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Sylvain Chamot, Abdallah Al-Salameh, Pascal Petit, Vincent Bonneterre, Christophe Cancé, et al.. Does prenatal exposure to multiple airborne and tap-water pollutants increase neonatal thyroid-stimulating hormone concentrations? Data from the Picardy region, France. *Science of the Total Environment*, 2023, 905, pp.167089. 10.1016/j.scitotenv.2023.167089 . hal-04213094

HAL Id: hal-04213094

<https://u-picardie.hal.science/hal-04213094>

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Does prenatal exposure to multiple airborne and tap-water pollutants increase neonatal thyroid-stimulating hormone concentrations? Data from the Picardy region, France

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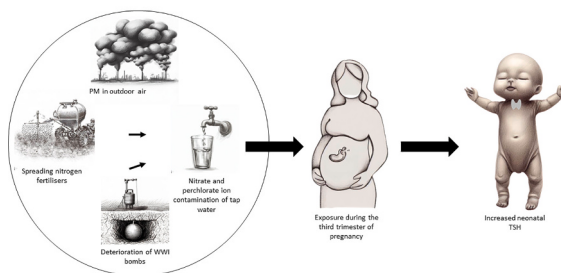
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HIGHLIGHTS

- Spatial distribution of neonatal TSH levels is heterogeneous in Picardy, France.
- Environmental pollutants could impact neonatal TSH levels.
- Evaluation of exposure to certain pollutants in the third trimester of pregnancy
- Prenatal exposure to perchlorate and nitrate increased neonatal TSH levels.
- Prenatal exposure to particulate matter increased neonatal TSH levels.

GRAPHICAL ABSTRACT

Does prenatal exposure to multiple airborne and tap-water pollutants increase neonatal thyroid-stimulating hormone concentrations? Data from the Picardy region, France
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<https://doi.org/10.1016/j.scitotenv.2023.167089>

Received 17 July 2023; Received in revised form 12 September 2023; Accepted 13 September 2023

Available online 17 September 2023

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ARTICLE INFO

Editor: Lidia Minguez Alarcon

Keywords:

Prenatal exposure
Endocrine disruption
Pesticides
Perchlorates
Nitrates
Air pollution

ABSTRACT

Objective: Systematic screening for congenital hypothyroidism by heel-stick sampling has revealed unexpected heterogeneity in the geographic distribution of newborn thyroid-stimulating hormone concentrations in Picardy, France. We explored a possible relationship with environmental pollutants.

Methods: Zip code geolocation data from mothers of newborns without congenital hypothyroidism born in 2021 were linked to ecological data for a set of airborne (particulate matter with a diameter of 2.5 μm or less [$\text{PM}_{2.5}$] or 10 μm or less [PM_{10}]) and tap-water (nitrate and perchlorate ions and atrazine) pollutants. Statistical associations between mean exposure levels during the third trimester of pregnancy and Thyroid-stimulating hormone (TSH) concentrations in 6249 newborns (51 % male) were investigated using linear regression models.

Results: Median neonatal TSH concentration (interquartile range, IQR) was 1.7 (1–2.8) mIU/L. An increase of one IQR in prenatal exposure to perchlorate ions (3.6 $\mu\text{g/L}$), nitrate ions (19.2 mg/L), $\text{PM}_{2.5}$ (3.7 $\mu\text{g/m}^3$) and PM_{10} (3.4 $\mu\text{g/m}^3$), were associated with increases in TSH concentrations of 2.30 % (95 % CI: 0.95–3.66), 5.84 % (95 % CI: 2.81–8.87), 13.44 % (95 % CI: 9.65–17.28) and 6.26 % (95 % CI: 3.01–9.56), respectively.

Conclusions: Prenatal exposure to perchlorate and nitrate ions in tap water and to airborne PM over the third trimester of pregnancy was significantly associated with increased neonatal TSH concentrations.

1. Introduction

Congenital hypothyroidism is defined as thyroid hormone deficiency present at birth. In the absence of prompt diagnosis, it can result in irreversible neurological deficits. All newborns in France are screened for congenital hypothyroidism on the basis of Thyroid-stimulating hormone (TSH) determinations, which have been performed as part of the national newborn screening program since 1978. This program is conducted at regional scale (France is subdivided into 22 administrative regions) by regional centers of newborn screening that organize and monitor the entire program in the region concerned, under the supervision of a national coordinating center.

Major geographic disparities in TSH concentrations have been found in newborns without congenital hypothyroidism in the Picardy region, and no clear explanation for the observed differences has yet been found (Fig. S1 and Table S1 in Supplementary Material).

Picardy is a region of northern France characterized by intensive agriculture, with high levels of pesticide and fertilizer use, in terms of both the amounts applied and the frequency of applications (Ministère de la Transition Ecologique et Solidaire, 2022; Solagro, 2022). Air pollution levels are also high (INERIS, 2020). However, it remains unclear whether there is any relationship between the observed disparities in newborn TSH concentrations and heavy pesticide use or air pollution.

