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Nitrate contamination in drinking water and adverse reproductive outcomes: a systematic review and meta-analysis

Authors

Luling Lin[1], Sophie St Clair[1], Caroline Crowther[1], Lesley Dixon[2], Frank Bloomfield[1], Jane Harding[1]

[1]Liggins Institute, University of Auckland, Auckland, New Zealand

[2]New Zealand College of Midwives, 376 Manchester Street, Richmond, Christchurch 8014, New Zealand

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Introduction

Nitrate is a water soluble ion made up of nitrogen and oxygen with the chemical formula NO_3^-. It is a naturally occurring ion that is part of the nitrogen cycle involving the interchange of nitrogen between the atmosphere, land and living organisms [1]. In New Zealanders, less than 10% of total nitrate intake is from drinking water, with most of the remainder coming from the diet [2].

Nitrogen is very important for plant nutrition and function, being incorporated by plants into amino acid synthesis, and is therefore commonly used in inorganic fertilisers. However, because nitrate is highly water soluble, it leaches through soils and into groundwater very easily, particularly after heavy rainfall. About 80-90% of the world's freshwater comes from groundwater [3], but in New Zealand about half of drinking water is pumped from the ground, with the remainder coming from surface sources [4]. The amount of nitrate ingested from drinking water varies based on the concentration in drinking water and an individual's consumption habits. The increasing use of artificial fertilisers, the disposal of wastes, particularly from animal farming, and changes in land use have become significant contributors to the progressive increase in nitrate levels in groundwater supplies [1].

The current New Zealand Maximum Acceptable Value (MAV) for nitrate in drinking water is 50 mg/L as nitrate (NO_3^-) or 11.3 mg/L as nitrate-nitrogen (NO_3-N) (multiply NO_3^- mg/L by 0.2259), which is the same as the World Health Organization (WHO) guideline [1]. This concentration is approximately equivalent to the current U.S. federal maximum contaminant level (MCL) for nitrate in public drinking water supply of 10 mg/L as NO_3-N. This limit was established to protect against methaemoglobinaemia in infants, or blue baby syndrome, the most widely recognised health consequence of high nitrate exposure [5].

While there is some evidence that nitrate in drinking water are associated with colorectal cancer [6, 7], the potential for adverse reproductive effects of chronic exposure to low levels of nitrate have also been raised recently [8-11]. Animal studies have indicated that nitrate from the mother can cross the placenta, affect the fetus *in utero*, and increase adverse outcomes, such as heart and neural-tube defects, gastroschisis, microphthalmia, anophthalmia, and craniofacial hypoplasia [12-14]. In addition, several epidemiological studies in humans have reported an association between prenatal nitrate exposure and adverse reproductive outcomes, including congenital abnormalities, preterm birth, low birth weight and small-for-gestational-age (SGA) infants [9, 15-18].

The purpose of this study was to systematically review the available evidence and determine the association between human exposure to nitrate in drinking water and adverse reproductive outcomes.

Methods

The study was reported according to the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines [19].

Criteria for considering studies for this review

Type of studies: randomised trials, cohort and case-control studies published in English from 1 January 2011. Studies that report the relationship between nitrate intake from drinking water and the risk of perinatal outcomes were eligible.

Type of participants: pregnant women and their infants.

Type of intervention: the exposure of interest is nitrate intake from drinking water during the antenatal period.

Type of outcome measure

Primary outcome: a composite of any of the following outcomes: preterm birth; small-for-gestational-age (SGA) infant; low birth weight infant; miscarriage; stillbirth; and neonatal death.

Secondary outcomes:

For infants: preterm birth, SGA, low birth weight, stillbirth, neonatal death, perinatal death, hypoglycaemia, need for respiratory support after birth, infection, congenital abnormality, necrotising enterocolitis, bronchopulmonary dysplasia, intraventricular haemorrhage, neonatal lung disease, neonatal intensive care unit (NICU) admission, jaundice, methaemoglobinaemia (as defined by the authors).

For women: any pregnancy complications (miscarriage, high blood pressure, preeclampsia, gestational diabetes, infection, obstetric haemorrhage; as defined by the authors).

Search strategy

We conducted a comprehensive search of databases from 1 January 2011 to 5 July 2021, including: Ovid MEDLINE via PubMed, Embase, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL, current issue) in the Cochrane Library, Web of Science, Scopus, GEOBASE and ProQuest Agricultural and Environmental Science Database, using search terms unique to the review topic (Supplement 1). We searched using both English and American spelling. We did not apply language restrictions, but only full text in English were included. Additionally, we reviewed the reference lists of all identified articles for relevant articles not identified in the primary search.

Two authors (LL and SSC) independently evaluated and appraised the retrieved studies using COVIDENCE, extracted data and assessed risk of bias. Any disagreements were resolved by discussion and if necessary in discussion with a third review author (JH).

Selection of studies followed the steps below:

1. Import all the records from the database into COVIDENCE.
2. Screen titles and abstracts to select relevant reports and exclude studies not relevant for this review.
3. Examine full-text studies for compliance with the eligibility criteria for this review.
4. Make final decisions on study inclusion and proceeded to data collection.

We recorded the selection process in sufficient detail to complete a PRISMA flow diagram.

We developed a data form to extract data for eligible studies. Information extracted included: source details, eligibility assessment, methodological details, characteristics of participants, details of intervention and outcomes reported.

We assessed the quality of the case-control and cohort studies according to the Newcastle-Ottawa Scale (NOS) [20]. The NOS evaluates nine methodological items and their reporting (participant selection, comparability of groups, and ascertainment of exposure/outcome), with values ≥ 7 compatible with good study quality (least bias, results are considered valid), between 2 and 7 with moderate study quality (susceptible to some bias but probably not enough to invalidate the results), and ≤ 2 with poor study quality (significant bias that may invalidate results).

