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Perfluoroalkyl substances and risk of type II diabetes: A prospective nested case-control study

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ABSTRACT

Background: Perfluoroalkyl substances (PFAS) have drawn much attention due to bioaccumulation potential and their current omnipresence in human blood. We assessed whether plasma PFAS, suspected to induce endocrine-disrupting effects, were prospectively associated with clinical type 2 diabetes (T2D) risk.

Methods: We established a nested case-control study within the Swedish prospective population-based Västerbotten Intervention Programme cohort. Several PFAS were measured in plasma from a subset of 124 case-control pairs at baseline (during 1990–2003) and at 10-year follow-up. T2D cases were matched (1:1) according to gender, age and sample date with participants without T2D (controls).

Conditional logistic regressions were used to prospectively assess risk of T2D by baseline PFAS plasma concentrations. Associations between long-term PFAS plasma levels (mean of baseline and follow-up) and insulin resistance (HOMA2-IR) and beta-cell function (HOMA2-B%) at follow-up were prospectively explored among 178 and 181 controls, respectively, by multivariable linear regressions.

Results: After adjusting for gender, age, sample year, diet and body mass index, the odds ratio of T2D for the sum of PFAS (Σ z-score PFAS) was 0.52 (95% confidence interval, CI: 0.20, 1.36), comparing third with first tertile; and 0.92 (95% CI: 0.84, 1.00) per one standard deviation increment of sum of log-transformed PFAS. Among the controls, the adjusted β of HOMA2-IR and HOMA-B% for the sum of PFAS were −0.26 (95% CI: −0.52, −0.01) and −9.61 (95% CI: −22.60, 3.39) respectively comparing third with first tertile.

Conclusions: This prospective nested case-control study yielded overall inverse associations between individual PFAS and risk of T2D, although mostly non-significant. Among participants without T2D, long-term PFAS exposure was prospectively associated with lower insulin resistance.

1. Introduction

A number of restricted and/or banned (organochlorine) chemical pollutants have been demonstrated to alter multiple endocrine mechanisms implicated in metabolic control and diabetes type 2 (T2D) development (Nadal et al., 2017; Alonso-Magdalena et al., 2011; Lee et al., 2014; Zong et al., 2018). However, evidence for later introduced pollutants, such as perfluoroalkyl substances (PFAS), is limited.

PFAS belong to a large class of highly fluorinated organic chemicals with a wide range of uses in industrial and consumer products. They are extremely persistent and have become wide-spread in the environment and accumulate in wildlife and humans (elimination half-life in humans: 3.8–8.5 years) (Olsen et al., 2007; Stubleski et al., 2017). Humans are exposed to PFAS in daily life, irrespective of proximity to industry or surfaces with contaminated drinking water (Bowman, 2015). Although the exposure to PFAS occurs through different pathways, diet is the main route. Important sources are fish and seafood (Domingo and Nadal, 2017), but also drinking water and indirect contamination from

Abbreviations: PFAS, perfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexane sulfonic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluoroundecanoic acid; HOMA2-IR, computerized homeostatic model assessment of insulin resistance; HOMA2-B%, computerized homeostatic model assessment of beta cell function; T2D, type 2 diabetes; PPAR, peroxisome proliferator-activated receptor

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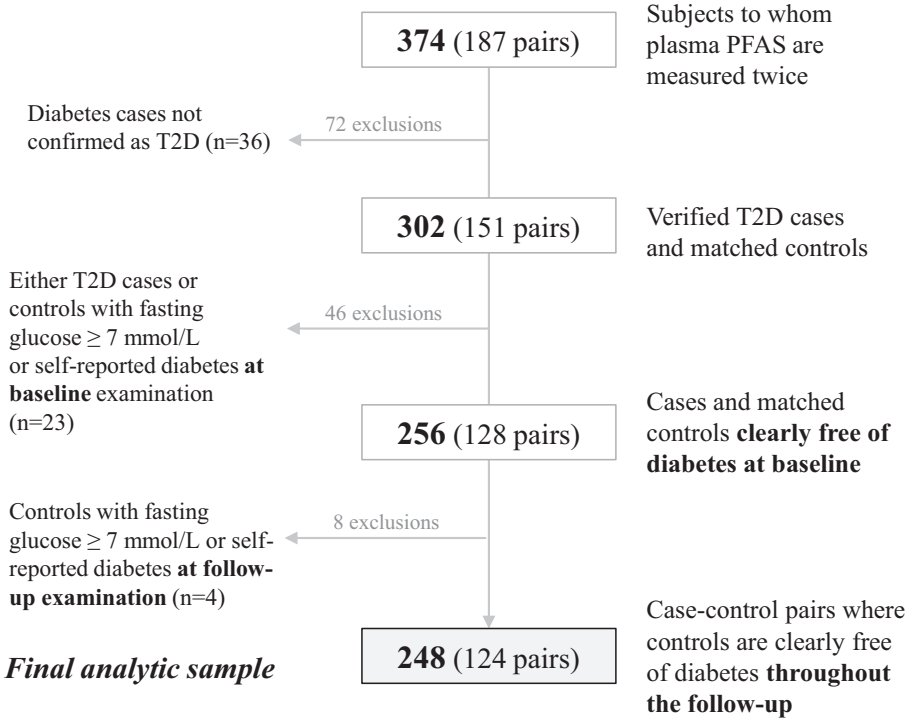