Indeed, inconsistent associations have been reported between exposure to environmental pollutants and various biomarkers of thyroid homeostasis in newborns. Significant associations have been reported for bisphenols (Xiong et al., 2023), dioxin, polychlorinated biphenyls (PCB) and polybrominated diphenyl ethers (PBDE) (Baccarelli et al., 2008; Maervoet et al., 2007; Wang et al., 2005), the polycyclic aromatic hydrocarbon (PAH) acenaphthene (Dehghani et al., 2022), cadmium and cesium (Iijima et al., 2007; Wang et al., 2020), paraben (Li et al., 2020), perfluorinated-alkyl-acids (PFAAs) (Boesen et al., 2020) and particulate matter with a diameter of 2.5 μm or less ($\text{PM}_{2.5}$) or 10 μm or less (PM_{10}) (Howe et al., 2018; Janssen et al., 2017).

Variable associations have been reported with organochlorine pesticides levels (Asawasinsoy et al., 2006; Freire et al., 2011; Li et al., 2014; Luo et al., 2017; Maervoet et al., 2007), whereas no association has been retrieved for organophosphates (Mulder et al., 2019).

In Picardy, two well-known thyroid disruptors are also found in significant amounts in tap water: perchlorate (Garnier et al., 2012) and nitrate ions (Direction régionale de l'environnement, de l'aménagement et du logement des Hauts-de-France, 2021). Perchlorate ions are the products of the degradation of buried World War I bombs and from certain fertilizers that have been used along the 20th century. Nitrates ions mostly originate from the nitrogen fertilizers used in agriculture. Perchlorate and nitrate ions can disrupt thyroid functions by blocking the uptake of iodine, which is required for hormone production. They inhibit the transport of iodide ions (I^-) in the thyroid gland, as they share

the same transport mechanism (French Agency for Food, Environmental and Occupational Health, and Safety, 2012; Ward et al., 2018). This inhibition may lead to a decrease in thyroid hormone secretion (T_4 , T_3), inducing in turn increases TSH concentrations. Both perchlorate and nitrate ions cross the placental barrier (French Agency for Food, Environmental and Occupational Health, and Safety, 2012; Shuval and Gruener, 1972).

The aim of this study was to investigate the possible association between environmental prenatal exposures to the aforementioned airborne and tap water pollutants and neonatal TSH concentrations. For this purpose, we used the Picardy congenital hypothyroidism registry of the Regional center of newborn screening of Picardy and linked it to ecological data.

2. Methods

2.1. Neonatal TSH concentrations

We studied samples from every newborn born between January 1, 2021 and December 31, 2021 from the Picardy congenital hypothyroidism registry. All samples were taken from the newborn's heel on the third day of life and analyzed at Amiens' University Hospital. Information on the place of residence (zip code) of the mothers of newborns born in Picardy was available. Other available information included the sex of the child, time of birth, gestational age, and TSH concentration. A TSH value >17 mIU/L on the third day of life was considered abnormal and, if confirmed on a second sample, led to the diagnosis of congenital hypothyroidism (GSP hTSH Neonatal kit from PerkinElmer). A data management step was required to delete duplicates, samples from newborns with aberrant gestational ages, and samples for which the sex of the infant or the zip code was not noted. Inclusion criteria were: birth in the Picardy region between January 1st, 2021 and December 31st, 2021; available data for the sex and gestational age and available ecological data for the zip code of the mother's residence. Exclusion criteria were: newborns with congenital hypothyroidism; newborns with missing data for sex or gestational age and newborns with missing ecological data."

2.2. Environmental pollution data

The only information available for estimating the child's prenatal exposure to environmental pollutants was the zip code of the municipality in which the mother was living when the child was born. We matched the data from the Picardy congenital hypothyroidism registry with the data for water and air quality in the area corresponding to the zip code available from public or open-access databases.

2.2.1. Tap water

Tap water quality has been monitored since 1994 in France

(Direction Générale de la Santé, 2023). The database containing tap-water monitoring data can be consulted at municipality level and is open-access since 2016. Decisions about sampling and its frequency depend on the molecule, contamination history, the flow rate of the network sampled and the size of the population supplied. Our choice of appropriate pollutants for study was guided by the spatial distribution of the data recorded in the database. Only substances associated with changes in neonatal thyroid hormone concentrations and potential endocrine disruptors were studied. Endocrine disruptors were identified by selecting substances with an action on thyroid homeostasis according to the DEDuCT database (Karthikeyan et al., 2019, 2021). We chose to focus on the tap-water levels of perchlorate ions, nitrate ions and atrazine for this study (Figs. S2 to S5).

2.2.2. Outdoor air

Air quality has been monitored and mapped at municipality level in France since 2000 (INERIS, 2020; Real et al., 2022). Assessments are made daily and are simulated by kriging with the CHIMERE chemistry transport model (Menut et al., 2013). We focused on PM_{2.5} and PM₁₀, which have been shown to be associated with variations of neonatal thyroid hormones. The spatial distribution of the results is illustrated in Figs. S6 and S7.

2.3. Assessment of prenatal exposure

The fetal thyroid gland becomes functional during the second trimester of gestation, providing the fetus with its own supply of thyroid hormones in addition to those supplied by the mother. Fetal T4 concentrations reach adult concentrations at the start of the third trimester of gestation. We therefore focused exclusively on exposure during the third trimester, as in a previous study on air pollution (Janssen et al., 2017). We assessed prenatal exposure to each pollutant by using the mean of the available results on the zip code for each child during the third trimester of pregnancy.

