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Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto Region, Italy

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Background: Perfluoroalkyl substances (PFAS), a heterogeneous group of highly stable man-made chemicals, have been widely used since 1960s and can be detected almost ubiquitously in all environmental matrices. In Italy, on January 2014, drinking water contamination in an area of the Veneto Region was detected mainly due to the drain of fluorinated chemicals by a manufacturing company operating since 1964. **Methods**: The present ecological mortality study was aimed at comparing mortality for some causes of death selected on the basis of previous reported associations, during the period 1980–2013, in municipalities with PFAS contaminated and uncontaminated drinking water on the basis of the levels indicated by the Italian National Health Institute (ISS). Sex-specific number, standardized mortality rates and rate ratios (RR) for PFAS contaminated and uncontaminated areas were computed for each cause of death through the ENEA epidemiological database. **Results**: In both sexes, statistically significant RRs were detected for all causes mortality, diabetes, cerebrovascular diseases, myocardial infarction and Alzheimer's disease. In females, RRs significantly higher than 1.0 were also observed for kidney and breast cancer, and Parkinson's disease. Increased risk, although not statistically significant, was observed for bladder cancer in both sexes, and for testicular cancer, pancreatic cancer and leukemia in males only. **Conclusions**: Higher mortality levels for some causes of death, possibly associated with PFAS exposure, were detected in contaminated municipalities in comparison with uncontaminated ones with similar socioeconomic status and smoking habits. These results warrant further individual level analytic studies to delineate casual associations.

Introduction

Perfluoroalkyl substances (PFAS) are a heterogeneous group of highly stable man-made chemicals, composed of a fluorinated carbon backbone of various lengths (generally C4–C14) with an hydrophilic functional group at the extremity. The most common PFAS are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), both constituted by eight carbons with, respectively, a carboxylic or sulfonic acid functional group at one end.[1,2]

Due to their thermal stability and lipid/water repellent properties, PFAS have been widely used since 1960s in several processes and products such as lubricants, polishes, adhesives, pesticides, stain and soil repellents, paper and textile coatings, personal care products, and fire-retarding foams. The best-known commercial applications are the widespread non-stick cookware (Teflon) and the waterproof-breathable fabrics (Goretex). Consequently, PFAS represent an emerging class of global environmental pollutants, which can be detected almost ubiquitously in all environmental matrices, are highly persistent and accumulate along the food chain.[1,3,4] Moreover, in their anionic forms, which are water-soluble, they can migrate from soil to groundwater and be transported at long distance.[5] They have even been detected in liver of bears from the remote Arctic regions.[6]

The main human exposure to PFAS is the ingestion of contaminated drinking water,[7] food[8] and household dust.[7]

PFAS, whose half life is 3.5–7.3 years (geometric mean),[9] bind to proteins, can interfere with several metabolic pathways and are mainly distributed to blood serum proteins, kidney and liver.[10,11] The main target for PFAS in mice is peroxisome proliferator-activated receptor alpha (PPARα), whose isoform in man is PPARγ, a major regulator of lipid metabolism in the liver.[12,13]

Moreover, PFAS have been shown to be endocrine disruptors as they can bind to estrogen receptor α,[14] thyroid hormone receptor[15] and leptine receptor.[16]

As far as human health effects are concerned, most of them were observed in PFAS professionally exposed groups and included increased levels of uric acid and cholesterol among workers engaged in PFOA production plants[17]; increased risk for liver and kidney cancer and leukemia among workers employed in the production of fluorinated polymers[18]; excesses of mortality and/or incidence for prostate, bladder and pancreatic cancer, cerebrovascular diseases, diabetes and chronic renal diseases among other exposed workers.[19–22]

Some epidemiological studies carried out on communities exposed to PFOS, PFOA and perfluorononanoic acid (PFNA) have shown increases of total and non-high-density cholesterol,[23,24] and uric acid.[25] In a cross-sectional survey, homocysteine and systolic blood pressure were shown to increase significantly with the increase of serum PFOA concentration.[26]

The largest study on PFOA blood concentrations and health effects on human communities has been carried out in Virginia, due to the contamination of Ohio river, which provides drinking water for 69 000 people.[27] Positive associations have been found for testicular, kidney, ovarian, prostate cancer and non-Hodgkin lymphoma.[28,29]

Suggestive associations have been observed for female breast cancer in Danish women.[30]

In an exposed community living near a chemical plant, a positive association with stroke incidence has been found, although a dose–response was apparent only excluding the most exposed subjects.[31]

The effect of PFOA has also been studied among 1216 subjects from the National Health and Nutritional Examination Survey.

