* extrapolation and the involved toxicokinetics and –dynamics (Dingemans et al., 2019; Groothuis et al., 2015). Another alternative are epidemiological studies on the relation between drinking water quality and health. Unlike in laboratory studies, in epidemiological studies on adverse effects of chemical exposure to humans in real life conditions, extrapolation factors for differences between species can be avoided. Environmental epidemiology cannot only play a role in the health hazard identification, but also in health impact assessment in which the expected burden of disease due to an environmental exposure is quantified (World Health Organization, 2000).

The increasing availability of national databases with cause-of-death statistics on individual level, offers opportunities to investigate associations between environmental exposure and health in large administrative cohorts. This approach was earlier applied in the Netherlands to assess the association between air pollution and mortality (Fischer et al., 2015; Fischer et al., 2020). In this study we explored whether it is feasible to apply a comparable approach for drinking water contaminants by assessing the associations between individual drinking water quality parameters and cause-of-death among about seven millions Dutch inhabitants.

2. Methods

2.1. Choice of relevant associations

We carried out a literature review using Scopus (literature until September 2020) to identify associations between individual drinking water quality parameters as specified in the EU Drinking Water Directive and diseases that could lead to mortality. Potential associations between these parameters and health effects were preferably selected from *meta*-analyses and reviews, supplemented with individual studies to describe the range of the drinking water concentrations related to health effects. We only further carried out our statistical analyses with regard to the associations identified via this literature search, to prevent false positives.

2.2. Drinking water provision areas and exposure data

Drinking water provision areas for 2015 were provided as GIS files by the Dutch drinking water utilities, detailed to four digit postal code areas (on average about 4,000 inhabitants). Each provision area is linked to one or more drinking water production stations. For each production station the type of source water used is given, i.e. groundwater (both phreatic and confined), surface water, dune filtrate or river bank filtrate, and the advanced water treatment technologies applied per production station are known.

Information about the exposure to chemicals in drinking water per provision area was based on the REWAB database, which reports drinking water quality for parameters as mentioned in the EU Drinking Water Directive and -more fragmented - information on parameters without a reporting obligation. The REWAB database is based on routine monitoring programs by the Dutch drinking water utilities. Yearly in the Netherlands over 80,000 individual analyses on chemical parameters are performed by accredited drinking water laboratories. The drinking water samples are taken at the drinking water production stations after the final treatment step, but also in the distribution networks. The REWAB data are used for yearly reports on drinking water quality by the Dutch Human Environment and Transport Inspectorate. The REWAB database provides per production station and per parameter the yearly average, minimum and maximum values, and occasionally 10th and 90th percentiles. Original raw data are not stored in the database.

Data from samples taken at the production stations for the period 2000 to 2010 were used in this study as exposure variables, data before this period are not used as these are more fragmented. We only selected

drinking water quality parameters for which the data at the production station predict exposure in the provision area, and that show sufficient variability between production locations. Data taken in the distribution system in the provision area were used for this comparison and not included in further analysis as the exact location where the samples in the provision area were taken is not reported in REWAB. Drinking water quality data were retrieved for arsenic (As), cadmium (Cd), calcium (Ca), chromium (Cr), copper (Cu), iron (Fe) mercury (Hg), lead (Pb), nickel (Ni), nitrate (NO3–), manganese (Mn), magnesium (Mg), selenium (Se), and zinc (Zn). The average concentration over the period 2000–2010 was used as exposure indicator. Water hardness was derived using hardness (mmol/L) = 0.02495*calcium (mg/L) + 0.04115*magnesium (mg/L).

Individual production stations may have missing values for drinking water constituents, i.e. no measurements were carried out in the period 2000 to 2010, or concentrations in samples were below the reporting level (RL). The RLs per parameter vary between years and between individual drinking water laboratories. To reduce uncertainty in the exposures, therefore only provision areas were included in the main statistical analyses where all available exposure data exceed RL.

If multiple production stations provide an area, the averages over the production stations were used. In case a drinking water constituent of one or more of these production stations was below RL, the provision area was classified for that constituent as below RL.

2.3. Definition cohort and cause-of-death statistics

This study builds upon earlier research regarding the relation between air pollution and mortality (Fischer et al., 2015; Fischer et al., 2020). The main differences with these earlier studies are the starting date of enrollment of the participants and the period of follow-up.

The Netherlands Population Statistics contains personal data of people who live in the Netherlands (residents) including age, sex, marital status, country of origin and changes of address (Prins, 2016), and is linked to the cause-of-death registration. This data was accessed through the System of Social Statistical Datasets of Statistics Netherlands (Bakker et al., 2014). For this study we selected all Dutch inhabitants of 30 years or older on January 1, 2008, living at the same residential address since January 1, 2003. We enriched the individual demographical information with individual standardised disposable household income, adjusted for individual household size and composition.