For tap water monitoring results, values below the limits of quantification were replaced with random variables ranging from 0 (excluded) to the limit of quantification value. The quantification limits were systematically specified in the database and the R “runif” function was used to generate random values. Newborns for whom ecological data were absent for at least one of the pollutants studied during their exposure

period were excluded from the study. The final analysis was performed on data for 6249 of the 17,825 newborns born in 2021 for whom we had information for the pollutants studied during the 3rd trimester of pregnancy (Fig. 1). The data for perchlorate ions were the most limited in scope, due to the low frequency of testing and the restriction of tests to certain geographic areas deemed by public authorities to be contaminated, which could be debated scientifically as the degradation of buried World War I bombs is an ongoing dynamic process.

2.4. Statistical analysis

Baseline demographic and clinical characteristics are expressed as medians and interquartile ranges (IQR) for continuous variables and as frequency (percent) for categorical variables. Pearson's correlation analyses were performed to assess the association between prenatal exposure to pollutants. Simple and multiple linear regression models were used to assess the association between the levels of various pollutants and neonatal TSH concentrations. The TSH concentrations were log-transformed to obtain a normal distribution. Multiple regression analyses were adjusted for two potential confounders: gestational age and sex. The regression models were based on the ordinary least squares method with a normal distribution and the identity link function.

The threshold selection method ($P > 0.2$) was used for the multiple regression models. We successively run a simple linear regression models for gestational age and sex, multivariate single-pollutant regression models and multivariate multi-pollutant regression models. The conditions of validity for the linear regression of each model were investigated by checking the independence of model residuals (Durbin-Watson test), the normality of the distribution of residuals (Shapiro-Wilk test) and the homogeneity of residual variances (Breusch-Pagan test).

For multiple linear regression models, covariates that were collinear (variance inflation factor > 2.5) were excluded. A subgroup analysis by sex was also performed. The interactions between the variables of the models were studied. We considered P values < 0.05 in two-tailed tests to be statistically significant for all models. All statistical tests were performed with R software (R Core Team, 2022) with the “stats” package version 4.4.0 and the “performance” package version 0.10.4 (Lüdtke et al., 2021). The full script used to select our study population, to link the Picardy congenital hypothyroidism registry with ecological data, and the statistical analyses described are available in the

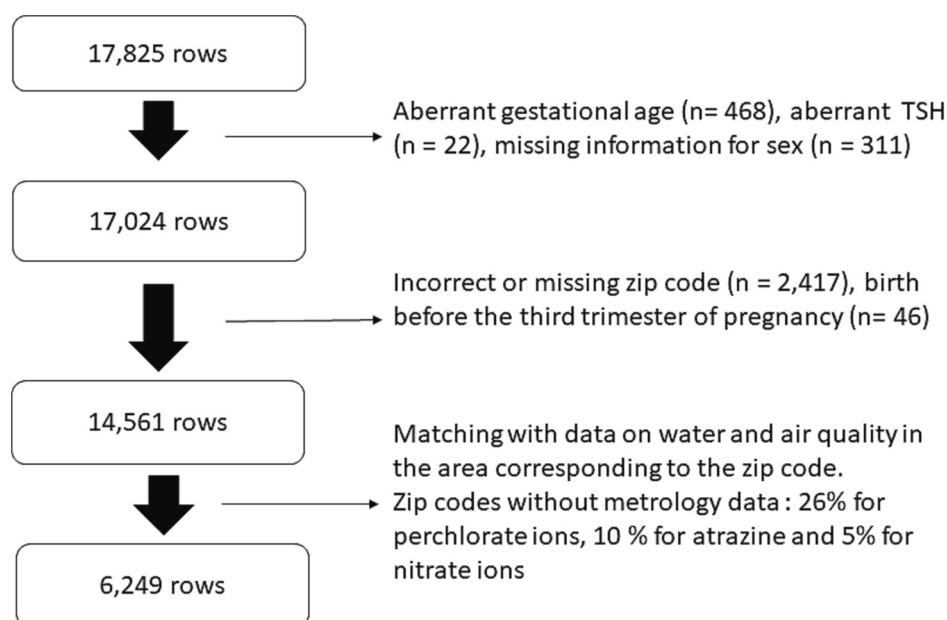


Fig. 1. Flow chart describing the procedure for selecting the study population from the Picardy congenital hypothyroidism register for newborns in 2021.

Supplementary Material (Script File).

2.5. Ethics statement

This study was performed in accordance with the reference methodology for research not involving human subjects in the health field, CNIL MR 004, under the authority of Amiens University Hospital (authorization number PI2021_843_0127).

3. Results

3.1. Characteristics of the study population

The characteristics of the study population and the environmental pollutants studied over 2020–2021 in the geographic area considered are shown in Table 1. For perchlorate ions, the recorded values exceeded the control limit of 4 µg/L for children ≤6 months of age in 28.5 % (544 of 1910) of the samples (French Agency for Food, Environmental and Occupational Health, and Safety, 2012). Only 2 % (501 of 25,045) of the samples exceeded the quality limit of 50 mg/L for nitrate ions (French Agency for Food Safety, 2008). For atrazine, we did not compare the results to the regulatory maximum concentration (10 µg/L) since it is not based on a toxicological approach (Ministères des solidarités et de la santé, 2020). Levels were below the limit of quantification for 30.9 % (590 of 1910) of samples for perchlorate ions, 53.1 % (2376 of 4479) of samples for atrazine and 2.8 % (707 of 25,045) of samples for nitrate ions. There were no missing values in the environmental databases. The characteristics of the population not studied because of the absence of pollution data are presented in the supplementary Table S2.