Fig. 1. The exclusions and number of subjects (and case-control pairs) in the final analytical sample for the prospective assessment of associations between baseline (1990–2003) plasma PFAS concentrations and Type 2 Diabetes incidence.
T2D: Type 2 Diabetes.

food packaging materials or cookware could be important. Dust inhalation or skin absorption via certain consumer products are other potential exposure pathways (Haug et al., 2011).

PFAS have a chemical structure analogous to fatty acids and both are activators of the PPARs (peroxisome proliferator-activated receptors) (Takacs and Abbott, 2007). The PPARs induce adipocyte differentiation and play a critical role as regulators of lipid and glucose metabolism and inflammation (Berger et al., 2005; Staels and Fruchart, 2005). While fatty acids have been identified as natural ligands for the PPARs, (Berger et al., 1996; Vanden Heuvel et al., 2006) some hypolipidemic and antidiabetic drugs targeting PPAR, such as fibrates and thiazolidinediones, have been widely used (Berger et al., 1996; Vanden Heuvel et al., 2006).

Although there are animal data supporting a potential favorable effect of PFAS in T2D pathology (Kees et al., 1989; Kees et al., 1992; Yan et al., 2015), the epidemiological evidence on PFAS exposure and T2D is limited and inconsistent, and only three of the existing studies are prospective (Karnes et al., 2014; Sun et al., 2018; Cardenas et al., 2017). There are some reports showing null (Karnes et al., 2014; Cardenas et al., 2017; Lind et al., 2014) or inverse associations (MacNeil et al., 2009), but also positive associations (Sun et al., 2018; Lind et al., 2014; Christensen et al., 2016), such as the recent prospective nested case-control US-study (Nurses' Health Study II) (Sun et al., 2018). This study (Sun et al., 2018) yielded positive associations with T2D for perfluorooctane sulfonic acid (PFOS) and for perfluorooctanoic acid (PFOA), though not for the other three PFAS (perfluorohexane sulfonic acid [PFHxS], perfluorononanoic acid [PFNA] and perfluorodecanoic acid [PFDA]) assessed.

Thus, although the experimental evidence suggests that PFAS can disrupt the endocrine system and alter glucose metabolism, the prospective epidemiologic evidence on PFAS effects at environmentally relevant concentrations remains conflicting.

The main aim of the present study was, therefore, to examine the associations between plasma PFAS concentrations and the risk of clinical T2D in the general population by using a prospective nested case-control design. In addition, we assessed the associations of long-term PFAS exposure (i.e. measured twice in a 10-year period) with insulin resistance and beta cell function among the controls at follow-up.

2. Material and methods

2.1. Study population

The study used data from the Västerbotten Intervention Programme (VIP), a sub-cohort in the Northern Sweden Health and Disease Study initiated in 1985 (Norberg et al., 2010). Briefly, residents in Västerbotten County were eligible to be invited for standardized health examinations to their primary care center during the year of their 30th (until 1995), 40th, 50th and finally 60th birthday. The participation rate exceeded 56%, but was often around 70% (Norberg et al., 2011), of which the vast majority (90.5%) donated blood samples for research.

We used the data collected as part of VIP to conduct the present prospective nested case-control study to disentangle whether exposure to persistent organic pollutants, including PFAS, were associated with the risk of T2D. The study included VIP participants with T2D identified in the DiabNorth register (Rolandsson et al., 2012) that had previously donated samples of blood to the biobank on two occasions, of which at least one occurred prior to T2D diagnosis. Cases of T2D were matched (1:1) with VIP participants without T2D (controls) that were alive at the time of T2D diagnosis for the corresponding case and had donated blood on two occasions. The matching was according to gender, age, sample date (± 90 days) and type of questionnaire at baseline examination.