Statistical analysis

The relationships between nitrate intake from drinking water and the risk of adverse birth outcomes were examined based on the effect size. Nitrate intake from drinking water, odds ratios (ORs), risk ratios (RRs), hazard ratios (HRs), with 95% confidence intervals (CIs) were extracted (both crude and adjusted).

Because different studies used different exposure categories and have presented data in a variety of ways, we pooled the study-specific risk per mg/L increase in nitrate for each outcome, using the mid-point of each reported exposure category. If the lower and upper limits of the category were given, the midpoint intake of nitrate in drinking water was calculated as: midpoint intake = (lower limit + upper limit) divided by 2. If the midpoint intake was given, the data were used directly. If the interval for any category of nitrate intake was not provided, we assigned a value following the algorithms suggested by Il'yasova et al [21]. For the upper open-ended category, we assigned the value of its lower limit plus the width of the previous (second-to-highest) interval. For

the lower open-ended category, we assigned the value of its upper limit minus half the width of the next (second-to-lowest) interval. If the range of lower open-ended category was smaller than the half width of the next (second-to-lowest) interval, we assigned the value of half of the upper limit.

Generalised least squares regression analysis was used to generate study-specific slopes representing the estimated increase in log odds ratio (OR) per mg/L increase in drinking water nitrate concentration and standard errors for these slopes. Study-specific slopes and their standard errors were then used to calculated ORs and 95% confidence intervals (CIs) per mg/L increase in nitrate for each outcome. When the OR per mg/L was given, the data were used directly. We then incorporated the OR per mg/L into meta-analysis using a random effects model to derive a weighted pooled estimate with 95% CIs based on the DerSimonian and Laird method [22]. A random effects model was used instead of a fixed effects model in order to account for both within-study and inter-study variation. Heterogeneity tests were performed using the I-square and Q-statistic, and significant heterogeneity was defined as $I^2 > 50\%$ or $p < 0.10$ [23]. We planned to assess potential bias due to small study effects by visual inspection of funnel plots when there were more than 10 studies. We planned to conduct sensitivity analyses by examining only studies considered to be of good quality.

Statistical analyses were performed using Stata Statistical Software (version 14, STATA).

Results

Search results and study characteristics

In total, 565 records were identified from database searching. After removal of the duplicates, we completed title and abstract screening for 249 records and then full-text screening for 48 records, of which 37 did not meet our inclusion criteria. The remaining 5 eligible studies (11 records) were included in the quantitative analysis (Figure 1).

Among the 28 studies that did not meet the study design criteria for this review, we identified three ecological and two cross-sectional studies exploring the association between nitrate exposure in drinking water and adverse reproductive outcomes. These five studies were included in the qualitative analysis, and are presented as additional (less reliable) evidence.

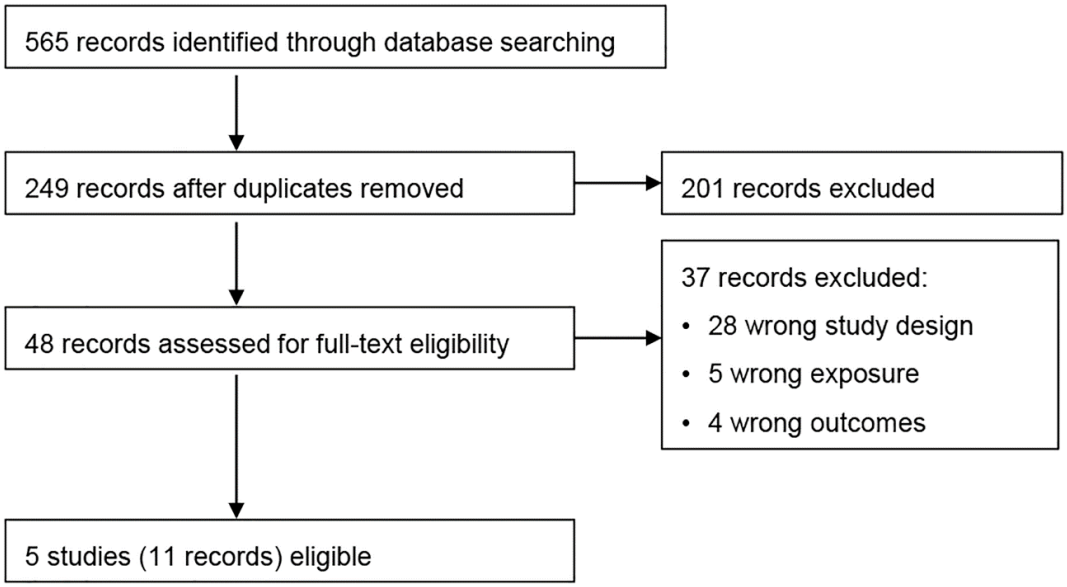

Figure 1. Flow diagram of included studies.

The five studies included in the analysis were published between 2013 and 2021, and included 5,031,454 participants (range from 2,241 to 4,160,998). Three were cohort studies and the other two were case-control studies. Two studies were carried in United States, one in Canada, one in France and one in Denmark. The study characteristics are described in Table 1.

Table 1. Study Characteristics.