3.2. Single-pollutant models

In single-pollutant models, after adjusting for sex and gestational

Table 1
Characteristics of the study population and of raw metrology results/assessments in the study area for 2020–2021.

Characteristics	n (%) or median (Interquartile range)
Newborns (n = 6249)	
TSH (mUI/L)	1.7 (1–2.8)
Female	3067 (49.1 %)
Gestational age (weeks)	39.9 (38.9–40.7)
PM _{2.5}	
PM ₂₅ (µg/m ³)	8.5 (4.7–10.1)
PM ₁₀	
PM ₁₀ (µg/m ³)	15.1 (10–18.4)
Perchlorate ions (n = 1910)	
Perchlorate ion (µg/L)	2.0 (0.7–4.5)
Below LQ	590 (30.9 %)
Above control limit (4 µg/L)	544 (28.5 %)
Atrazine (n = 4479)	
Atrazine (µg/L)	0.007 (0.003–0.02)
Below LQ	2376 (53.1 %)
Nitrate ions (n = 25,045)	
Nitrate ion (mg/L)	25.9 (18.0–35.9)
Below LQ	707 (2.8 %)
Above quality limit (50 mg/L)	501 (2 %)

n: number of people in the population studied for newborns or number of samples taken for water in the zip codes of the population studied. Median and interquartile range for continuous variables and frequency (percent) for categorical variables. TSH: Thyroid-stimulating hormone. PM_{2.5}: particulate matter with a diameter of 2.5 µm or less. PM₁₀: particulate matter with a diameter of 10 µm or less. LQ: limit of quantification.

age, an increase of one interquartile range (IQR) in exposure to perchlorate ions (equivalent to 3.6 µg/L), nitrate (equivalent to 19.2 mg/L), PM_{2.5} (equivalent to 3.7 µg/m³) and PM₁₀ (equivalent to 3.4 µg/m³) during pregnancy was associated with an increased TSH concentrations in newborns of 2.30 % (95 % CI: 0.95–3.66; *p* < 0.001), 5.84 % (95 % CI: 2.81–8.87; *p* < 0.001), 13.44 % (95 % CI: 9.65–17.28; *p* < 0.001) and 6.26 % (95 % CI: 3.01–9.56; *p* < 0.001), respectively (Fig. 2 and Table 2). By contrast, prenatal atrazine exposure was not significantly associated with neonatal TSH concentration. Being male and an older gestational age were also associated with higher neonatal TSH concentrations.

3.3. Multipollutant models

Exposures to PM_{2.5} and PM₁₀ were strongly correlated (*r* = 0.88, *p* < 0.001) as shown in Fig. S8. We did not, therefore, incorporate these two variables together in the same model. With the exception of PM_{2.5} and PM₁₀, none of the variables were found to be collinear. The multipollutant models yielded similar results to the individual pollutant models (Table 3, Figs. 3 and 4). A significant interaction was observed between the levels of exposure to perchlorate and nitrate ions (*p* = 0.012 for the model including PM_{2.5} and *p* = 0.002 for the model including PM₁₀). Subgroup analysis, by sex, also yielded similar results, but with fewer significant differences, probably due to the smaller number of cases.

4. Discussion

We found that prenatal exposure to nitrate and perchlorate ions in tap water and to PM_{2.5} and PM₁₀ in outdoor air were associated with higher TSH concentrations in newborns. Tap-water contamination with atrazine was not significantly associated with TSH concentrations in newborns.

To our knowledge, only two other studies have investigated the link between exposure to PM in outdoor air and thyroid function. The ENVIRONAGE cohort study (*n* = 499) investigated PM_{2.5} exposure during the third trimester of pregnancy, based on umbilical cord blood assays (Janssen et al., 2017). They found an inverse association between exposure and TSH concentrations and reported a decline in FT4/FT3 ratio due to a decrease in free thyroxine (FT4) concentrations and an increase in free triiodothyronine (FT3) concentrations, suggesting changes in deiodinase activity. The association between exposure and TSH concentrations was almost significant, as an increase by one IQR in PM_{2.5} levels was associated with an 11.6 % [95 % CI: −21.8, −0.1; *p* < 0.05] decrease in cord blood TSH concentrations. These results are not consistent with those reported here, but the timing of sampling differed between the two studies. Cord-blood samples are collected immediately after delivery, whereas heel-stick samples are obtained on the third day of life. The difference in the methods used (heel-stick in this study and umbilical cord blood in the study by Janssen et al.) may account for the difference in the results obtained. The physiological surge in TSH production during the neonatal phase leads to an increase in TSH concentrations and dynamic changes in thyroxine (T4) and triiodothyronine (T3) concentrations in the first 24 or 48 h after birth. Most centers collect heel-stick blood samples >24 h after birth, to limit the rate of false-positive high TSH concentrations (Büyükgöbüz, 2013). A study based on data from the Children's Health Study (*n* = 2050) found a positive association between PM_{2.5} and PM₁₀ exposure and total thyroxine (TT4) concentrations (Howe et al., 2018). The authors suggested that PM might increase Thyroxine Binding globuline (TBG) concentrations, potentially complementing a stimulation of type 2 deiodinase activity.