Based on the four digit postal code of the residential address, the drinking water quality data per individual parameter was linked to the study population. As potential confounders at the neighborhood level, we used a social status indicator at four digit postal code level which is derived every four years by the Netherlands Institute for Social Research based on income level, unemployment rate and education level (Knol, 2012). We used the indicator of 2006, or 2010 when 2006 data were missing. Also, the annual averaged air concentrations of particulate matter (PM10) and nitrogen dioxide (NO$_2$) for 2008 were assessed for the residential address by linkage of maps yielding 1 by 1 km grids of the concentrations. These concentrations were based on emissions extracted from the National Emission Registration (Jimmink et al., 2015) and calculations with a dispersion model (Van Jaarsveld and de Leeuw, 1993).

The follow-up period of the cohort was from January 1, 2008 until December 31, 2012. Subjects were lost to follow-up if their final record in the Netherlands Population Statistics ended before January 1, 2013 and death was not registered. Emigration was the main cause of censoring. As Statistics Netherlands introduced an automated coding system for cause-of-death statistics in 2013 (Harteloh, 2020) which led to a shift in cause-of-death occurrence, we did not use statistics for 2013 and later.

Cause-of-death statistics were provided by Statistics Netherlands, based on municipal population registers on individual level (Harteloh et al., 2010). The following non-accidental causes-of-death were

analysed according to WHOs International Classification of Diseases (ICD-10) (World Health Organization, 2010): codes A00-R99 except mortality due to external causes S00-T98, V01-Y98, and mortality due to cardiovascular disease (CVD, I10-I70), amongst which coronary heart disease (I20-I25) as a subset of CVD or colorectal cancer (C18-C21).

2.4. Statistical analyses

Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). We applied 1-year age stratified Cox proportional hazards regression models with time-on-study as time-to-event to estimate adjusted associations (hazard ratio HR and 95% confidence interval CI) between mortality outcomes and exposure data. Adjustments were made for sex, marital status, country of origin, standardized household income, social status at the neighbourhood level and air quality (base model). As within the Netherlands differences in regional mortality rates exist (Mackenbach, 1992) that may bias associations between drinking water quality and cause-of-death statistics, we extended the Cox model to a frailty model by incorporating the twelve Dutch provinces as random effect in the analysis. A Dutch province is an administrative region of 0.4 to 4 million inhabitants. The concentrations of the drinking water parameters were included as continuous exposure variables in the models. The hazard ratios were expressed over a concentration range comparable with the range that was found for the study population. In addition, we repeated the statistical analyses with six to eight exposure categories to gain insight in the exposure response relation.

To evaluate the sensitivity of the results when the provision areas with data below the reporting levels (RL) are included, we carried out per parameter two separate analyses. First, a dummy category < RL which consists of production stations with all data below the RL was added to the model and the concentration of the drinking water parameter for these stations were set to 0. Second, category U (Uncertain) consists of production stations with both data below and exceeding the RL. The average concentration for these stations was calculated by setting concentrations < RL to 0.5 RL. Also a dummy variable indicating the stations belonging to category U was added to the Cox model.

To evaluate the sensitivity of the results to missing individual lifestyle factor data, we assessed the association between the drinking water parameters and lifestyle factors in a separate survey of adults across the Netherlands. We obtained data from health surveys conducted in the period 2008–2010 by all Community Health Services (Van den Brink, 2011). We used data from 21 of the 29 Community Health Services with available information on self-reported four digit postal code area, age, gender, marital status, level of education, country of origin, smoking and body mass index (BMI). We assessed the age- and sex-adjusted differences in drinking water quality level for different categories of smoking (current smoker, former smoker, and never smoker as reference) and BMI (≤18.5, 18.5–25, 25–30, > 30, with 18.5–25 as reference) with a regression model with the community health services as random effect. Subsequently we additionally adjusted for the individual and neighbourhood confounders that were also included in the Cox proportional hazard regression models using level of education instead of standardized household income, which was not available in the survey data.

2.5. Privacy and ethics

The System of Social Statistical Datasets of Statistics Netherlands provides the ability to link pseudo-anonymised data at the individual level and serves as a Trusted Third Party. Dutch Civil Code allows the use of health records for statistics or research in the field of public health under strict conditions. All data management and statistical analyses were carried out within a secured remote access environment provided by Statistics Netherlands and the results could only be exported after control for privacy and security issues. No informed consent from patients nor approval by a medical ethics committee is obligatory for this type of registry based health studies without directly identifiable data.