Thus, PFAS were measured in plasma in a subsample of 187 case-control pairs (n = 374), where cases included different diabetes types. To evaluate the risk of T2D, we only kept those cases (and corresponding controls) with verified type 2 diabetes (151 case-control pairs). From these refined T2D case-control pairs, we additionally excluded: *i*) subjects (either case or control) that, at baseline, had self-reported diabetes or a fasting glucose ≥7 mmol/L (n = 46); *ii*) controls

that, at follow-up examination, had self-reported diabetes or a fasting glucose ≥7 mmol/L (n = 8). Hence, the final analytic sample for the main analyses of this study consisted of 124 case-control pairs (N = 248) (Fig. 1).

The second aim of the study was performed only based on controls. From the initial 187 controls, we excluded those with elevated (≥7 mmol/L) baseline fasting glucose, or self-reported diabetes at baseline (n = 3), or missing data on glucose, insulin or C-peptide at follow-up. Thus, the prospective associations of PFAS with insulin resistance (HOMA2-IR) and beta cell function (HOMA2-B%) were assessed in 178 and 181 controls, respectively.

Oral/written informed consent was obtained from the participants and the study was approved by the regional ethics review board, Umeå University [Dnr 2013/414-31, 2014/147-32M].

2.2. Measurements of PFAS, metabolic markers and covariates

The first medical examination and blood sampling were carried out during 1990 to 2003 (baseline) and the second one during 2001 to 2013 (follow-up). All samples were collected after an 8-h overnight fasting. PFAS were measured at the National Institute for Health and Welfare in Finland, using a method based on liquid chromatography-triple quadrupole mass spectrometry (LC-MS/MS) (Koponen et al., 2013). The limit of quantitation (LOQ) ranged from 0.15 to 1.0 ng/mL. Out of the 13 different PFAS measured in plasma, concentrations of **PFOA**, **PFOS**, **PFNA** and **PFHxS** were > LOQ (0.15 ng/mL) in all subjects. However, concentrations of perfluorododecane acid (PFDoA), perfluorotridecane acid (PFTrA), perfluorotetradecane acid (PFTA), perfluorohexane acid (PFHxA), perfluoroheptane sulfonate (PFHpS), perfluoroheptane acid (PFHpA) and perfluorodecane sulfonate (PFDS) were < LOQ in all subjects (LOQ was 0.30 ng/mL except for PFHpS that was 1.0 ng/mL). Baseline concentrations of **PFDA** and perfluoroundecanoic acid (**PFUnDA**) were < LOQ (0.15 ng/mL) in 26% and 42% of the subjects (n = 374), respectively; and follow-up concentrations were < LOQ in 10% and 34% of the subjects (n = 374), respectively. Thus, ultimately, six long-chain PFAS – four perfluoroalkyl carboxylic acids (PFOA, PFNA, PFDA, PFUnDA), and two perfluoroalkyl sulfonic acids (PFHxS and PFOS) – were available to be properly assessed. We assigned the corresponding LOQ/2 value when concentrations were < LOQ.

The covariates considered were age, gender, education level, smoking habits, body mass index (BMI), Cambridge index for physical activity, history of certain diseases and medication, alcohol consumption and validated groups of food intakes (Johansson et al., 2002; Johansson et al., 2001), from which the healthy diet score was retrieved (Nettleton et al., 2013).

2.3. Outcome assessment

The primary outcome of the study was T2D diagnosed during the follow-up period, retrieved from medical records (i.e., diagnosed by general practitioners) and later validated by specialists according to WHO recommendations and analysis of autoantibodies (to differentiate from type 1).

As secondary analyses, we further examined if PFAS were associated with a dysregulation of glucose, which is a metabolic state intermediate between normal glucose homeostasis and diabetes. Thus, among controls only, we prospectively evaluated the association between PFAS and biomarkers of glycaemic status. Capillary plasma glucose, insulin and C-peptide were measured in the blood samples. The computerized homeostatic model assessment (HOMA2) (Levy et al., 1998) was applied to determine IR from glucose and insulin values (HOMA2-IR) and %B from glucose and C-peptide values (HOMA2-B%) by using the HOMA2 Calculator v2.2.3 (Anon, 2007). The HOMA2, made by Levy J, et al. at Oxford, is an update and adaptation of the HOMA index, described by Turner RC and later perfected by Matthews DR. HOMA2 establishes a non-linear relationship between glucose and insulin (better physiological agreement), takes into account variations in hepatic resistance and peripheral tissue and considers increases in the insulin secretion curve when glucose in blood exceed 180 mg/dL (10 mmol/L) (Levy et al., 1998). Hence, the HOMA2-IR was used to measure insulin sensitivity and the HOMA2-B% was used to measure beta cell function (insulin secretion capacity). Both indices are indicators of glucose homeostasis.