Study name	Country, Region	Study design	Years of outcome ascertainment	Exposure description	Perinatal outcomes reported
Brender 2013 [18]	USA, Iowa and Texas	Population-based case-control study	1997-2005	Maternal addresses linked to public water utility nitrate measurements; nitrate ingestion (NO_3^-) estimated from reported water consumption. Exposure measured period: 1 month before conception through the end of third months of pregnancy; or 1 month before conception through 1-month post-conception for neural tube defects.	Neural tube defects, limb deficiencies, oral cleft defects, congenital heart defects
Holtby 2014 [17]	Canada, Kings County, Nova Scotia	Population-based case-control study	1988-2006	Maternal addresses at birth linked to municipal water supply; the median of all nitrate concentration measurements taken within each municipal water supply was used as the nitrate exposure estimate for all study participants living in each municipality; nitrate in rural private wells estimated using geographic information system from the nitrate concentrations of monthly samples taken. The latitude and longitude of the maternal address at the time of delivery was then used to determine a nitrate-exposure estimate for each study participant. Exposure measured period: not specified.	Congenital malformations as a single group
Migeot 2013 [24][a]	France, Deux-Sèvres	Historic cohort study	2005-2009	Measurements of nitrate in community water systems (263 municipalities) were linked to maternal place of residence on the date of birth. Exposure measured period: second trimester (taking season into account)	SGA births
Limousi 2014 [25][a]			2005-2010		SGA births

Albouy-Llaty 2016 [26][a]			2005-2010		Preterm birth
Coffman 2021 [9]	Denmark	Prospective cohort study	1991-2011	Nitrate in drinking water estimates were taken from the Danish national geodatabase Jupiter. The residential addresses of mothers were taken from the Danish Civil Registration System. Exposure was assigned per month of pregnancy and then time-weighted averages used to calculate an overall pregnancy exposure. Data linkage was done using the unique personal identification number assigned to each resident in Denmark. Exposure measured period: duration of the pregnancy	Low birth weight, birth weight, body length, head circumference
Sherris 2021 [10]	USA, California	Retrospective cohort study	2000-2011	Geocoded residences were linked to water supplies, and public monitoring records of nitrate levels were used. Births were then assigned into exposure categories (low, medium, high). Exposure measured period: duration of the pregnancy	Preterm birth

[a]The cohorts reported by Migeot 2013, Limousi 2014 and Albouy-Llaty 2016 are births in the same place in different periods, but there are overlaps between these three cohorts. SGA = small-for-gestational-age.

Quality of the included studies

According to the NOS, all included studies were considered of high quality.

Table 2. Quality of the included studies using the Newcastle-Ottawa scale [20]

	Selection	Comparability	Outcome	Total
Cohort study				
Coffman 2021	★ ★ ★ ★	★ ★	★ ★	8
Migeot 2013	★ ★ ★ ★	★ ★	★ ★	8
Sherris 2021	★ ★ ★ ★	★ ★	★ ★	8
Case-control study				
Brender 2013	★ ★ ★	★ ★	★ ★	7
Holtby 2014	★ ★ ★	★ ★	★ ★	7

Scale is from 0-9, where values ≥ 7 are compatible with good study quality

Primary outcome

Two studies reported the ORs for preterm birth, one study reported the OR for SGA and one study reported the OR for low birth weight, but it was not possible to pool data about the number of individual infants who experienced any of these outcomes (Table 3).

Secondary outcomes

Preterm birth: There was no evidence of an association between nitrate in drinking water and preterm birth (2 studies, 4,005,298 participants, odds ratio for 1 mg/L (OR_1) = 0.98, 95% CI 0.93, 1.03, p = 0.423; Figure 2) with evidence of substantial heterogeneity (I^2 = 100%, p < 0.0001).

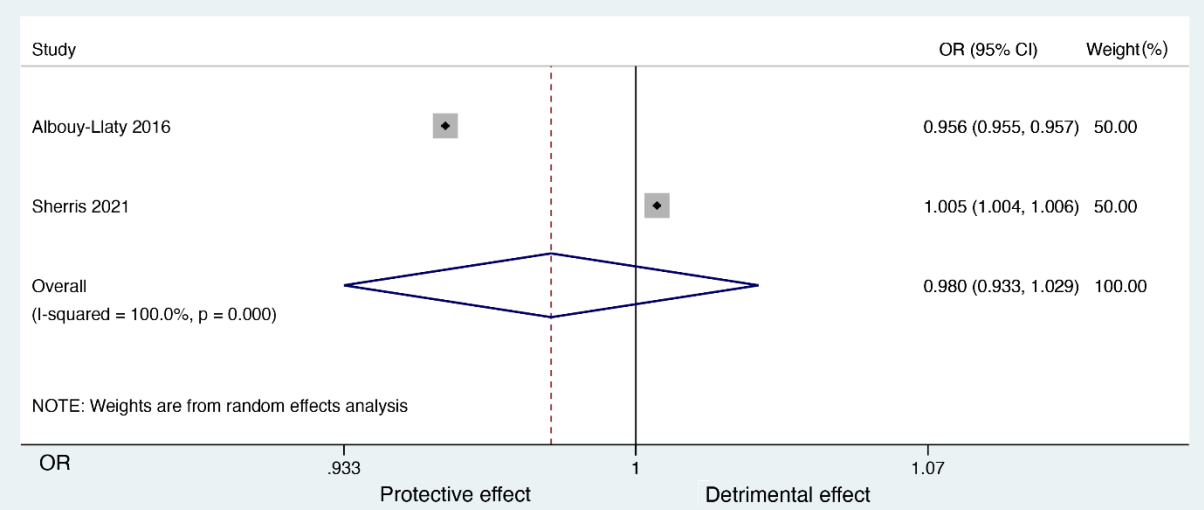

Figure 2. Forest plot for the association between nitrate in drinking water and preterm birth.

The overall pooled odds ratio estimates per mg/L increase in nitrate. Odds ratio of Albouy-Llaty 2016 was obtained by exponentiating (e^x) the study-specific slope estimates from generalised least squared regression to obtain log risk ratio estimates per mg/L increase in nitrate. Odds ratio of Sherris 2021 was obtained by pooling the odds ratios of two subgroups. The area of each square is proportional to the inverse of the variance of the odds ratio. OR: Odds ratio; CI: confidence intervals.