Our study is the first, to our knowledge, to investigate the association between exposure to pollutants in tap water and neonatal TSH concentrations. Nitrate competitively inhibits sodium iodide symporter (NIS)-mediated iodide uptake, the first limiting step in thyroid hormone production. This association has been reported in several studies

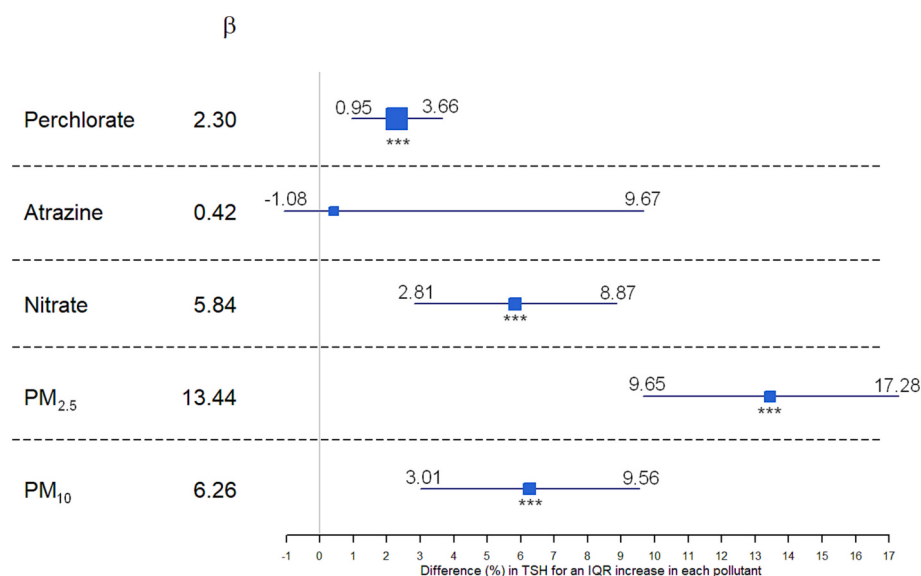


Fig. 2. Forest plot of beta coefficients with their 95 % confidence intervals in a single-pollutant linear regression model for an increase of one interquartile range for each pollutant, adjusted for sex and gestational age.

*** $p < 0.001$. The interquartile ranges for prenatal exposure were 3.6 $\mu\text{g/L}$ for perchlorate ions, 0.013 $\mu\text{g/L}$ for atrazine, 19.2 mg/L for nitrate ions, 3.7 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ and 3.4 $\mu\text{g}/\text{m}^3$ for PM_{10} .

Table 2
Single-pollutant models raw results.

Model	Variable	β [CI95%]	F	p value for F
Perchlorate	Intercept	-0.9 [-1.4, -0.4]	15.9	2.76e-10
	Perchlorate	0.006 [0.003, 0.01]		
	Gestational age	0.005 [0.003, 0.007]		
	Male	0.07 [0.03, 0.11]		
Atrazine	Intercept	-0.9 [-1.4, -0.3]	12.2	6.1e-08
	Atrazine	0.26 [-1.6, 2.1]		
	Gestational age	0.005 [0.003, 0.007]		
	Male	0.07 [0.03, 0.11]		
Nitrate	Intercept	-0.9 [-1.4, -0.4]	16.9	6.0e-11
	Nitrate	3e-06 [1e-06, 5e-06]		
	Gestational age	0.005 [0.003, 0.007]		
	Male	0.07 [0.04, 0.11]		
PM _{2.5}	Intercept	-1.1 [-1.7, -0.6]	28.7	<2e-16
	PM _{2.5}	0.04 [0.03, 0.05]		
	Gestational age	0.005 [0.003, 0.007]		
	Male	0.08 [0.04, 0.11]		
PM ₁₀	Intercept	-1.1 [-1.7, -0.6]	16.9	6.0e-11
	PM ₁₀	0.02 [0.01, 0.03]		
	Gestational age	0.005 [0.003, 0.007]		
	Male	0.07 [0.04, 0.11]		

β : regression coefficient with its 95 % confidence interval; F: Fisher's statistic and its p -value is indicated on the right.