2.4. Statistical analyses

All statistical analyses were performed using the statistical software STATA/SE version 14.0 (Stata Corp LP, College Station, TX, USA). P values were calculated based on 2-sided tests and the level of statistical significance was set at 0.05. Distributions of participant characteristics in the full analytic samples were first examined. Spearman's rank correlation (r_s) was used to assess pairwise correlations between the different PFAS and the intra class correlation (ICC) was used to assess the within person variability between baseline and follow-up PFAS measurements (among controls only).

As primary exposure of interest, the different PFAS were first rescaled to have a mean = 0 and standard deviation (SD) = 1 and then were summarized (Σ z-score PFAS). In addition, each of the PFAS was assessed separately. The associations between baseline PFAS concentrations and subsequent T2D diagnosis were prospectively examined using multivariable conditional logistic regression. Results were presented as odds ratios (OR) with corresponding 95% confidence intervals (CI). To relax the assumption of a linear association between PFAS and the outcomes, we categorized the PFAS plasma concentrations into tertiles according to the distribution among controls. To test for linear trends across increasing categories of PFAS plasma concentrations, the median concentrations within each category were assessed as a continuous exposure in the conditional logistic model. OR were also estimated per one SD-increment of log transformed (base 10) PFAS concentrations.

We tested for interactions between PFAS and both gender and BMI for the T2D development using the likelihood ratio test, comparing multivariable conditional logistic regression with and without interactions term (for interaction on the multiplicative scale).

Long-term PFAS exposure was determined by the average of concentrations measured at baseline and at follow-up examinations. The average time between measurements was 10 years. In controls, prospective associations between the long-term PFAS concentrations and HOMA2-IR and HOMA2-B% values (measured at follow-up examination) were evaluated by multivariable linear regressions, providing slope coefficients (β) and their 95% CI. Regression model assumptions were checked by visual inspection and diagnostic tests of the models' residuals.

For the first confounder identification, we employed directed acyclic graphs (Fig. A1). Then, the minimal set of covariates was selected using the change-in-estimate approach through backward elimination. The change-in-estimate between the full logistic model and the full model without the variable of interest was calculated. If the change in OR estimate was > 10%, the variable was kept in the final model (Dunkler et al., 2014). Thus, we presented a univariate model estimate including only matching variables (gender, age and sample year), a second model further adjusted for red/processed meat and fish intakes, and a third model additionally controlled for BMI. Because any effect of PFAS on lipid metabolism may be in the underlying pathway through which PFAS affect T2D pathology, we considered the plasma lipids as potential mediators (Fig. A1). Consequently, we did not adjust for lipids. Missing values of weight or height in one of the samples were replaced by the corresponding value reported in the other sample (below 2%).

Table 1
Baseline (1990–2003) main characteristics by type 2 diabetes cases and controls (N = 248).

Characteristics	Cases (n = 124)	Controls (n = 124)
Baseline examination year	1995 (3)	1995 (3)
Female, n (%)	52 (42)	52 (42)
Age (years)	46 (6)	46 (6)
Body mass index (kg/m^2)	29.1 (4.3)	25.4 (3.3)
Education > 12 years, n (%)	92 (74)	94 (75)
Smoking status, n (%)		
Current	30 (24)	27 (22)
Former	51 (41)	48 (39)
Physical activity, n (%) Inactive	60 (48)	67 (58)
Healthy diet (1–22 score)	11 (4)	11 (3)
Meat (servings/week)	5.0 (2.9)	4.5 (2.2)
Fish (servings/week)	1.3 (1.1)	1.4 (0.9)
Alcohol consumption, n (%)		
0.1–5 g	90 (73)	81 (65)
5.1–15 g	28 (23)	32 (26)
> 15 g	1 (0.8)	3 (2)
Blood pressure lowering medication, n (%)	29 (23)	12 (10)
Cholesterol lowering medication, n (%)	2 (< 2)	0 (0)
Laboratory analyses	*Mean (SD)*	*Mean (SD)*
Total cholesterol (mmol/L)	5.8 (1.3)	5.4 (1.2)
Triglycerides (mmol/L)	1.8 (1.0)	1.3 (0.6)
Systolic blood pressure (mm Hg)	135.5 (16.8)	126.0 (15.6)
Diastolic blood pressure (mm Hg)	85.2 (10.6)	79.2 (9.9)
Fasting glucose (mmol/L)	5.8 (0.7)	5.4 (0.5)
Fasting insulin (pmol/L)	103.2 (62.7)	57.2 (41.7)
C-Peptide (nmol/L)	1.0 (0.4)	0.7 (0.3)
HOMA2-IR	1.9 (1.1)	1.1 (0.7)
HOMA2-B%	134.7 (76.3)	106.9 (26.9)
Plasma PFAS concentrations (ng/mL)	*Median* (IQR)	*Median* (IQR)
ΣPFAS	24.1 (19.0–31.0)	26.8 (20.3–34.2)
PFOA	2.8 (2.15–3.6)	3.0 (2.3–4.2)
PFOS	19 (15–25)	20 (16–27)
PFNA	0.55 (0.40–0.76)	0.53 (0.42–0.78)
PFHxS	0.99 (0.69–1.40)	1.10 (0.76–1.40)
PFDA	0.21 (< LOQ −0.29)	0.23 (0.17–0.30)
PFUnDA	0.16 (< LOQ −0.23)	0.18 (< LOQ–0.26)