3. Results

3.1. Drinking water quality and choice of relevant associations

In the Netherlands there are 233 drinking water production stations and 1,800 provision areas (Fig. 1) with an unique water quality. Drinking water provision areas are fed by one to a maximum of five different production stations.

A high correlation between water quality at the production station and in the provision area was found for arsenic, cadmium, chromium, nitrate, calcium, magnesium, hardness, manganese and selenium. Correlations were low for copper, mercury, lead, nickel, iron and zinc, which can be explained as these compounds are used in the distribution system and in in-house installations.

Table S1 in the Supplement summarizes for the high correlated drinking water parameters the associations with health outcomes identified in the literature search and that can potentially be assessed in administrative cohorts.

An overview of the concentrations of drinking water for calcium, magnesium hardness and nitrate in the various provision areas is given in Fig. 2. For arsenic, cadmium, chromium, manganese and selenium the number of provision areas where concentrations exceed the lowest reporting level is too limited to be of use in our study, so our study focusses on the contaminants as shown in Fig. 2.

3.2. Cohort description

At January 1, 2008 6,998,623 Dutch residents of 30 years and older were living at least five years at the same home address, and could be linked to one or more of the drinking water parameters studied. The demographic and socio-economic characteristics of the study cohort are provided in detail in the Supplement (Table S2). In the study cohort 453,035 persons died during the five year follow up period of a 'natural cause' (Table 1). The spatial variation in mortality rates is shown in the Supplement (Fig. S1) and illustrates the necessity to adjust for differences between provinces.

Given the availability of sufficient valid drinking water exposure data and of associations described in Table S1 in the Supplement, associations with drinking water parameters were studied for non-accidental mortality (all parameters), mortality due to cardiovascular diseases (hardness, calcium and magnesium), for mortality related to coronary heart disease (all parameters, except nitrate) and mortality due to colorectal cancer (nitrate). Table 2 describes the exposure for the studied parameters in drinking water in the cohort. Due to missing exposure data, the cohort size was limited to 4,808,840 for nitrate (68.7% valid). Details about the exposure distributions are given in Table S3 in the Supplement.

3.3. Associations between mortality and drinking water quality

Table 3 describes the association between the concentrations of calcium, magnesium, nitrate and water hardness and mortality for the base and frailty model.

In general, the hazard ratios in the frailty model are more close to one than in the base models. Magnesium is associated with a reduced risk for mortality due to coronary heart diseases in both models, leading to a HR of 0.95 [95% CI: 0.90–0.99] per 10 mg/L for magnesium in the frailty model. The protective effect for magnesium in the base model for non-accidental mortality and for mortality due to cardiovascular diseases disappears in the frailty model. Calcium and water hardness are associated with a higher mortality risk for cardiovascular diseases in both the base and the frailty model, leading to a HR of 1.06 [95% CI: 1.01–1.10] per 2.5 mmol/L for water hardness, a HR of 1.08 [95% CI: 1.03–1.13] per 100 mg/L for calcium in the latter model.
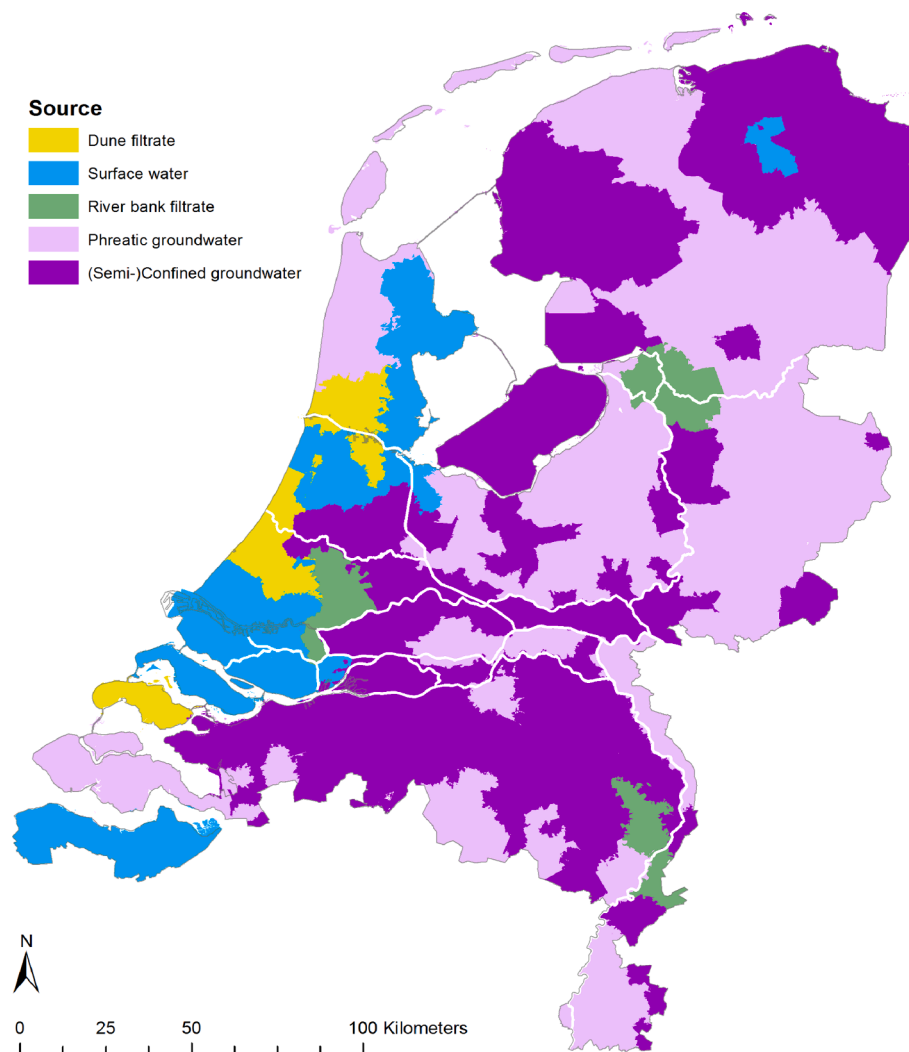
Fig. 1. Drinking water provision areas in the Netherlands related to the type of source water.