Positive correlations with cardiovascular disease and peripheral arterial disease have been found.[32]

In 2000, the 3 M Company, the main manufacturer of PFOS, voluntarily started a phase-out of PFOS production that had to be completed by 2003.[33] In the same year, a ban on many PFOS applications was introduced in USA. In 2006, US EPA invited eight major leading companies of PFAS industry to join in a global stewardship program aimed at the reduction of all PFOA emissions and products and at their definite elimination by 2015.[34]

In 2006, in Europe, an EC Directive (2006/122/ECOF) limited PFOS uses. In 2009, it was added as Annex B to the Stockholm Convention on Persistent Organic Pollutants (POPs). In 2015, more than 200 scientists signed the Madrid statement[35] requiring the international community to cooperate in limiting the production and use of PFAS, and raising concern about the new short-chain perfluorinated compounds.

Carcinogenicity of PFOA has been recently re-evaluated by IARC[36] and they have been classified as possible carcinogen for human, group 2B.

In Europe, as well as in USA, national drinking water regulations for PFOA and PFOS have not been established yet. US EPA recommended a health protective approach for PFOA in drinking water, setting a level of 0.07 μg/l. The same level was also indicated when PFOA and PFOS are both present (Supplementary Web Appendix 3: ref. 1).

The UK Health Protection Agency (HPA) focused on levels of 0.3 μg/l for PFOS and 10 μg/l for PFOA in drinking water (Supplementary Web Appendix 3: ref. 2). Other Regulatory Institutes set limits in terms of tolerable daily intake (TDI): the European Food Safety Authority (EFSA) indicated 0.15 μg/kg body weight (bw) for PFOS and 1.5 μg/kg bw for PFOA (Supplementary Web Appendix 3: ref. 3). The German Commission for drinking water (Supplementary Web Appendix 3: ref. 4) set 0.1 μg/kg bw for both PFOS and PFOA.

In Italy, as well as in the rest of Europe, there is no limit for PFAS in drinking water. For this reason on January 2014, after the detection of an important water contamination (surface, underground and drinking water) in an area of the Veneto Region by the local Regional Agency for Environmental Protection and Prevention (ARPAV), the Italian Government asked the Italian National Health Institute (ISS) to define maximum levels of PFAS in drinking water in order to protect people from health risks. The levels indicated by ISS as performance limits were the following: PFOS $\leq$ 30 ng/l; PFOA $\leq$ 500 ng/l; other PFAS $\leq$ 500 ng/l. The present ecological study was aimed at comparing mortality for some causes of death, selected on the basis of previous reported associations between municipalities exceeding the above ISS performance limits in drinking water and municipalities with uncontaminated underground water, used as source of drinking water. The main cause of PFAS contamination in this area is draining of fluorinated chemicals from a manufacturing company operating since 1964 in the municipality of Trissino in the Vicenza province.

Methods

The municipalities considered as 'contaminated area' were selected from the Veneto Region report of 2015 (Supplementary Web Appendix 3: ref. 5), which listed municipalities with PFOS, PFOA and the other PFAS exceeding at least one of the ISS performance limits of 30 ng/l for PFOS, 500 ng/l for PFOA and 500 ng/l for the other PFAS in drinking water but did not report PFAS concentration level.

The information source of PFAS drinking water levels were the Regional Informative System on drinking water, which collects the official monitoring data for water quality control, and the data set of analyses carried out inside the framework of the specifically activated Health Surveillance System, aimed at monitoring local critical areas. The monitored data referred to the period July 2013–June 2015.