Note: Continuous variables are shown as mean (standard deviation) and categorical variables as number (%). PFAS levels are presented as medians and interquartile ranges (IQR). Abbreviations: **PFOA**, perfluorooctanoic acid; **PFOS**, perfluorooctane sulfonate; **PFNA**, perfluorononanoic acid; **PFHxS**, perfluorohexane sulfonic acid; **PFDA**, perfluorodecanoic acid; **PFUnDA**, perfluoroundecanoic acid; **HOMA2-IR**, computerized homeostatic model assessment of insulin resistance; **HOMA2-B%**, computerized homeostatic model assessment of beta cell function.

3. Results

Table 1 shows the baseline characteristics of the study participants (mean 46 years). All biochemical markers of lipids, glucose, insulin and blood pressure were higher in cases than in controls. In general, no major differences were observed between cases and matched controls for the main characteristics, with the exception of BMI and the use of anti-hypertensive lowering drugs, which both were also somewhat higher in cases than in controls.

PFOS and PFOA showed the highest concentrations of the PFAS measured. With the exception of PFNA, PFAS were generally slightly lower in cases than controls (Table 1 and Fig. 2). As displayed in Fig. 3, all PFAS were low-to-moderately intercorrelated with r_s ranging from 0.16 (for PFOA–PFUnDA) to 0.66 for (PFOS–PFOA). The ICCs based on repeated measurement ranged from 0.52 (PFNA) to 0.85 (PFHxS).

On average, the time from baseline to follow-up was 10 years and the time between baseline measurement and T2D diagnosis was 8.2 years. Overall, PFAS showed to be inversely associated with the risk of future T2D, which with few exceptions did not reach statistical significance. The fully adjusted OR of T2D for Σ z-score PFAS was 0.52 (95% CI: 0.20, 1.36), comparing those in the highest with those in the lowest tertile. When modelling the associations for a SD increment of log transformed PFAS, we observed a 35% (95% CI: 3% to 57%) lower odds of T2D for PFOA and 8% (95% CI: 0% to 16%) for the Σ z-score PFAS (Table 2). There were no significant interactions by gender or by categories of BMI (p for interaction of z-score PFAS was 0.62 and 0.70, respectively).

The examination of the long-term PFAS exposure with the insulin resistance at follow-up conducted among the controls alone, also disclosed inverse associations, reaching statistical significance for some of the PFAS. Based on the maximally adjusted models, the mean difference in HOMA2-IR was −0.26 (95% CI: −0.52, −0.01) comparing the highest with the lowest tertile of the Σ z-score PFAS. With the exception of PFUnDA, no PFAS was significantly associated with HOMA2-B% (Table 3). The cross-sectional associations between PFAS and HOMA2-IR and HOMA2-B% at baseline and at follow-up were appreciably in line with the prospective assessment but attenuated (Table A1).

4. Discussion

This prospective nested case-control study yielded overall inverse associations between individual PFAS and risk of T2D, which with few exceptions did not reach statistical significance. In a similar manner, the long-term PFAS exposures were inversely associated with insulin resistance at follow-up among the controls.