The results of the categorical analyses using a frailty model reveal that individual exposure categories have relative large confidence intervals (Figs. S2-S4 in the Supplement). The results for water hardness and calcium in relation to cardiovascular disease and for magnesium in relation to mortality for coronary heart disease are in line with the result of the statistical analyses with the continuous exposure indicators and suggest a linear relation over the exposure range present in the study cohort. An isolated elevated HR of 1.11 [95% CI: 1.02–1.11] was observed for the lowest (≤30 mg/L) compared to the reference exposure category (40–50 mg/L) for calcium in relation to mortality due to coronary heart disease, but over the whole exposure range no exposure response relation was visible.

No associations are found for nitrate and non-accidental mortality or mortality due to colorectal cancer. Fig. S5 in the Supplement on individual exposure categories supports the results in Table 3. About 30% of the provision areas have concentrations of nitrate which are at least partly below reporting levels; residents from these provision areas are not included in the statistical analyse carried out for Table 3. Table S4 in the Supplement reports the results of the sensitivity analysis for nitrate including provision areas with data in the category < RL (all data below RL) and U (uncertain, both data below and exceeding RL). The inclusion of category < RL or category U in the frailty model did not lead to substantial changes in the hazard ratios (Fig. S5).

The number of individuals in the sensitivity analyses on missing lifestyle factors varied between 123,707 for calcium, 122,466 for

magnesium and water hardness (from 21 community health services) and 83,088 for nitrate (from 20 community health services).

In Fig. S6 in the Supplement, the difference in drinking water quality for different categories of smoking and BMI is shown. The sensitivity analysis reveals no differences in mean exposure between different categories of smoking or BMI, with the exception that current smokers live in four digit postal code areas with, on average, a lower water hardness or calcium concentration than never smokers. The differences, respectively 0.007 [95 %CI 0.001–0.012] mmol/L for water hardness and 0.25 [95 %CI 0.06–0.44] mg/L for calcium, are small in the light of the concentration distributions in Table 2.