There were insufficient data to allow meta-analysis for any of the other outcomes. The direction of findings from the included studies are summarised in Table 3, with the detailed individual study results provided in Table 4.

Table 3. Direction of findings.

Outcome	**Direction of association**		
	Studies showing no clear difference	**Studies showing possible harm**	**Studies showing possible benefit**
Preterm birth	Albouy-Llaty 2016	Sherris 2021	-
SGA	-	Migeot 2013	-
LBW	Coffman 2021	-	-
Congenital anomalies	-	Holtby 2014	-
Any neural tube defects	-	Brender 2013	-
Spina bifida	-	Brender 2013	-

Anencephaly	Brender 2013	-	-
Limb deficiencies	-	Brender 2013	-
Any oral cleft defects	-	Brender 2013	-
Cleft lip without cleft palate	-	Brender 2013	-
Cleft palate	-	Brender 2013	-
Conotruncal heart defects	Brender 2013	-	-
Right ventricular outflow tract obstruction heart defects	Brender 2013	-	-
Left ventricular outflow tract obstruction heart defects	Brender 2013	-	-
Septal heart defects	Brender 2013	-	-

"-": no study falls into this category.

Migeot 2013 [24] reported exposure to the second tertile (3.19 - 6.10 mg/L NO_3-N) of nitrate was associated with a possible increased risk of SGA birth (OR 1.74 [1.10, 2.75]), but there was no association between exposure to the highest tertile (> 6.10 mg/L NO_3-N) of nitrate with SGA birth (OR 1.51 [95% CI 0.96, 2.40]) (historic cohort study of 11,446 woman-infant pairs) [24] (Table 4).

Coffman 2021 [9] reported a linear inverse association between nitrate in drinking water and birth weight. Compared to the lowest exposure group (≤ 0.23 mg/L NO_3-N), exposure to increased nitrate in drinking water was associated with a small decrease in birth weight, but there was no evidence of association between nitrate in drinking water and low birth weight. They also reported that mean body length at birth decreased with increased nitrate in drinking water, but only in second highest exposure group (1.13 to ≤ 5.65 mg/L NO_3-N) not the highest exposure group (> 5.65 mg/L NO_3-N). They reported no association between nitrate in drinking water and head circumference at birth (prospective cohort study of 898,206 woman-infant pairs).

Holby 2014 [17] reported there was no association between increased nitrate exposure in drinking water and risk of congenital anomalies for the study period 1986-2006 (population-based case-control study of 606 cases and 1,635 controls).

Brender 2013 [18] reported that compared to the lowest tertile (< 0.65 mg/L or < 0.71 mg/L NO_3-N) of nitrate in drinking water, babies exposed to the highest tertile (> 3.5 mg/L or > 3.86 mg/L NO_3-N) of nitrate in drinking water had a potential increased risk of

neural tube defects, particularly spina bifida, limb deficiencies and oral cleft defects (case-control study of 3,300 cases and 1,121 controls woman-infant pairs).

Table 4. Adverse outcomes from included studies.

Outcome	Study	Case	Controls	Total	Exposure groups NO_3-N (mg/L)	Unadjusted OR/ MD (95% CI)	Adjusted OR/ MD (95% CI)
Preterm birth	Albouy-Llaty 2016	186	4,307	4,493	< 3.64[a]	1	1
		209	4,299	4,508	3.64 to 6.14[a]	1.17 (0.92, 1.38)	0.89 (0.55, 1.43)[b]
		187	4,293	4,480	> 6.14[a]	1.01 (0.82, 1.24)	0.75 (0.46, 1.23)[b]
	Sherris 2021	148,599	3,404,894	3,553,493	< 5.0	-	1
		18,946	404,732	423,678	5 to < 10	-	1.01 (1.009, 1.013)[c]
		966	22,464	23,430	≥ 10	-	1.003 (1.002, 1.004)[c]
SGA	Migeot 2013	120	1,642	1,762	< 3.19a	1	1
		281	2,835	3,116	3.19 to 6.10[a]	1.40 (1.12, 1.74)	1.74 (1.10, 2.75)
		257	2,739	2,996	> 6.10[a]	1.29 (1.03, 1.63)	1.51 (0.96, 2.40)
Low birth weight	Coffman 2021	2,026	184,156	186,182	≤ 0.23[a]	-	1
		2,057	180,813	182,870	0.23 to ≤ 0.45[a]	-	0.98 (0.92, 1.05)
		3,573	295,895	299,468	0.45 to ≤ 1.13[a]	-	1.01 (0.94, 1.08)
		1,972	148,047	150,019	1.13 to ≤ 5.65[a]	-	1.02 (0.95, 1.09)
		400	33,409	33,809	> 5.65[a]	-	0.99 (0.88, 1.12)

Outcome	Study	Case	Controls	Total	Exposure groups NO_3-N (mg/L)	Unadjusted OR/ MD (95% CI)	Adjusted OR/ MD (95% CI)
Birth weight (g)	Coffman 2021	-	-	186,182	≤ 0.23[a]	-	0
		-	-	182,870	0.23 to ≤ 0.45[a]	-	-3.6 (-6.8, -0.5)
		-	-	299,468	0.45 to ≤ 1.13[a]	-	-7.4 (-10.8, -4.1)
		-	-	150,019	1.13 to ≤ 5.65[a]	-	-8.1 (-11.6, -4.6)
		-	-	33,809	> 5.65[a]	-	-7.0 (-13.3, -0.7)
Body length at birth (mm)	Coffman 2021	-	-	185,379	≤ 0.23[a]	-	0
		-	-	182,001	0.23 to ≤ 0.45[a]	-	-0.1 (-0.2, 0.1)
		-	-	297,885	0.45 to ≤ 1.13[a]	-	-0.2 (-0.3, -0.02)
		-	-	149,114	1.13 to ≤ 5.65[a]	-	-0.4 (-0.5, -0.2)
		-	-	33,727	> 5.65[a]	-	-0.2 (-0.5, 0.1)
Head circumference at birth (mm)	Coffman 2021	-	-	140,486	≤ 0.23[a]	-	0
		-	-	126,561	0.23 to ≤ 0.45[a]	-	0.02 (-0.1, 0.2)
		-	-	218,398	0.45 to ≤ 1.13[a]	-	-0.2 (-0.4, -0.1)
		-	-	81,085	1.13 to ≤ 5.65[a]	-	0.1 (-0.1, 0.2)
		-	-	22,451	> 5.65[a]	-	0.1 (-0.2, 0.3)
Any congenital anomalies	Holtby 2014	127	353	480	< 1.0	-	1
		351	931	1,282	1.0 to 5.56	-	1.65 (0.83, 3.27)