Some of them exceeded the limit for PFOS only, some for both PFOS and PFOA and some other for PFOS, PFOA and the other PFAS. The group of other PFAS included perfluorobutyric acid (PFBA), perfluorobutane sulfonate (PFBS), perfluorodecanoic acid (PFDeA), perfluorododecanoic acid (PFDoA), perfluoroheptanoic acid (PFHpA), perfluorohexanoic acid (PFHxA), perfluorohexane sulfonate (PFHxS), PFNA, perfluoropentanoic acid (PFPeA) and perfluoroundecanoic acid (PFUnA).

In order to avoid potential confounding due to urban residence, the three province chief towns (Padova, Treviso and Vicenza) were not included in the study.

PFAS uncontaminated municipalities were spotted from the results of the 2013 and 2014 monitoring campaigns on underground water carried out by the Regional Agency for Environmental Protection and Prevention of the Veneto Region. The first campaign included 205 sampling points for an overall 2460 concentration measures. The limit of quantification (LOQ) was 10 ng/l. Samples with at least one PFAS compound >LOQ were 71 out of 205 (35%) with the highest levels associates to PFOA (1173 ng/l) and PFUnA (640 ng/l). The second campaign included 226 sampling points and 2712 measures with 40 samples with at least one PFAS concentrations >LOQ (18%), with the highest levels associated to PFOA (1009 ng/l). The uncontaminated municipalities were selected from the above campaign data including those with PFAS levels <LOQ in underground water and consequently in drinking water supply (Supplementary Web Appendix 3: refs. 6, 7).

On the basis of the scientific evidence reported in the Introduction, a list of *a priori* health adverse outcomes has been prepared (Supplementary Web Appendix 1). Mortality for all causes was also considered in order to assess the overall difference between populations living in PFAS exposed and unexposed municipalities. Even though neurological diseases are not considered associated to PFAS by the available scientific literature, we decided to include also mortality for Alzheimer and Parkinson diseases. Indeed PFAS are considered responsible for developmental neurotoxic effects and, in particular, impairment of behavior and cognitive functions.[37] Moreover, hormonal disruptors have been generally associated with neurodegenerative diseases.[38]

General and specific cause mortality (data source: National Institute of Statistics, ISTAT) was calculated by the epidemiological database operating at the National Agency for New Technologies, Energy and the Environment (ENEA). The investigated period was 1980–2013 but, due to the unavailability of 2004 and 2005 mortality data from ISTAT, actually referring to 31 years. The selected period includes the 9th (1980–2002) and 10th (2003–2013) International Classifications of Diseases (ICD) revisions. The 16 selected causes of death with the relative 9th and 10th ICD code are listed in Supplementary Web Appendix 1.

Sex-specific number of deaths, standardized mortality rates (SMRate) using the 2001 Italian population census as standard, the corresponding standard errors (SE) for PFAS contaminated and uncontaminated areas were computed (Supplementary Web Appendix 2).

The age population structure based on the 2011 ISTAT Italian census was represented by age pyramids (Supplementary Web Appendix 2). Rate ratios (RR) and 95% confidence intervals for each cause of death between the PFAS contaminated and uncontaminated municipalities were computed.

In order to take into account the potential confounding effect of socio-economic status in the comparison between municipalities of the two areas, the deprivation index was considered (Supplementary Web Appendix 3: ref. 8). It is based on five deprivation indicators, namely the percentages of population with a low school instruction level, unemployed people, rented houses, mono-parental families and residential density.

Moreover, specific data on smoking habits were also considered. Due to the unavailability of specific data on smoking for all Italian municipalities, they were extracted from a multi-scope investigation on daily life aspects carried out on randomly selected families by ISTAT in 2015 (Supplementary Web Appendix 3: ref. 9). In the framework of the lifestyle session, tobacco consumption was reported for macro-areas. The percentage of smokers (the sum of smokers and ex-smokers) was selected as smoking habit indicator and calculated on the total of the smoking and non-smoking interviewed people of the macro-area. The value obtained for each macro-area was subsequently assigned to each of the municipalities included and the overall differences in smoking habits of the PFAS contaminated and uncontaminated areas were evaluated by the χ^2 test.