4. Discussion

4.1. Associations between cause-of-death statistics and drinking water quality

In the current study, associations between drinking water quality and cause-of-death statistics were evaluated based on data at individual level for almost 7 million Dutch inhabitants. Given the availability of sufficient valid drinking water exposure data and of associations described in literature, associations were studied for calcium, magnesium, hardness and nitrate and mortality related to cardiovascular diseases, coronary heart disease and colorectal cancer. Due to missing exposure data, cohort size was limited to 4.8 million for nitrate.
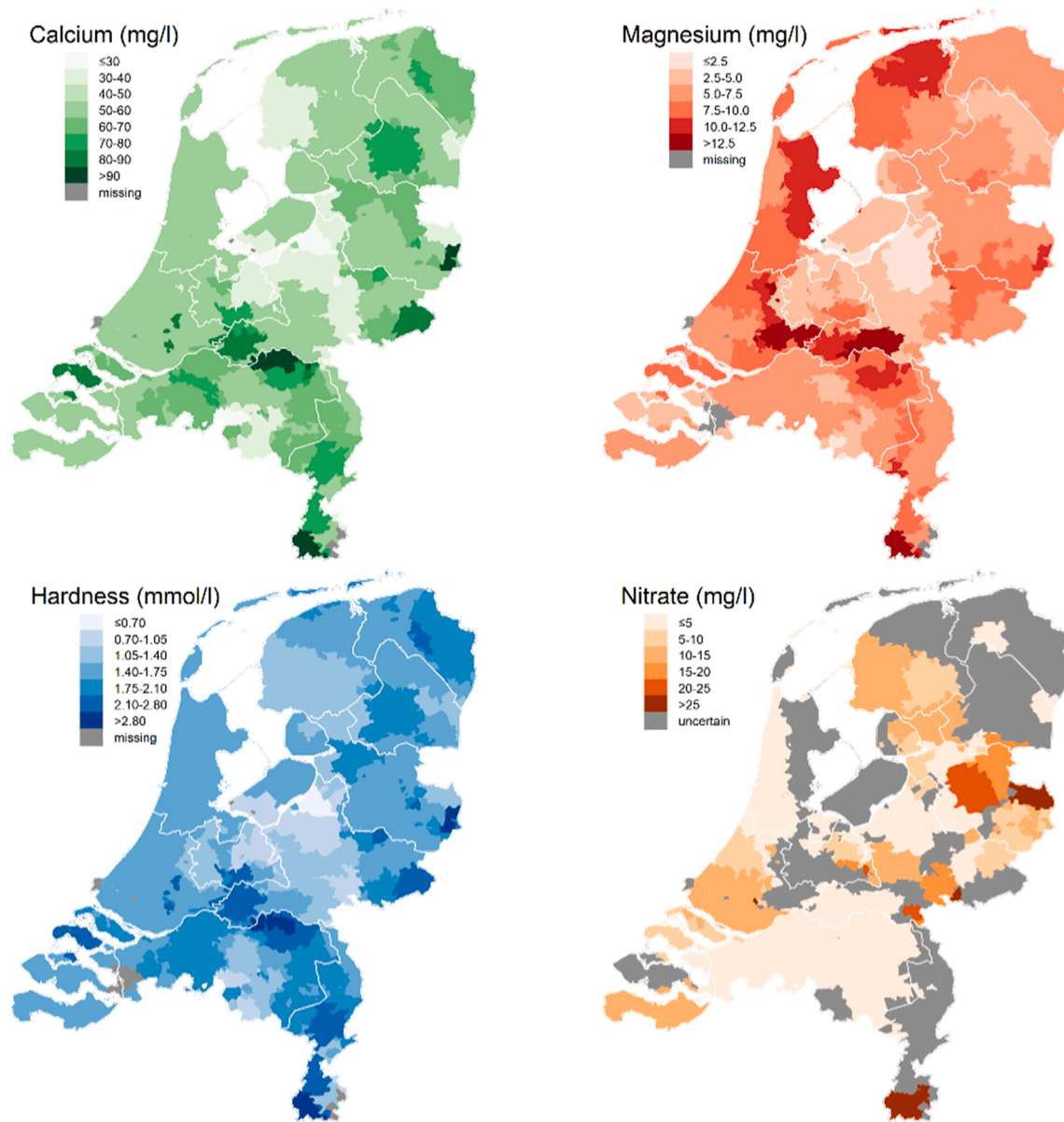
Fig. 2. Spatial distribution of concentrations in drinking water for calcium, magnesium, hardness and nitrate.

Table 1

Mortality and selected cause-of-death in the 5-yr follow-up period (N = 6,998,623).

Death and underlying cause-of-death	n (%)
Non-accidental death	453,035 (6.5%)
Cardiovascular diseases	132,793 (1.9%)
Coronary heart disease[a]	37,208 (0.5%)
Colorectal cancer	23,458 (0.3%)

[a] Subset of cardiovascular diseases.

4.2. Calcium, magnesium and water hardness

Several studies evaluated the relationship between water hardness, or magnesium and calcium, and cardiovascular or coronary heart diseases.

A cohort study in the Netherlands among 120,852 inhabitants did not find a significant association between tap water hardness, magnesium or calcium concentrations and coronary heart disease mortality or stroke mortality (Leurs et al., 2010). The study had comparable concentration ranges as the current study.

Table 2

Distribution of concentrations of drinking water parameters in the study population.