Outcome	Study	Case	Controls	Total	Exposure groups NO_3-N (mg/L)	Unadjusted OR/ MD (95% CI)	Adjusted OR/ MD (95% CI)
		127	351	478	> 5.56	-	1.66 (0.81, 3.42)
Any neural tube defects	Brender 2013	67	367	434	< 0.65[d]	1	1
		65	360	425	0.65 to 3.5[d]	0.99 (0.68, 1.43)	1.00 (0.68, 1.45)
		95	374	469	> 3.5[d]	1.39 (0.99, 1.96)	1.43 (1.01, 2.04)
Spina bifida	Brender 2013	30	367	397	< 0.65[d]	1	1
		42	360	402	0.65 to 3.5[d]	1.43 (0.87, 2.33)	1.41 (0.86, 2.32)
		62	374	436	> 3.5[d]	2.03 (1.28, 3.21)	2.02 (1.27, 3.22)
Anencephaly	Brender 2013	31	367	398	< 0.65[d]	1	1
		17	360	377	0.65 to 3.5[d]	0.56 (0.30, 1.03)	0.58 (0.32, 1.08)
		23	374	397	> 3.5[d]	0.73 (0.42, 1.27)	0.78 (0.44, 1.37)
Any limb deficiencies	Brender 2013	23	370	393	< 0.71[d]	1	1
		29	367	396	0.71 to 3.86[d]	1.27 (0.72, 2.24)	1.17 (0.66, 2.07)
		42	368	410	> 3.86[d]	1.84 (1.08, 3.11)	1.79 (1.05, 3.08)
Any oral cleft defects	Brender 2013	122	370	492	< 0.71[d]	1	1
		120	366	486	0.71 to 3.86[d]	0.99 (0.74, 1.33)	0.98 (0.73, 1.32)
		173	367	540	> 3.86[d]	1.43 (1.09, 1.88)	1.45 (1.10, 1.92)
		24	370	394	< 0.71[d]	1	1

Outcome	Study	Case	Controls	Total	Exposure groups NO_3-N (mg/L)	Unadjusted OR/ MD (95% CI)	Adjusted OR/MD (95% CI)
Cleft lip without cleft palate	Brender 2013	29	366	395	0.71 to 3.86[d]	1.22 (0.70, 2.14)	1.13 (0.64, 1.99)
		47	367	414	> 3.86[d]	1.97 (1.18, 3.30)	1.82 (1.08, 3.07)
Cleft palate	Brender 2013	23	370	393	< 0.71[d]	1	1
		29	366	395	0.71 to 3.86[d]	1.12 (0.66, 1.88)	1.12 (0.66, 1.90)
		42	367	409	> 3.86[d]	1.88 (1.17, 3.01)	1.90 (1.17, 3.09)
Conotruncal heart defects	Brender 2013	58	370	428	< 0.71[d]	1	1
		41	367	408	0.71 to 3.86[d]	0.71 (0.47, 1.09)	0.72 (0.47, 1.11)
		65	368	433	> 3.86[d]	1.13 (0.77, 1.65)	1.18 (0.80, 1.74)
Right ventricular outflow tract obstruction heart defects	Brender 2013	36	370	406	< 0.71[d]	1	1
		31	367	398	0.71 to 3.86[d]	0.87 (0.53, 1.43)	0.89 (0.54, 1.48)
		53	368	421	> 3.86[d]	1.48 (0.95, 2.32)	1.47 (0.93, 2.33)
Left ventricular outflow tract obstruction heart defects	Brender 2013	44	370	414	< 0.71[d]	1	1
		58	367	425	0.71 to 3.86[d]	1.33 (0.88, 2.02)	1.31 (0.86, 2.00)
		54	368	422	> 3.86[d]	1.23 (0.81, 1.88)	1.16 (0.75, 1.78)
Septal heart defects	Brender 2013	203	370	573	< 0.71[d]	1	1
		210	367	577	0.71 to 3.86[d]	1.04 (0.82, 1.33)	0.92 (0.69, 1.22)
		156	368	524	> 3.86[d]	0.76 (0.59, 0.98)	0.98 (0.71, 1.34)

[a]NO_3^- (mg/L) were converted to NO_3-N (mg/L): Nitrate-N (mg/L) = 0.2259 x Nitrate-NO_3 (mg/L) [b]The adjusted analysis only included 4,937 woman-infant pairs.

[c]Rate Ratio for one mg/L of nitrate in water.

[d]Converted mg/day to mg/L by dividing by average water consumption (1.4 L/day).

'-': data not available. OR: odds ratio. MD: mead difference

Evidence from other study types

Blake 2014 [27] used a spatial analysis to explore the relationship between nitrate exposure level within ZIP codes and low birth weight. The authors reported there was no correlation between low birth weight and unsafe nitrate levels (> 10 mg/L as NO_3-N). Two ecological studies [11, 16] from the same cohort explored the association between average county-level nitrate concentrations in drinking water and adverse outcomes. Antenatal exposure to nitrate in drinking water was associated with a possible increased risk of limb deficiencies, but no association was found between antenatal exposure to nitrate in drinking water and preterm birth, low birth weight, neural tube defects or oral cleft defects.