performed in animals (El-Wakf et al., 2015; Eskiocak et al., 2005; Zaki et al., 2004) and *in vitro* (Costamagna et al., 1998). It has never been reported in humans, but all the studies performed to date focused on adult human subjects (Lambers et al., 2000; Ward et al., 2010). Fetuses and newborns are highly sensitive to endocrine disruption, so it is not surprising to find an association between nitrate ions exposure and neonatal TSH concentrations, potentially reflecting a tendency towards congenital hypothyroidism. Perchlorate ions act *via* a mechanism very similar to that described for nitrate ions (Serrano-Nascimento and Nunes, 2022). The interaction between these two ions in our multi-pollutant regression models suggests that the effect of perchlorate ions exposure on TSH concentrations depends on the level of nitrate ions exposure, and *vice versa*, consistent with a common mechanism of action. This is supported by the fact that perchlorate is taken up by the same ion transporter as nitrate. Previous studies of the association between perchlorate exposure and human thyroid function have reported inconsistent results. Environmental perchlorate exposure has been found to be negatively associated with circulating FT4 concentrations in women in the third trimester of pregnancy (Knight et al., 2018). No

association was detected for atrazine, but more than half of the samples were below the limit of quantification. Studies of the impact of atrazine on the thyroid gland have mainly been performed in animals (Laws et al., 2000; Stoker et al., 2000, 2002). A study in Thailand investigating thyroid hormone concentrations in farmers found an association between occupational exposure to atrazine and increased TSH and T3 and decreased FT4 (Kongtip et al., 2019). For 2020 and 2021, exposure levels to $\text{PM}_{2.5}$ and PM_{10} in the Picardy region were slightly higher than those in most other regions of France (INERIS, 2020), and comparable with results at European level (Europe's air quality status 2022, 2022; Europe's air quality status 2023, 2023).

The positive associations of being male and gestational age with neonatal TSH concentrations are consistent with published results, strengthening the credibility of our model (Cortés-Castell et al., 2019; Di Dalmazi et al., 2020).

The major limitation of our work is that we have very little individual information for the newborns, and none at all for the mothers, particularly as regards potential confounding factors such as maternal smoking, which has been reported to be associated with decreases in TSH concentrations and increases in T3 and T4 concentrations (Meberg and Marstein, 1986; Shields et al., 2009). It should be noted, however, that smoking during pregnancy is decreasing in France, with only 12.2 % of pregnant women continuing to smoke during pregnancy in 2021 (Cinelli et al., 2022). We have no information on maternal conditions during pregnancy, nor on iodine intake, but for the second point, the WHO does not consider France to be a problem area in terms of iodine deficiency (De Benoist, 2004). However, the needs of pregnant women are greater than those of the general population, and iodine intake in France may be insufficient for them (Kadawathagedara et al., 2017; Taylor et al., 2018), with no evidence to suggest that this distribution is not homogeneous between different regions (Caron, 2007).

We also used a macroscopic exposure proxy to estimate the exposure of our population. This approach was used by Howe et al. (2018) and Janssen et al. (2017) for PM. For other pollutants described as potentially affecting neonatal TSH concentrations, all studies were based on biomarkers of exposure. We were not able to perform such investigations within the framework of this study, so we focused on the most widespread forms of exposure: exposure to pollutants in outdoor air and tap water. We did not know the precise level of exposure for each mother and child in the study, but daily tap water consumption has been increasing in France over the last few years, with 68 % of the French population in 2021 reporting the consumption of tap water (Baromètre annuel d'opinion, 2021: les français et l'eau, 2021).