Component	n	Mean	P0.01[a]	P10	P25	P50	P75	P90	P95	P99	P99.99
Calcium (mg/L)	6,942,711	51.29	23.36	37.09	43.22	49.90	57.98	68.10	75.52	97.94	102.82
Magnesium (mg/L)	6,889,775	6.98	0.75	3.74	5.10	7.29	8.45	10.06	12.23	13.13	17.03
Hardness (mmol/L)	6,889,775	1.54	0.67	1.09	1.42	1.54	1.66	1.98	2.16	2.98	2.98
Nitrate (mg/L)	4,808,840	7.30	1.16	1.61	2.41	4.21	11.56	13.18	19.92	37.40	37.40

[a] Percentile.

Table 3

Hazard ratios for calcium, magnesium, nitrate and water hardness and non-accidental and cause specific mortality.[a]

Outcome and component	# of events	Base model[b]		Frailty model[c]	
		HR (95% CI)[d]	p-value	HR (95% CI)[d]	p-value
Non-accidental					
Calcium	439,059	1.004 (0.982,1.028)	0.702	1.011 (0.986,1.037)	0.393
Magnesium	436,029	0.975 (0.963,0.986)	<0.0001	0.990 (0.976,1.004)	0.178
Water hardness	436,029	0.991 (0.972,1.012)	0.403	1.005 (0.982,1.027)	0.693
Nitrate	310,652	0.999 (0.986,1.011)	0.825	1.001 (0.983,1.019)	0.930
Cardiovascular diseases					
Calcium	120,769	1.119 (1.072,1.168)	<0.0001	1.080 (1.030,1.133)	0.002
Magnesium	120,002	0.967 (0.945,0.989)	0.004	0.989 (0.963,1.016)	0.416
Water hardness	120,002	1.076 (1.036,1.118)	<0.0001	1.057 (1.013,1.102)	0.010
Coronary heart disease					
Calcium	36,032	1.033 (0.954,1.117)	0.426	1.011 (0.927,1.102)	0.806
Magnesium	35,798	0.943 (0.904,0.983)	0.006	0.947 (0.903,0.993)	0.026
Water hardness	35,798	0.999 (0.931,1.072)	0.980	0.986 (0.914,1.065)	0.727
Colorectal cancer					
Nitrate	16,156	0.971 (0.920,1.026)	0.295	0.985 (0.915,1.061)	0.688

[a] Number of observations for calcium 6,851,692; for magnesium and water hardness 6,799,142 and for nitrate 4,738,598.

[b] Stratified for age and adjusted for sex, marital status, country of origin, standardised household income, social status of the four digit postal code area and air quality (PM10 and NO_2).

[c] Extended base model with province as random effect.

[d] Hazard ratio (HR) and 95% confidence interval (95% CI) expressed per 25 mg/L for nitrate; per 2.5 mmol/L for water hardness, per 100 mg/L for calcium and per 10 mg/L for magnesium.

Catling et al., concluded based on a review of epidemiology studies that evidence for a relation between calcium or exposure and cardiovascular mortality remains unclear (Catling et al., 2008). The degree of heterogeneity in the results of five case-control studies was too high to derive a summary risk estimate for calcium. The heterogeneity for studies into magnesium was moderate: a pooled Odds ratio of 0.75 (95 % CI 0.68–0.82) was obtained from six case-control studies comparing the highest exposure category (8.3–19.4 mg magnesium/L) with the lowest category (2.5–8.2 mg/L). Gianfredi et al., estimated for calcium and cardiovascular disease mortality, based on six case-control studies, a pooled relative risk of 0.82 (95% CI 0.70–0.95) between the highest and lowest exposure categories in the studies (Gianfredi et al., 2017). Similar for magnesium, a pooled risk estimate of 0.75 (95% CI 0.66–0.86) was found for seven case-control studies (five studies similar to (Catling et al., 2008)). The high heterogeneity of the estimates limits the generations of the findings for calcium and magnesium. Lake et al., applied an ecological time series approach and did not find evidence for an association between step changes in drinking water hardness or drinking water calcium and cardiovascular mortality (Lake et al., 2010). The authors point to the need for large populations (>500,000) to be able to detect a change of the size as suggested by previous studies.

The result of the current study points in a different direction. As well as for calcium as for water hardness an increase of the concentration is associated with a rise of the hazard ratio for cardiovascular mortality: the HR is 1.08 (95% CI: 1.03–1.13) per 100 mg calcium/L and for water hardness 1.06 (95% CI: 1.01–1.10) per 2.5 mmol/L after taking into account differences in regional mortality rates for cardiovascular disease. No association was found with magnesium in drinking water in the frailty model, however in the base model, a protective effect of magnesium for CVD mortality is found.