Two cross-sectional studies [28, 29] linked birth record, maternal and infant hospital discharge records to CalEnviro Screen 3.0 dataset from California Communities Environmental Health Screening Tool to explore the relationship between preterm birth, gestational hypertension, eclampsia and environmental factors including nitrate in drinking water. The investigators reported that nitrate in drinking water is potentially associated with preterm birth in California. There was insufficient evidence suggesting that nitrate in drinking water was associated with hypertensive disorders or eclampsia in pregnancy.

Table 5. Characteristics of ecological studies.

Study name	Country, Region	Study design	Years of Outcome Ascertainment	Exposure description	Perinatal outcomes reported	Summary of findings
Blake 2014	USA, California	Ecological study	2011	Drinking water source data in the study ZIP codes were accessed from the California State Ground Water Ambient Monitoring and Assessment Program (GAMA) (California Water Board [CWB], 2013), a public geo-database that provides locations and water quality data by ZIP code and address. Unsafe nitrate levels at ZIP code level: > 10 mg/L as NO_3-N	Low birth weight	ZIP codes with more dairy farms and a higher dairy cow density had higher levels of nitrate contamination. No correlation was detected between low birth weight and unsafe nitrate levels at the ZIP code level.
Blaisdell 2019	USA, Missouri	Ecological study	2004-2008	Average monthly concentrations of nitrate in drinking water were calculated from the finished water measurements taken from each Missouri community water system during the years 2004 – 2008. Monthly county-level average nitrate concentrations were linked to each birth by county and month of birth to estimate mean exposure during the 12 months prior to birth and during the first trimester of pregnancy. Range of nitrate concentrations reported: 0.03 to 6.36 mg/L as NO_3-N	Neural tube defects, congenital heart defects, oral cleft defects, limb deficiencies, gastroschisis, hypospadias, Down Syndrome	Antenatal exposure to nitrate in drinking water was only associated with an increased rate of limb deficiencies. Rate Ratio for 1 mg/L = 1.26, 95% CI 1.05, 1.51
Stayner 2017	USA, Indiana,	Ecological study	2004–2008	Average monthly county-level mean nitrate concentrations in counties were calculated from finished water (water that has passed through all the processes in a water treatment plant) for each community water system and	Preterm birth Low birth weight	There were no associations between antenatal exposure to nitrate in drinking water and preterm birth or low birth weight overall.

	Iowa, Missouri, and Ohio			weighted by the population; Monthly county-level average nitrate concentrations were linked to each birth. The mean of the monthly county-level nitrate concentrations measured was 0.95 ± 0.92 mg/L as NO_3-N. 1.8% of the monthly estimates for nitrate exceeded 10 mg/L as NO_3-N		
Huang 2018	USA, California	Cross-sectional study	2009-2012	Birth cohort file from the California Office of Statewide Health linked to CalEnviro Screen 3.0 dataset from California Communities Environmental Health Screening Tool. Range of nitrate level reported: 1.41 - 85.48 mg/L as NO_3^- or 0.32 - 19.30 mg/L as NO_3-N	Preterm birth	Nitrate in drinking water was potentially associated with preterm birth in California. Odds ratio per increase in interquartile range (9.33 mg/L NO_3^- or 2.11 mg/L NO_3-N) is 1.02 (95 % CI 1.01, 1.03)
Padula 2021	USA, California	Cross-sectional study	2007- 2012	California birth certificates and maternal and infant hospital discharge records from the Office of Statewide Health Planning and Development linked to CalEnviro Screen 3.0 dataset from California Communities Environmental Health Screening Tool. Range of nitrate level reported: 1.41 - 85.48 mg/L as NO_3^- mg/L or 0.32 - 19.30 mg/L as NO_3-N	Gestational hypertension, eclampsia	Nitrate was not associated with hypertensive disorders, severe preeclampsia/ eclampsia in pregnancy in the single pollutant model. Nitrate was associated with hypertensive disorders, severe preeclampsia/ eclampsia in pregnancy only in the multipollutant model including all contaminates (arsenic, cadmium,1,2-Dibromo-3-chloropropane, hexavalent chromium, lead, nitrate, perchlorate, tetachloroethylene, radium, trichloroethylene, 1,2,3-trichloropropane, trihalomethane, uranium)

Discussion

Five observational studies, assessed as high quality, involving 5,031,454 participants were included. However, the overall association between nitrate in drinking water and adverse reproductive outcomes is uncertain.

The evidence did not support a linear association between nitrate in drinking water and increased preterm birth risk (OR 0.98 [95% CI 0.93, 1.03]), and findings were different amongst studies. Although ecological and cross-sectional studies cannot establish causal inferences, they do permit further investigation of statistical relationships and identify hypotheses for future research to determine causality [30]. Taken together, the evidence of a relationship between nitrate in drinking water and preterm birth is inconsistent and inconclusive.

We observed substantial heterogeneity in our analysis of preterm birth ($I^2 = 100\%$, $p < 0.0001$). Several factors may contribute to the inconsistent findings amongst studies. The first reason is the different study characteristics. Albouy-Llaty 2016 was conducted in France with a reported preterm birth rate of 7.5% of all live births in 2016 [31]; while Sherris 2021 was conducted in the US with reporting preterm birth rate of 10.1% of all live births in 2020 [32]. In addition, the two studies monitored different exposure periods: Albouy-Llaty 2016 estimated the nitrate exposure during the second trimester of pregnancy, while Sherris 2021 measured the nitrate exposure throughout pregnancy. Moreover, while Albouy-Llaty 2016 studied 13,481 participants, only 4,625 participants were included in their adjusted analytical model. In comparison, Sherris 2021 analysed data from 3,832,090 participants. Another factor may be the different statistical models used and adjustment for different confounding factors. Albouy-Llaty 2016 used a multivariable logistic regression model adjusted for rural area, season, maternal age, mother's occupation, smoking during pregnancy, single-parent family, history of preterm birth, primiparity and quality of follow-up; while Sherris 2021 used mixed-effects logistic regression adjusted for maternal age, parity, education, race, payer for delivery, and prenatal care initiation.