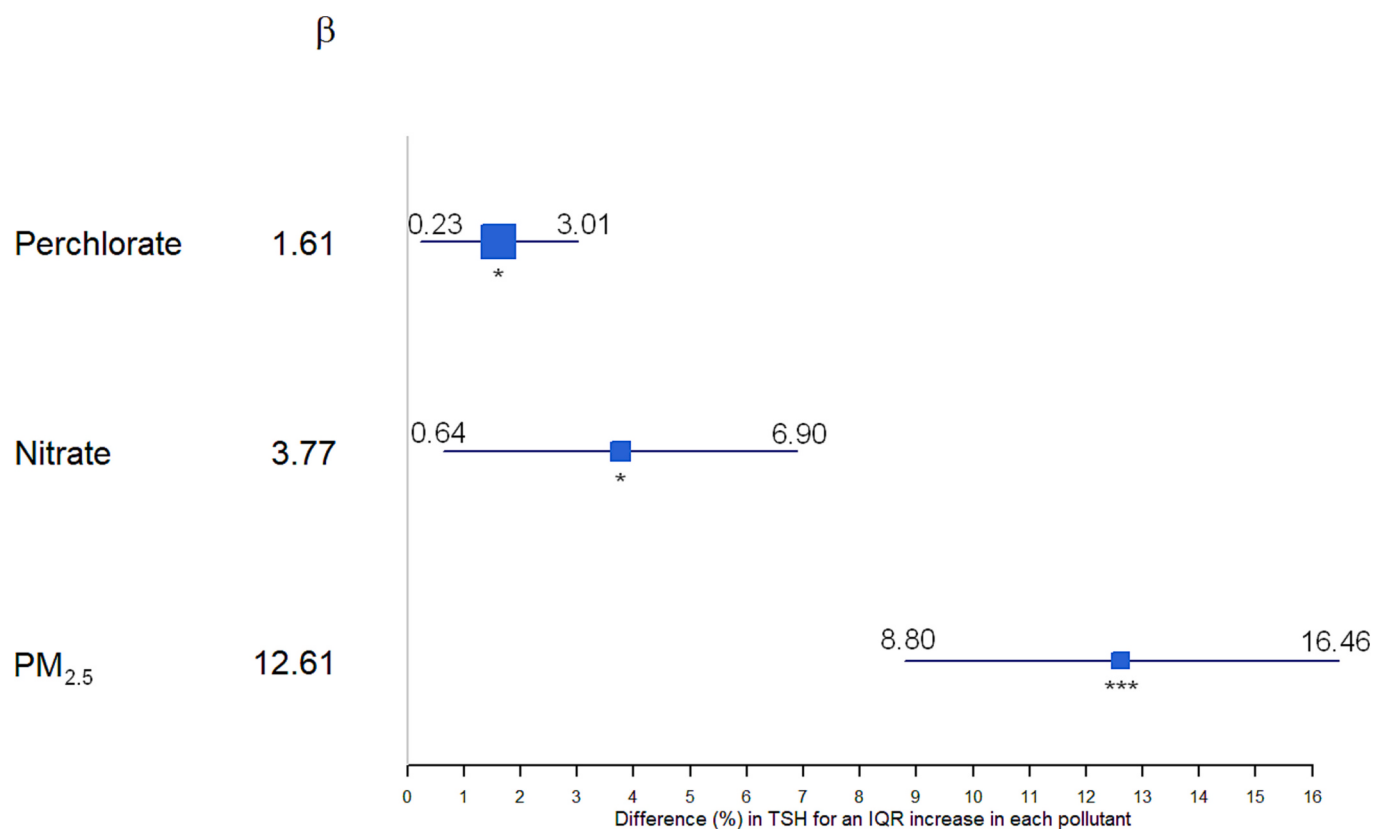


Fig. 3. Forest plot of beta coefficients with their 95 % confidence intervals in a multipollutant linear regression model including perchlorate ions, nitrate and PM_{2.5} for an increase of one interquartile range for each pollutant, adjusted for sex and gestational age.

* $p < 0.05$; *** $p < 0.001$ The interquartile ranges for prenatal exposure were 3.6 $\mu\text{g/L}$ for perchlorate ions, 19.2 mg/L for nitrate ions, 3.7 $\mu\text{g}/\text{m}^3$ for PM_{2.5} and 3.4 $\mu\text{g}/\text{m}^3$ for PM₁₀.

We were also unable to take relocations (human mobility) into account because this information was not available. Janssen et al. (2017) reported that 10.8 % of the women in their population moved home during the study period (Janssen et al., 2017). However, we had access to the zip code for the place of residence of the mothers at the time of delivery, and this information is clearly more accurate than address at the start of pregnancy for determinations of exposure.

The reduction in our initial population size is due to the lack of perchlorate ions samples. Nevertheless, this approach, taking into account only the exposure samples from the corresponding zip code area during the 3rd trimester of pregnancy for each individual, generates the least measurement bias. Despite this reduction, this study remains the largest to date in terms of absolute numbers of subjects for the investigation of associations between environmental factors and neonatal thyroid function.

5. Conclusion

The results of this study suggest that prenatal exposure during the third trimester of gestation to airborne PM, perchlorate and nitrate ions in tap water is significantly associated with higher neonatal TSH concentrations. Prenatal exposure to atrazine was not statistically significantly associated with TSH concentrations in the newborn. The use of blood nitrate and perchlorate assays in future studies could confirm the existence of a link with neonatal TSH concentrations. The clinical impact of neonatal TSH variations, particularly on neurodevelopment, also needs to be assessed.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2023.167089>.

CRediT authorship contribution statement

All authors meet all four criteria for authorship in the ICMJE Recommendations. All authors had full and direct access to all the data in the study, verified the underlying data in the study, and had final responsibility for the decision to submit for publication. All authors contributed to interpretation, reviewing, editing of the manuscript, and approved the submitted version. All authors affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any potential discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Sylvain Chamot: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization.

Abdallah Al-Salameh: Methodology, Validation, Writing - Review & Editing, Supervision.

Pascal Petit: Methodology, Validation, Writing - Review & Editing, Supervision.

Vincent Bonneterre: Methodology, Validation, Writing - Review & Editing.

Christophe Cancé: Methodology, Validation, Writing - Review & Editing.

Guillaume Decocq: Methodology, Validation, Writing - Review & Editing.

Agnès Boullier: Methodology, Writing - Review & Editing.

Karine Braun: Methodology, Writing - Review & Editing.

Rachel Desailoud: Conceptualization, Methodology, Validation, Review & Editing, Supervision.