Results

The map of PFAS *contaminated and uncontaminated municipalities* is reported in Figure 1. The contaminated area included 24 municipalities, with a resident population (data source: Italian National Institute of Statistics – ISTAT census) of 143 605 inhabitants in 2011 (74 599 males and 69 006 females); the uncontaminated area included 56 municipalities with a resident population of 588 012 inhabitants (302 425 males and 285 587 females).

The deprivation index among the municipalities of the two areas was rather homogeneous: most of them were classified in the 'very rich' group (87% and 84% in the contaminated and uncontaminated areas, respectively) and many others in the 'rich' one (12.5% in both areas). Only 2 out of the 56 uncontaminated municipalities were classified in the 'mean' and 'deprived', group, respectively. As far as smoking habits is concerned, the percentage of smokers of the contaminated (43.0–52.8%) and uncontaminated (42.4–45.0%) areas were not statistically different.

Tables 1, 2 and 3 show for males, females and total persons, respectively, the comparison of mortality levels between the contaminated and uncontaminated areas.

In both sexes, statistically significant higher RRs were detected for general mortality (1.19 and 1.21 in males and females, respectively), diabetes (1.21 and 1.48), cerebrovascular diseases (1.34 and 1.29), myocardial infarction (1.22 and 1.24) and Alzheimer's disease (1.33 and 1.35).

In females, RR values significantly higher than 1 were also observed for kidney cancer (1.32), breast cancer (1.11) and Parkinson's disease (1.35). Bladder cancer and leukemia were also higher than 1 in both sexes, although not statistically significant. In males, a not significant higher risk was observed for testicular cancer, pancreatic cancer and Parkinson's disease.

No increased risks for liver cancer, non-Hodgkin's lymphoma and prostate cancer were detected but a significant lower risk for liver cancer when males and females were considered altogether was detected.

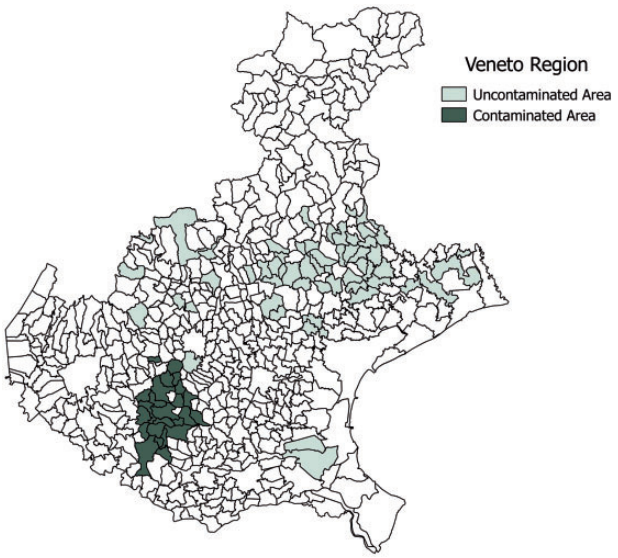

Figure 1 Contaminated and uncontaminated municipalities on the basis of the ISS performance limits in drinking water in the Veneto region. *Contaminated municipalities*: Montagnana, Albaredo d'Adige, Arcole, Bevilacqua, Bonavigo, Boschi Sant'Anna, Cologna Veneta, Legnago, Minerbe, Pressana, Roveredo di Guà, Terrazzo, Veronella, Zimella, Brendola, Grancona, Lonigo, Montorso Vicentino, Noventa Vicentina, Orgiano, Poiana Maggiore, San Germano dei Berici, Sarego and Sossano. *Uncontaminated municipalities*: Altivole, Arcade, Asolo, Breda di Piave, Cerano di San Marco, Cappella Maggiore, Castelfranco Veneto, Cessalto, Codognè, Conegliano, Cordignano, Cornuda, Follina, Fontanelle, Gaiarine, Giavera del Montello, Godega di Sant'Urbano, Mareno di Piave, Maser, Maserada sul Piave, Montebelluna, Moriago della Battaglia, Nervesa della Battaglia, Oderzo, Ormelle, Pederobba, Ponte di Piave, Ponzano Veneto, Resana, San Biagio di Callata, San Pietro di Felletto, San Polo di Piave, San Vendemiano, San Zenone degli Ezzelini, Santa Lucia di Piave, Sernaglia della Battaglia, Trevignano, Vazzola, Villorba, Volpago del Montello, Zero Branco, Cavarzere, Cona, Portogruaro, Santo Stino di Livenza, Scorzè, Teglio Veneto, Arcugnano, Asiago, Marostica, Montecchio Precalcino, Pedemonte, Posina, Thiene, Valdagno and Valstagna