Most of the human evidence to date (limited and discordant) comes from cross-sectional studies. Thus, in a cross-sectional large case-control study (N = 13,922; 1055 cases of T2D) of community residents and workers exposed to high concentrations of PFOA via contaminated drinking water (C8 Health Project), serum PFOA showed an inverse linear association with prevalent T2D (MacNeil et al., 2009). In a similar but larger cross-sectional study also from C8 Health Project (N = 60,439; 4291 T2D cases), higher concentrations of PFOA, PFOS, PFHxS and PFNA were associated with a lower T2D prevalence (Conway et al., 2016). In line, PFOA, PFNA and PFUA were inversely associated with prevalent T2D, though not PFOS, which was associated with increased T2D prevalence in Taiwanese adults (Su et al., 2016). Also PFNA levels were linked to increased prevalent T2D in another cross-sectional study (Lind et al., 2014). Plasma PFAS concentration might be influenced by factors affected by a diabetes diagnose: changes in diet and other factors related to treatment can affect exposure, distribution or excretion, and the disease itself can affect physiology. Therefore, the cross-sectional studies may be subject to reverse causation, emphasizing the necessity of prospective evaluations ensuring that all subjects are free of T2D at baseline.

However, the three prospective studies published so far also arrived at disagreeing findings. A large study conducted in the C8 Health Project did not find any evidence of an association between estimated (not measured) cumulative PFOA exposure and incidence of T2D, neither in the retrospective (N = 30,424; 3756 cases of T2D) nor prospective analyses (N = 27,921; 814 cases of T2D) (Karnes et al., 2014). Similarly, in another study conducted among overweight and obese individuals at high risk of developing T2D (N = 957; 204 cases of T2D; participants were recruited for a multicentre randomized clinical trial), plasma PFAS, including PFOA, PFOS, PFHxS and PFNA, were not associated with incident T2D after a median follow-up of 3 years (Cardenas et al., 2017). Likewise, there was no evidence that baseline plasma PFAS influenced trajectories of insulin resistance and beta-cell function during these 3 years follow-up (Cardenas et al., 2017).

Nevertheless, the most recent prospective study revealed consistent positive associations between PFOA and PFOS – the two PFAS found in highest concentrations in blood – and incident T2D (Sun et al., 2018). In that nested case-control study on U.S women followed from 1995 to

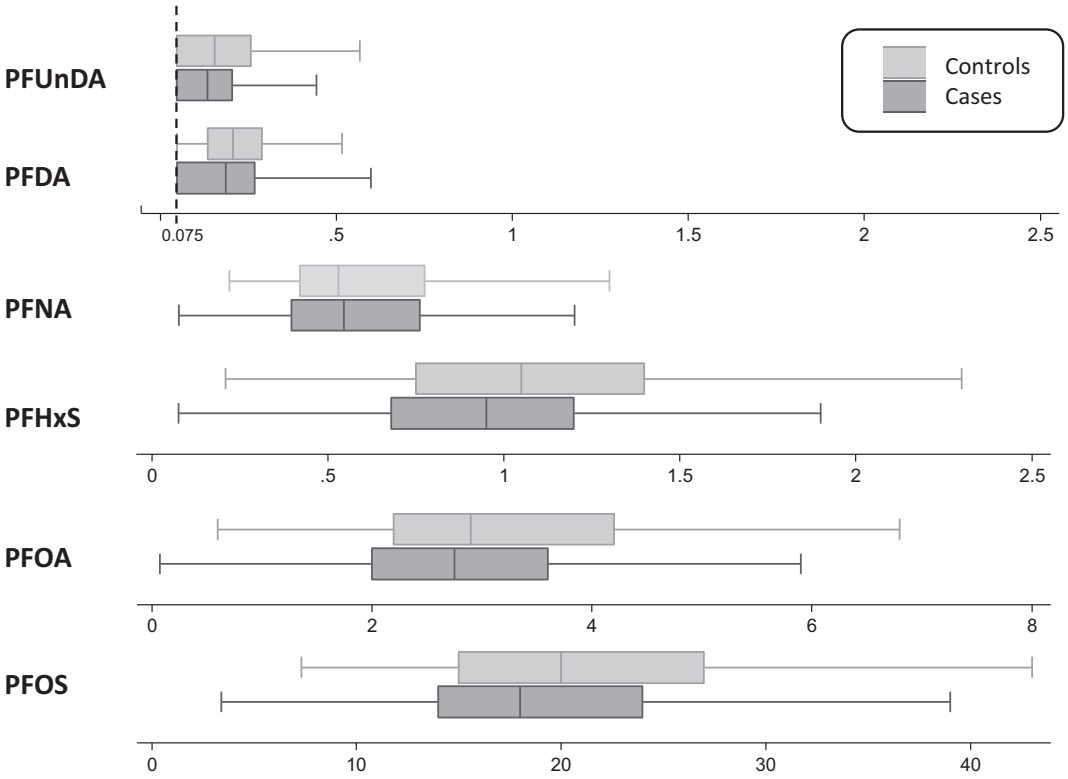

Fig. 2. Differences in plasma PFAS concentrations measured at baseline between cases and controls. Boxes display median and interquartile range and whiskers the total range. For PFUnDA and PFDA the lower interquartile is the value of LOQ/2.