A direct comparison with the estimates reported in the *meta*-analyses is difficult to make, since in the *meta*-analyses only the difference in risk between the highest and lowest exposure category is reported. Nevertheless, in the current study there is no indication of a protective effect of calcium, magnesium, or water hardness on overall cardiovascular disease mortality. With almost 133,000 cases of cardiovascular disease mortality the current study includes about four times more cases than considered in the *meta*-analyses of Gianfredi et al., (Gianfredi et al., 2017).

Chao et al., carried out a *meta*-analysis for calcium and coronary heart disease mortality and found moderate heterogeneity for six

European studies with in total 67,529 cases (Chao et al., 2016). The pooled relative risk was 0.91 (95% CI 0.82–0.99) between the highest and lowest exposure categories. The authors conclude that the analyses suggest that the higher levels of calcium in drinking water could reduce the risk of coronary heart disease mortality, especially in Europe. In our study we observed for in total 37,208 coronary heart mortality cases an isolated elevated HR of 1.11 for the lowest exposure category (≤30 mg/L) compared with the reference category (40–50 mg/L). The difference expressed as HR is 0,89 when we compare in Fig. S2 the estimate of the highest (>90 mg/L) with the estimate of the lowest calcium category (≤30 mg/L). This HR is comparable with the pooled estimate reported by Chao et al., (Chao et al., 2016). However, there is in our study no indication of an exposure response relation; the observed HR is 1.01 (95% CI: 0.93–1.10] per 100 mg/L if we treat the calcium concentration as continuous exposure indicator. We cannot exclude exposure–response relation with a different shape than linear or monotonic increasing. No exposure response relation was found for water hardness. So, from our results there is some suggestion that only calcium concentration below 30 mg/L may increase the risk for of coronary heart disease mortality. However, this observation is based on the HR of only one exposure category and needs confirmation and further elucidation in large cohort studies before any conclusion can be drawn.

Reviews consistently support the inverse relation between magnesium levels in drinking water at concentrations that are relevant for the Netherlands and mortality due to coronary heart diseases (Jiang et al., 2016; Momeni et al., 2014; Monarca et al., 2006; Shlezinger et al., 2018). Shlezinger et al., report on an increase in coronary heart disease after installation of desalination techniques and thereby lower magnesium content in drinking water in Israel (Shlezinger et al., 2018). Liang et al., carried out a *meta*-analysis with three cohort and seven case-control studies into coronary heart disease mortality and found an inverse association with magnesium in drinking water (Jiang et al., 2016). The pooled relative risk for the highest compared to the lowest exposure category was 0.89 (95% CI: 0.79–0.99); there was a high degree of heterogeneity between the study estimates. The results of our study for magnesium are in line with the outcome of the *meta*-analysis. We observed an inverse exposure response relation; with increasing magnesium concentrations the hazard rate declined (HR = 0.95 per 10 mg/L with a 95% CI of 0.90–0.99). Based on the calculation of the population attributable fraction, about 1% of the mortality due to coronary heart disease could, in theory, be prevented if the magnesium concentration in

drinking water in the Netherlands would be 10 mg/L. Given the heterogeneity between studies in the *meta*-analysis of Liang et al., (Jiang et al., 2016), large studies are needed to confirm the shape of the exposure response relation.

4.3. Nitrate

Recent epidemiological studies on nitrate in drinking water were summarized by Ward et al., (Ward et al., 2018). The authors concluded that there is relatively strong evidence for a relationship between nitrate in drinking water nitrate and colorectal cancer. Four out of five discussed studies including one cohort study (Espejo-Herrera et al., 2016; Fathmawati et al., 2017; McElroy et al., 2008; Schullehner et al., 2018; Weyer et al., 2001) found evidence of an increased risk of colorectal cancer or colon cancer associated with water nitrate levels that were mostly below the respective regulatory limits. Most studies did not account for co-exposure to other water contaminants, nor adjust for potential risk factors. The authors therefore conclude that the number of well-designed studies of individual health outcomes is still too few to draw firm conclusions about risk from drinking water nitrate ingestion (Ward et al., 2018).

The design of our study is comparable with a national registry based cohort study in Denmark (Schullehner et al., 2018). Differences are that the Danish study used interpolation to adjust for lacking exposure data, included data on private wells and supply areas were not given by the utilities but delineated by the researchers (see also (Schullehner et al., 2017). Although exposure ranges in the current study (Table 2) are comparable to the aforementioned studies and the number of cases is about four time larger, in the current study no association between nitrate and colorectal cancer mortality was found. These results are consistent throughout the various statistical models used. An important limitation of the current study is that mortality for colorectal cancer is a less specific indicator for cancer incidence; for persons in the Netherlands diagnosed with colorectal cancer in the period 2011–2015, the relative five-year survival rate is 65.8%.