Further, the limits of exposure categories were different between the two studies. To calculate the exposure-response relationship for nitrate in drinking water and preterm birth risk, we used several transformations. For the study by Albouy-Llaty 2016, when adjusting for confounders, both relationships between preterm birth and second tertile nitrate exposure group (OR 0.89 [95% CI 0.55, 1.43]), and preterm birth and third tertile nitrate exposure group (OR 0.75 [95% CI 0.46, 1.23]) were non-significant, but the direction of the findings was towards a protective effect. Therefore, the result of the generalised least squares regression analysis yielded negative study-specific slopes and

the odds ratio for 1 mg/L increase in nitrate that indicated a protective effect. For the study by Sherris 2021, the odds ratio for 1 mg/L was reported by the authors but for different gestational age subgroups (20-31 gestational weeks and 32-36 gestational weeks). We pooled the odds ratios for these subgroups to obtain the results for 1 mg/L increase in nitrate for overall preterm birth. This pooled estimate indicates nitrate in drinking could be a risk factor for preterm birth, but the several steps of conversion may reduce the accuracy of the estimation.

Studies included in this systematic review suggest that there is no association between nitrate in drinking water and the risk of low birth weight [9] or congenital heart defects overall [16, 18]. Further, the evidence of a relationship between nitrate in drinking water and neural tube defects or oral cleft defects is inconsistent. One case-control study [18] indicated that nitrate in drinking water may be associated with an increased risk of neural tube defects and oral cleft defects, while an ecological study [16] did not find an association. Moreover, the association between nitrate in drinking water and increased risk of SGA was only seen in the second tertile of nitrate exposure group not in the highest tertile group, so there was no significant positive linear association between nitrate in drinking water and the risk of SGA.

Nitrate in drinking water may be associated with an increased risk of limb deficiencies. Specifically, expectant women exposed to > 3.86 mg/L of NO_3-N in drinking water had nearly twice the odds of giving birth to a child with limb deficiencies compared to women exposed to less than 0.71 mg/L NO_3-N in drinking water (OR 1.79 [95% CI 1.05, 3.08]) in the Brender study [18]. Blaisdell 2019 using Poisson regression models, found that the risk of limb deficiencies increased with estimated nitrate exposure (Rate Ratio for 1 mg/L = 1.26 [95% CI 1.05, 1.51]) [16]. However, the durations of nitrate exposure are varied. Brender 2013 measured the nitrate exposure from 1 month before conception to 1 month post conception, while Blaisdell 2019 measured the nitrate exposure from 12 months prior to birth and during the first trimester of pregnancy. In New Zealand, in the past eight years on average 13 infants (range from 2 to 21 infants) per year have been born with limb deficiencies. If the association is causal, this would potentially result in three additional infants born with limb deficiencies per year per 1 mg/L increase in NO_3-N exposure [33].

The nitrate levels in drinking water reported in the different studies vary, but most of the high-quality studies investigated levels that were within the New Zealand MAV (11.3 mg/L NO_3-N). However, Sherris, who reported a relationship between high nitrate exposure and preterm birth [10] selected the high exposure cut-off as > 10 mg/L NO_3-N and median exposure cut-off as 5 mg/L NO_3-N to correspond to MCL level and half MCL level respectively for nitrate in drinking water in USA, although only 0.6% of the

population were exposed to this level. Further, the ecological study by Blake et al [27], which did not find the correlation between preterm birth and unsafe nitrate level in drinking water, also assessed exposure to the unsafe nitrate level in drinking water of 10 mg/L NO_3-N. The maximum nitrate level in drinking water (19.3 mg/L NO_3-N) reported in the two cross-sectional studies [28, 29] was almost equivalent to twice the US MCL of 10 mg/L NO_3-N, but 75% of the population in the study region were exposed to < 2.44 mg/L NO_3-N.

About half of New Zealand's drinking water is pumped from the ground, with the remainder coming from surface sources [4]. Groundwater is recharged from the surface, predominantly from rainfall, but can also receive leakage from rivers and lakes [3]. Drinking water suppliers in New Zealand are not required to routinely monitor or report on nitrate levels if levels have been previously found to be below 25 mg/L as NO_3^- (50% of the MAV) [34]. Richard 2020 [35] estimated the variability of nitrate levels in drinking water in New Zealand, and found the nitrate levels in drinking water from registered supplies ranged from less than detection (< 0.01 mg/L) to 41.8 mg/L. More than 60% of the population were exposed to less than 2 mg/L as NO_3^-, 8.2% of the population were exposed to more than 5 mg/L as NO_3^-, 2.2% were exposed to more than 10 mg/L as NO_3^-, and 0.1% of the population were exposed to more than 25 mg/L as NO_3^- [35]. Although the nitrate level in groundwater in New Zealand is lower than the MAV, long-term trends (10 years, 2009-2018) showed 28-35% of sites had increasing levels of nitrate over time [36]. Further, nitrate contamination present in the groundwater would likely stay there for years or decades, so exposures identified are likely to continue or increase if nitrate removal technologies are not utilised [37].