Discussion

The present ecological study is the first epidemiological investigation carried out in Italy on a population living in an area contaminated by PFAS in drinking water and possibly affecting the food chain.

One limit of the study is that we considered exposed all the inhabitants of the municipalities where the public water supply exceeded at least one of the performance limits established by ISS, assuming that all the inhabitants were consuming drinking water in the same way.

The possible effects of other toxic compounds present in drinking water can reasonably be excluded on the basis of the Veneto region monitoring data (Supplementary Web Appendix 3: ref 10,11). Indeed, most of the toxic heavy metals (such as Al, As, Cd, Cr VI, Pb and Ni), nitrates compounds, trihalomethanes, tricloroethilene, tethracloroethilene and IPA were below the normative limits in all the municipalities of our study and, in most cases, even below the LOQ.

Moreover, other possible exposures to PFAS, such as dietary intake or private wells were not taken into account. Food can be contaminated directly through the food chain (mainly fish and meat, but also cereals, dairy products, vegetables and fruit),[7,8] or indirectly by food packaging (wrappers, paperboard and paper cups). A recent investigation evidenced that most Italian food packages are PFAS free or have low contamination and are aligned with the European mean levels (Supplementary Web Appendix 3: ref 12).

The potential misclassification of the individual intake, both for exposed and unexposed people, could underestimate the real risk of populations considered as exposed.

Even though mortality could not be the most appropriate indicator of the health outcome because some causes of death connected to PFAS exposure are highly curable (e.g. testicular, prostate and female breast cancer) and others are long-lasting diseases (e.g. Parkinson disease), we found higher mortality levels for some of them in the contaminated area.

Moreover, the effects of PFAS as endocrine disruptors are manly connected with hormonal unbalances, fertility decrease, birth outcomes defects[39] and alterations of many biochemical parameters, not inducing fatal outcomes.[40]

Table 1 Number of deaths (Deaths), standard mortality rates (SMRate) and relative standard errors (SE) for PFAS contaminated and uncontaminated municipality areas in males in the period 1980–2013. Relative risk (RR) and 95% confidence intervals are also reported. Statistically significant RR are evidenced in bold

Mortality causes	Contaminated area			Uncontaminated area			
	Deaths	SMRate	SE	Deaths	SMRate	SE	RR
All causes	21149	1201.57	8.28	73745	1007.45	3.72	**1.19** (1.17–1.21)
Liver cancer	242	16.68	0.88	1132	15.31	0.46	0.89 (0.78–1.03)
Kidney cancer	155	8.69	0.70	602	8.09	0.33	1.07 (0.90–1.28)
Bladder cancer	225	12.96	0.87	830	11.54	0.40	1.12 (0.97–1.30)
Pancreatic cancer	361	20.55	1.08	1355	18.48	0.50	1.11 (0.99–1.25)
Leukemia	210	11.71	0.81	749	10.11	0.37	1.16 (0.99–1.35)
Non-Hodgkin's lymphoma	155	8.81	0.71	610	8.24	0.34	1.07 (0.90–1.28)
Breast cancer	4	0.22	0.11	18	0.24	0.06	0.89 (0.30–2.65)
Prostate cancer	401	23.46	1.17	1654	23.47	0.58	1.00 (0.90–1.12)
Testicular cancer	8	0.44	0.16	19	0.24	0.05	1.86 (0.81–4.27)
Diabetes	292	0.98	0.98	1002	13.83	0.44	**1.21** (1.06–1.38)
Cerebrovascular disease	1871	2.51	2.51	5776	80.97	1.07	**1.34** (1.27–1.41)
Myocardial infarction	1900	2.48	2.48	6478	88.43	1.10	**1.22** (1.16–1.28)
Alzheimer's disease	89	0.55	0.55	274	3.91	0.24	**1.33** (1.05–1.70)
Parkinson's disease	88	0.55	0.55	307	4.39	0.25	1.18 (0.93–1.50)