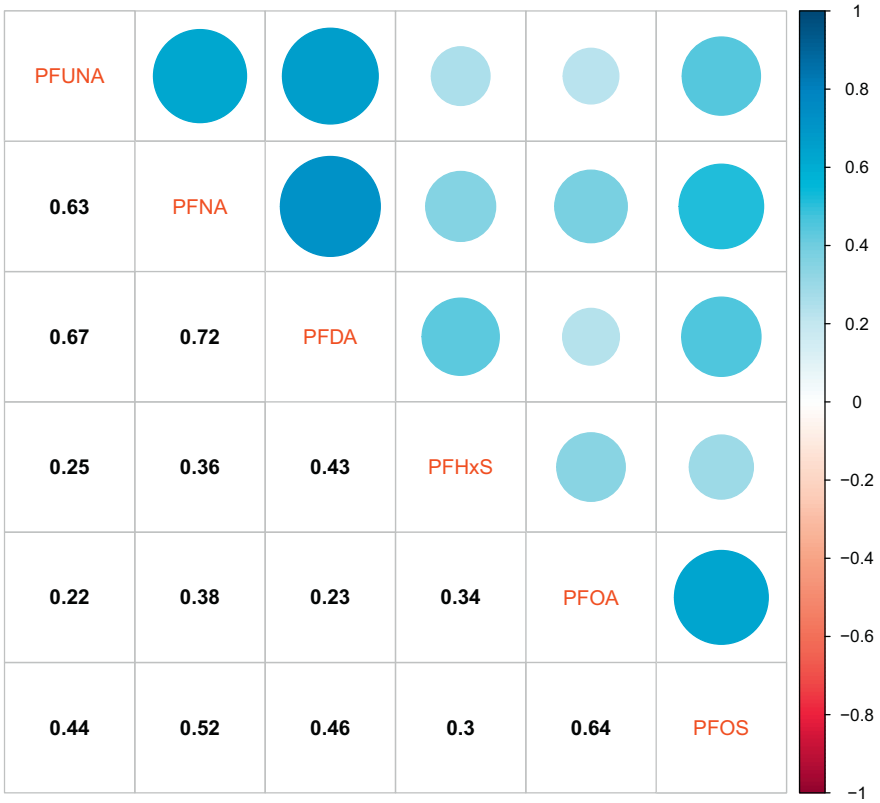

Fig. 3. Pairwise Spearman's rank correlations between PFAS at baseline.

Table 2
Prospective associations between baseline plasma PFAS concentrations and risk of Type 2 Diabetes.