The current evidence for relationships between exposure to nitrate in drinking water and reproductive outcomes is inconsistent. High quality, large epidemiology studies are needed to further assess any associations. However, nitrate concentrations in New Zealand are not regularly monitored if below 50% of MAV [34], and there is no national repository of nitrate exposure data for the New Zealand population [35]. In the recently published high quality studies, Sherris 2021 included around 6 million participants and Coffman 2021 included 852,348 participants. In New Zealand, there are around 58,000 births annually and the estimated preterm birth rate is 7.4% [38]. Thus, it will be difficult to reach adequate sample size to draw reliable conclusions about nitrate exposure and reproductive outcomes in New Zealand, since this would require matching at least 15 years of birth data with individual or regional nitrate exposure in drinking water.

Evidence from a recent report estimated that while New Zealanders have similar nitrate exposure from drinking-water to that in most other countries, total nitrate intake from

drinking water is less than 10% [2]. While this is of note, the conclusions drawn in the report should be interpreted with caution as the data analysed were from more than ten years ago and the outcome of interest was limited to the risk of colorectal cancer rather than adverse prenatal outcomes.

This review has some limitations. First, most of the studies were carried out in US and Europe. Given that nitrate levels in drinking water vary widely among different regions and countries, findings from these studies should be interpreted with caution when extrapolated to New Zealand. Second, the studies included in this systematic review do not consistently account for other potential confounding factors such as maternal diet, nitrosatable drug use, and antioxidant intake, to name a few. Third, the concentration of nitrate in water often fluctuates with the season [1]. Only three of the five studies included in this review took seasonal variation of nitrate into account in the measurement of exposure or as a factor in the adjusted model. In New Zealand, nitrogen shows significant seasonal relationships with high-intensity agriculture, with the difference between summer and winter water quality increasing as the proportion of high intensity agriculture in a catchment increases. Spatial modelling supports these findings, with regions dominated by high-intensity agriculture typically having poorer clarity, turbidity and nutrient concentrations in winter than in summer [39]. Fourth, in meta-analysis of observational studies, it is challenging or impossible to identify any unpublished studies, as pre-registration of a protocol is not mandatory [40]. Finally, of all of the pre-specified outcomes, only preterm birth could be incorporated into a meta-analysis to help determine the overall association.

We conclude that currently there is no consistent evidence of a relationship between nitrate in drinking water and adverse reproductive outcomes. However, there are sufficient studies suggesting possible relationships with specific congenital anomalies to warrant nitrate exposure monitoring and reporting in New Zealand, and regular review as new evidence becomes available.

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Supplement 1. Search strategies

Ovid MEDLINE(R) Epub Ahead of Print, In Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily, and Ovid MEDLINE (R) 1946-Present

1	Nitrates/	30035
2	nitrate*.af.	81519
3	1 or 2	81519
4	Drinking Water/	9261
5	water supply/ or water wells/	33977
6	Water/	165506
7	groundwater/	8824
8	(groundwater or aquifer*).ti,ab,kw.	24443
9	water.ti,ab,kw,kf.	840827
10	or/4-9	902829
11	exp Pregnancy/	929177
12	exp Pregnancy Complications/	442782
13	Maternal-Fetal Exchange/	29788
14	(maternal fetal exchange or maternal foetal exchange).mp.	29962
15	((transplacent* or trans-placent*) adj (exposure or exchange)).mp.	275
16	(stillbirth* or still-birth*).ti,ab,kw.	13936
17	(preeclamp* or pre-eclamp* or eclamp*).ti,ab,kw.	38825
18	((pregnan* or postpartum* or post-partum* or perinatal* or peri-natal* or puerperal) and (complication* or infecti* or haemorrhag* or hemorrhag* or sepsis or septic)).ti,ab,kw,kf.	129127
19	((neonatal or neo-natal or perinatal or peri-natal) adj death*).ti,ab,kw.	11850
20	or/11-19	1003918
21	infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, premature/ or infant, extremely premature/	70462
22	(low adj (birth weight* or birthweight*)).mp.	47316
23	(sga or "small for gestational age").mp.	16961
24	((fetal or foetal or intrauterin* or intra-uterin*) adj3 (restrict* or retard*)).mp.	27533
25	((preterm or pre-term or prematur*) adj2 (birth or births or born or labour or labor)).ti,ab,kw.	44229
26	(prematurity or congenital or spontaneous abort*).mp.	398821

27 ((preterm or pre-term or prematur*) adj2 (baby or babies or infant or infants)).ti,ab,kw. 52414

28 infant, premature, diseases/ or bronchopulmonary dysplasia/ or leukomalacia, periventricular/ or respiratory distress syndrome, newborn/ or hyaline membrane disease/ or "transient tachypnea of the newborn"/ 39921

29 jaundice, neonatal/ or neonatal sepsis/ 6817

30 ((intraventricular or intra-ventricular) adj3 (hemorrhag* or haemorrhag*)).mp. 8204

31 (severe brain injur* and (infant* or baby or babies or prematur* or newborn* or new* born* or neonat* or neo-nat* or preterm or pre-term)).mp. 285

32 Enterocolitis, Necrotizing/ 3846

33 Hypoglycemia/ 28300

34 (bronchopulmonary dysplasia* or broncho-pulmonary dysplasia*).ti,ab,kw. 7817

35 (necroti* enterocolitis o2r necroti* entero-colitis).ti,ab,kw. 8507

36 ((hypoglyc* or respirat* or infection* or sepsis or septic or jaundice or lung or lungs) and (infant* or baby or babies or prematur* or newborn* or new* born* or neonat* or neo-nat* or preterm or pre-term)).mp. 346137

37 Intensive Care, Neonatal/ 5891

38 (neonatal intensive care or nicu).ti,ab,kw. 25808

39 or/21-38 855194

40 20 or 39 1673064

41 3 and 10 and 40 159

42 limit 41 to last 10 years 63

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