Table 2 Number of deaths (Deaths), standard mortality rates (SMRate) and relative standard errors (SE) for the PFAS contaminated and uncontaminated municipality areas in females in the period 1980–2013. Relative risk (RR) and 95% confidence intervals are also reported. Statistically significant RR are evidenced in bold

Mortality causes	Contaminated area			Uncontaminated area			
	Deaths	SMRate	SE	Deaths	SMRate	SE	RR
All causes	20692	1040.54	7.24	69327	826.31	3.72	**1.21** (1.19–1.23)
Liver cancer	95	4.82	0.50	412	5.16	0.46	0.93 (0.75–1.17)
Kidney cancer	103	5.24	0.52	316	3.96	0.33	**1.32** (1.06–1.65)
Bladder cancer	57	2.88	0.38	199	2.50	0.40	1.15 (0.86–1.55)
Pancreatic cancer	302	15.33	0.88	1235	15.48	0.50	0.99 (0.87–1.12)
Leukemia	166	8.36	0.65	609	7.47	0.37	1.12 (0.94–1.33)
Non-Hodgkin's lymphoma	113	5.75	0.54	528	6.56	0.34	0.88 (0.71–1.07)
Breast cancer	809	40.87	1.44	3013	36.90	0.06	**1.11** (1.02–1.20)
Ovarian cancer	201	10.24	0.72	771	9.49	0.58	1.08 (0.92–1.26)
Diabetes	595	29.98	1.23	1620	20.29	0.44	**1.48** (1.34–1.62)
Cerebrovascular disease	2721	136.91	2.63	8508	106.33	1.07	**1.29** (1.23–1.34)
Myocardial infarction	1458	73.50	1.93	4733	59.27	1.10	**1.24** (1.17–1.32)
Alzheimer's disease	178	8.96	0.67	527	6.61	0.24	**1.35** (1.14–1.61)
Parkinson's disease	115	5.77	0.54	340	4.27	0.25	**1.35** (1.09–1.67)

Table 3 Number of deaths (Deaths), standard mortality rates (SMRate) and relative standard errors (SE) for the PFAS contaminated and uncontaminated municipality areas in the total population (males and females) in the period 1980–2013. Relative risk (RR) and 95% confidence intervals are also reported. Statistically significant RR are evidenced in bold

Mortality causes	Contaminated area			Uncontaminated area			
	Deaths	SMRate	SE	Deaths	SMRate	SE	RR
All causes	41841	1032.55	5.06	143072	932.56	2.47	**1.11** (1.10–1.12)
Liver cancer	337	8.43	0.46	1544	10.07	0.26	**0.84** (0.74–0.94)
Kidney cancer	258	6.39	0.40	918	5.96	0.20	1.07 (0.93–1.23)
Bladder cancer	282	7.15	0.43	1029	6.88	0.21	1.04 (0.91–1.19)
Pancreatic cancer	663	16.52	0.64	2590	16.93	0.33	0.98 (0.90–1.06)
Leukemia	376	9.24	0.48	1358	8.74	0.24	1.06 (0.94–1.19)
Non-Hodgkin's lymphoma	268	6.69	0.41	1138	7.38	0.22	0.91 (0.79–1.04)
Breast cancer	813	19.68	0.69	3031	19.15	0.35	1.03 (0.95–1.11)
Diabetes	887	21.76	0.73	2622	17.17	0.34	**1.27** (1.17–1.37)
Cerebrovascular disease	4592	113.51	1.68	14284	94.05	0.79	**1.21** (1.17–1.25)
Myocardial infarction	3358	83.23	1.44	11211	73.38	0.69	**1.13** (1.09–1.18)
Alzheimer's disease	267	6.59	0.40	801	5.30	0.19	**1.24** (1.08–1.43)
Parkinson's disease	203	5.05	0.35	647	4.33	0.17	1.17 (1.00–1.37)