4.4. Methodological limitations

This study was based on yearly averages over the large monitoring set of data available. For arsenic, cadmium, chromium, manganese and selenium, the number of provision areas where all concentrations exceed the lowest reporting level were too low to allow further analysis, and for nitrate for this reason the cohort size was limited. Reporting limits are in practice often higher than the actual detection limits by the analytical methods used, although not necessarily (Winslow et al., 2006). It would be beneficial for future epidemiological studies if the databases collecting the routine monitoring data give insight in the original raw data and the actual detection limits.

In the current study we, for reasons of excluding uncertainties, only used > RL data for the primary analysis (conform (Helsel, 2006), and included < RL or U data only for sensitivity comparison. Other authors propose to include the < RL data, following certain assumptions (Shumway et al., 2002; Weltje and Sumpter, 2017). However the results of the sensitivity analysis for nitrate indicate that our initial risk estimates are not substantially affected when other choices about inclusion of uncertain data are made.

Exposures were estimated by the average concentration in the period 2000–2010 and linked to the study population for a follow-up period from 2008 to 2013 based on the address in the year 2008 and the condition that the participants lived at least 5 years on this address. We assume that the 10 year average exposure represent reflects the relevant exposure also in the last decade of the twentieth century since the spatial distributions of the drinking water concentrations do not change much over time nor were there many changes in types of sources and treatment techniques being used for the drinking water production. Still people might have moved before 2003 and/or since 2008 from or to

other addresses which may have affected their long-term exposure level.

We adjusted for individual as well area-level social status to capture information about the contextual environment since no information was available on individual life style factors. In addition we evaluated whether missing information on smoking and BMI could have biased the results of our study by using survey data on about 123,000 participants spread over the Netherlands. The sensitivity analysis reveals that current smokers live in four digit postal code areas with, on average, a lower water hardness or calcium concentration than never smokers. These differences are small in the light of the variation between four digit postal code areas (see Table 2) but due to the size of the survey statistically significant. Smoking is an important risk factor for cardiovascular diseases. It is therefore unlikely that the elevated hazard ratios for mortality due to cardiovascular disease associated with an increase in water hardness or calcium concentration (Table 3) can be explained by the lack of adjustment for smoking in the main statistical analysis. However an earlier study showed that even small associations between air pollution and life style factors may affect the risk estimates (Strak et al., 2017). We can therefore not completely exclude that some bias in the results may have arisen due to the lack of adjustment for smoking or other lifestyle factors.

In the current study we considered an association relevant if it was observed after adjustment for spatial heterogeneity in regional mortality, which was not the case for associations found in the base model between magnesium or nitrate and cardiovascular diseases. We used a fixed boundary for this spatial heterogeneity here being the provinces, while in reality differences in regional mortality do not necessary follow these administrative boundaries. However the use of smaller administrative areas will decrease the variation in exposure which will affect the power of the study. There is little experience yet with the optimal choice for the administrative areas to take into account regional variation in mortality rates.

The current study was based on nationwide cause-of-death statistics. The reliability of cause-of-death statistics is high (>90%) for colorectal cancer and good to fair (>70%) for cardiovascular and coronary heart disease (Harteloh et al., 2010).

5. Conclusions

Based on the results of this explorative study, we identified a protective effect of magnesium for the risk of mortality to coronary heart disease, and an increase in risk of mortality due to cardiovascular disease associated with the concentration of calcium and the water hardness at the production sites of drinking water. For other combinations of water quality parameters and causes-of-death studied, no statistical significant associations were identified.

The results show an elevated risk for coronary heart disease mortality at calcium concentrations below 30 mg/L, but over the whole exposure range no exposure response relation was observed. To assess the consequences for public health, more large cohort studies are needed to identify the shape of the exposure response relation at low levels of calcium before conclusions on this relation can be drawn.

CRediT authorship contribution statement

Danny Houthuijs: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation,

Writing – original draft, Writing – review & editing, Visualization, Supervision. **Oscar R.P. Breugelmans:** Methodology, Software, Formal analysis, Investigation, Resources, Visualization. **Kirsten A. Baken:** Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Rosa M.A. Sjerps:** Formal analysis, Investigation, Data curation, Visualization. **Maarten Schipper:** Methodology, Software, Validation, Formal analysis, Resources, Data curation, Visualization. **Monique van der Aa:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Annemarie P. van Wezel:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107356.

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