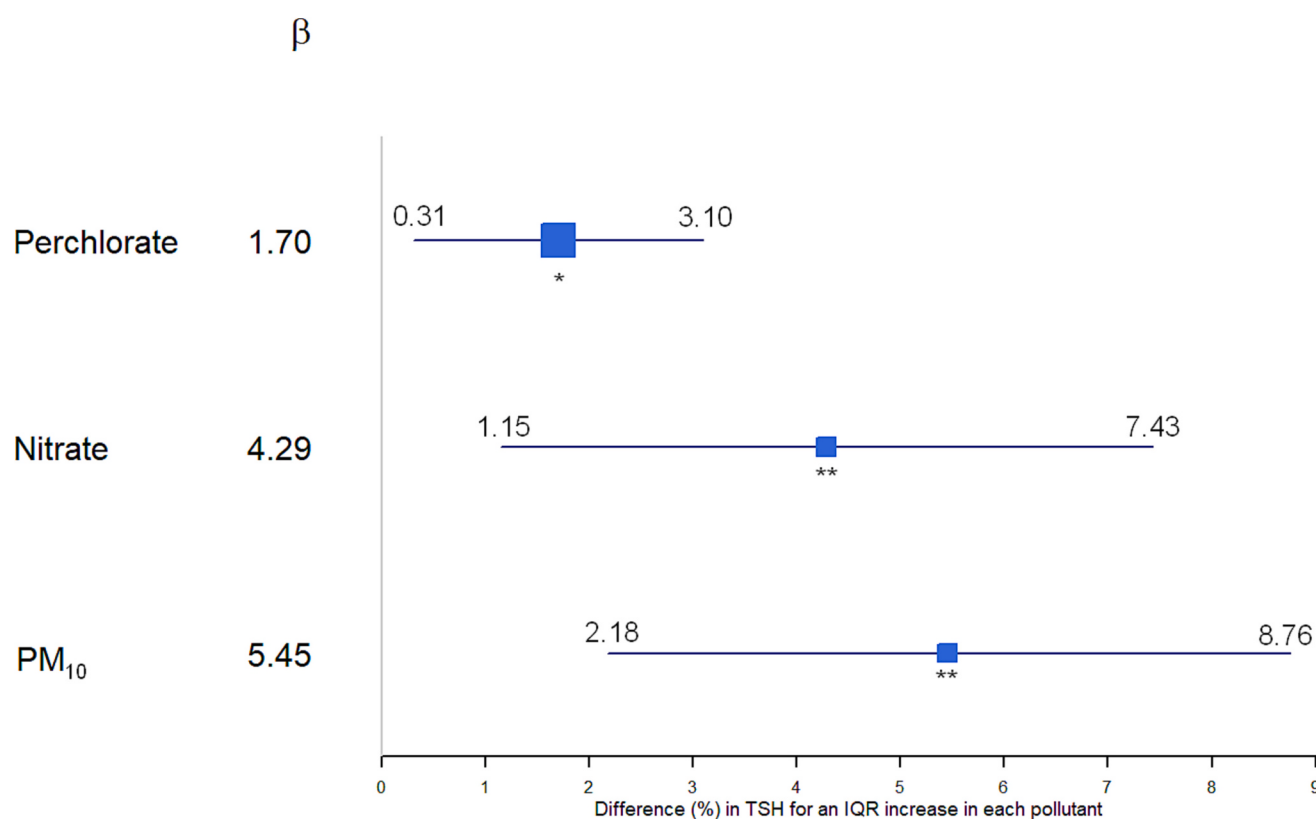


Fig. 4. Forest plot of beta coefficients with their 95 % confidence intervals in a multipollutant linear regression model including perchlorate ions, nitrate and PM₁₀ for an increase of one interquartile range for each pollutant, adjusted for sex and gestational age.

* $p < 0.05$; ** $p < 0.01$. The interquartile ranges for prenatal exposure were 3.6 $\mu\text{g/L}$ for perchlorate ions, 19.2 mg/L for nitrate ions, 3.7 $\mu\text{g/m}^3$ for PM_{2.5} and 3.4 $\mu\text{g/m}^3$ for PM₁₀.

Table 3
Multipollutant models raw results.

Model	Variable	β [CI95%]	F	p value for F
Perchlorate, nitrate and PM _{2.5}	Intercept	-1.2 [-1.7, -0.6]	20,1	<2e-16
	Perchlorate	0.005 [0.0006, 0.008]		
	Nitrate	2e-06 [3e-07, 6e-06]		
	PM _{2.5}	0.03 [0.02, 0.04]		
	Gestational age	0.005 [0.003, 0.007]		
	Male	0.08 [0.04, 0.11]		
	Intercept	-1.2 [-1.7, -0.6]	13.6	3.3e-13
Perchlorate, nitrate and PM ₁₀	Perchlorate	0.005 [0.0009, 0.009]		
	Nitrate	2e-06 [6e-07, 4e-06]		
	PM ₁₀	0.02 [0.006, 0.03]		
	Gestational age	0.005 [0.003, 0.007]		
	Male	0.08 [0.04, 0.12]		

β : regression coefficient with its 95 % confidence interval; F: Fisher's statistic and its p-value is indicated on the right.

Declaration of competing interest

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

Data availability

The data that has been used is confidential.

Acknowledgments

We would like to thank Prof. Cécile Manaouil, Head of the Department of Forensic and Social Medicine, Amiens University Hospital, and, more generally, Amiens University Hospital, for the purchase of the computer equipment required to carry out this study, which involved the manipulation of very large volumes of data. We would also like to thank Timothé Fiat, Head of the tap water sanitary control results database project at the *Direction Générale de la Santé*, for discussions about this database and its structure. We thank INERIS, particularly Laure Malherbe and Elsa Real of the “Data, technical applications and acquisition” unit, for making the air pollution data in the core library available on a municipality-by-municipality and day-by-day basis. We thank Dr. Areejit Samal of the Institute of Mathematical Sciences, Chennai, for exchanges concerning DEDuCT. Finally, we thank Christèle Thélou, neonatal screening manager, who entered all the administrative information on newborns, including the zip codes.

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