Even though some of the considered causes of death are dependent from smoking habits (e.g. kidney, bladder, pancreas, breast and possibly liver cancer, respiratory and cardiovascular diseases) and socio-economic status, the influence of such confounding variables as main leaders of the health outcome under study could reasonably be excluded. Indeed the municipalities included in the contaminated and uncontaminated areas were characterized by similar socio-economic conditions and no statistically significant difference was detected in smoker percentage between the respective populations. Many of our results were in agreement with previous findings in terms of increases of specific mortality causes, but the levels of such risks were generally lower than those reported in the scientific literature. This discrepancy could probably be due to the fact that the other studies were carried out on highly exposed workers or were cohort studies. In the present investigation significant higher risks were observed, besides general mortality, for diabetes, cerebrovascular diseases, myocardial infarction and Alzheimer's disease in both sexes and for kidney cancer, breast cancer and Parkinson's disease in females. As far as myocardial infarction is concerned, 13–45% higher risks were detected in a community living near a PFOA chemical plant,[31] the lowest percentage corresponding to the 13% we detected for the two sexes together; HR of 1.8–4.6 for cerebrovascular diseases[21] and HR of 3.7 for diabetes[22] were observed on workers involved in the production of PFOA in comparison with our RR of 1.13 and 1.21 respectively. A 44% higher risk for kidney cancer in a cohort study including all polytetrafluoroethylene production sites in Europe and North America[18] and a 58% higher risk in the highest exposed group of a community living near a PFOA producing chemical plant[28] were detected in comparison with our 7% in the overall population. The excess of risk we observed for female breast cancer was confirmed by a case-control study on Danish women.[30]

The higher but not statistically significant levels of mortality for bladder cancer and leukemia we detected are in agreement with the not significant HR of 1.66 for bladder cancer in an exposed cohort in Minnesota[19] and with the SMR of 1.48 for leukemia observed in the above European and North American cohort study,[18]; on the other hand, the not significant higher mortality for testicular cancer we observed was lower in comparison with the HR of 3.17 in the highest exposed group of a community living near the PFOA chemical plant.[28]

Differently from what emerged from other studies,[18,20,21] no increased risks for prostate and liver cancer were found, but a even significant lower risk for liver cancer was observed in the overall population.

In conclusion, the present investigation shows that an important set of *a priori* evidenced adverse health effects were detected in a population of an area of the Veneto Region exposed to PFAS levels above the performance limits indicated by ISS, in most cases well below the limits proposed by other regulatory Agencies. The results from this study could be a warning signal in order to start further individual level analytic studies, able to detect the causal association with PFAS exposure and the health outcomes evidenced, possibly using incidence rather than mortality data and focusing also on unexpected outcomes such as the lower liver cancer mortality in the population of the contaminated area. Moreover, our preliminary results could be a way to involve both the international scientific community and the public in the water pollution problem afflicting the Veneto region and sensitize the Authorities to start immediate actions to avoid further exposure of the population to PFAS in drinking water.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Conflicts of interest: None declared.

Key points

- It is the first epidemiological investigation carried out in Italy on a population living in area contaminated by PFAS in drinking water, on the basis of the performance limits indicated by the Italian National Health Institute, and possibly affecting the food chain.
- Higher mortality levels for some causes of death, selected on the basis of previous reported associations with PFAS exposure, were detected in contaminated municipalities in comparison with uncontaminated ones of the Veneto region, both characterized by similar socio-economic conditions and smoking habits.
- Statistically significant relative risks were detected for general mortality, kidney and breast cancer, diabetes, cerebrovascular diseases, myocardial infarction, Alzheimer's and Parkinson's diseases.
- The results of the present ecological investigation are a warning signal that could be a useful indication for public administration in order to start immediate actions to avoid further exposure of populations to PFAS in drinking water in Veneto region.

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