			Model 1	Model 2	Model 3
	n Cases/controls	Median (IQR)[a]	OR (95% CI)	OR (95% CI)	OR (95% CI)
Σ z-score PFAS[b]					
Tertile 1	51/42		1 (ref)	1 (ref)	1 (ref)
Tertile 2	40/41		0.75 (0.40, 1.40)	0.79 (0.41, 1.51)	0.56 (0.22, 1.42)
Tertile 3	33/41		0.62 (0.32, 1.20)	0.66 (0.33, 1.34)	0.52 (0.20–1.36)
p trend			0.16	0.28	0.33
1-SD $\log_{10}$-PFAS[c]			0.93 (0.87, 1.00)	0.94 (0.78, 1.00)	0.92 (0.84, 1.00)
PFOA					
Tertile 1	53/44	2.1 (1.7–2.3)	1 (ref)	1 (ref)	1 (ref)
Tertile 2	49/40	3.1 (2.8–3.5)	0.96 (0.52, 1.79)	0.96 (0.50, 1.85)	1.11 (0.46, 2.69)
Tertile 3	22/40	4.8 (4.2–5.4)	0.43 (0.21, 0.87)	0.40 (0.19, 0.85)	0.44 (0.17–1.12)
p trend			0.02	0.01	0.06
1-SD $\log_{10}$-PFOA[c]			0.71 (0.54, 0.93)	0.67 (0.50, 0.90)	0.65 (0.43, 0.97)
PFOS					
Tertile 1	50/43	13 (11–16)	1 (ref)	1 (ref)	1 (ref)
Tertile 2	41/41	21 (19–23)	0.80 (0.42, 1.53)	0.89 (0.45, 1.75)	0.79 (0.34, 1.87)
Tertile 3	33/40	30 (27–35)	0.67 (0.35, 1.31)	0.66 (0.33, 1.33)	0.53 (0.22–1.28)
p trend			0.25	0.23	0.17
1-SD $\log_{10}$-PFOS[c]			0.84 (0.64, 1.11)	0.83 (0.62, 1.11)	0.70 (0.47, 1.03)
PFHxS					
Tertile 1	49/42	0.63 (0.49–0.76)	1 (ref)	1 (ref)	1 (ref)
Tertile 2	43/47	1.1 (0.98–1.2)	0.76 (0.41, 1.42)	0.75 (0.39, 1.43)	0.85 (0.37–1.96)
Tertile 3	32/35	1.6 (1.5–1.9)	0.76 (0.39, 1.49)	0.73 (0.36, 1.47)	0.71 (0.28–1.81)
p trend			0.40	0.36	0.39
1-SD $\log_{10}$-PFHxS[c]			0.77 (0.58, 1.01)	0.75 (0.56, 1.00)	0.69 (0.46, 1.03)
PFNA					
Tertile 1	46/46	0.38 (0.3–0.42)	1 (ref)	1 (ref)	1 (ref)
Tertile 2	37/38	0.55 (0.49–0.61)	0.98 (0.52, 1.85)	0.95 (0.48, 1.86)	0.66 (0.27, 1.61)
Tertile 3	41/40	0.83 (0.76–1.1)	1.03 (0.53, 2.00)	1.26 (0.61, 2.60)	1.02 (0.40, 2.59)
p trend			0.92	0.44	0.66
Log-PFNA[c]			0.90 (0.70, 1.15)	0.95 (0.72, 1.24)	0.82 (0.57, 1.18)
PFDA					
Tertile 1	53/43	0.08 (0.75–0.17)	1 (ref)	1 (ref)	1 (ref)
Tertile 2	38/44	0.24 (0.22–0.26)	0.66 (0.36, 1.24)	0.62 (0.32, 1.19)	0.78 (0.34, 1.79)
Tertile 3	33/37	0.36 (0.31–0.42)	0.67 (0.34, 1.32)	0.68 (0.33, 1.40)	0.64 (0.26, 1.58)
p trend			0.22	0.39	0.52
1-SD $\log_{10}$-PFDA[c]			0.85 (0.65–1.12)	0.84 (0.62, 1.12)	0.85 (0.59, 1.23)
PFUnDA					
Tertile 1	60/53	0.08 (0.08–0.08)	1 (ref)	1 (ref)	1 (ref)
Tertile 2	31/30	0.18 (0.17–0.20)	0.87 (0.46, 1.62)	0.99 (0.51, 1.93)	0.98 (0.43, 2.23)
Tertile 3	33/41	0.29 (0.26–0.35)	0.63 (0.32, 1.26)	0.74 (0.34, 1.55)	0.81 (0.32, 2.05)
p trend			0.20	0.39	0.64
1-SD $\log_{10}$-PFUnDA[c]			0.80 (0.59, 1.07)	0.84 (0.61, 1.15)	0.89 (0.59, 1.34)

Note: Estimations of individual PFAS are not mutually adjusted. **Model 1**: Conditioned on matching factors, including gender, age (< or ≥ 45 years at baseline) and sample year (1990–93, 1994–97, 1998–2003). **Model 2**: Model 1 further adjusted for red and processed meat intake (< 3, 3–4, 4–6, > 6 times/week) and fish intake (< 3, 3–5, 6–7, > 8 times/months). **Model 3**: Model 2 further adjusted for body mass index (≤ 25, > 25–≤ 30, > 30 kg/m^2). Abbreviations**: OR**, odds ratio; **CI**, confidence interval; **PFAS**, perfluoroalkyl substances; **PFOA**, perfluorooctanoic acid; **PFOS**, perfluorooctane sulfonate; **PFNA**, perfluorononanoic acid; **PFHxS**, perfluorohexane sulfonic acid; **PFDA**, perfluorodecanoic acid; **PFUnDA**, perfluoroundecanoic acid

[a] IQR, interquartile range (percentiles 25–percentile 75).

[b] Sum of standardized PFAS.

[c] OR for 1-SD increase in log transformed PFAS.

2011 (N = 1586; 793 cases of T2D), tertiles of baseline plasma concentrations of PFOS (OR 1.62, 95% CI 1.09, 2.41) and PFOA (OR 1.54, 95% CI 1.04, 2.28) were associated with an elevated risk of T2D, but not PFHxS (OR 1.26, 95% CI 0.86, 1.86), PFNA (OR 0.99, 95% CI 0.67, 1.48) or PFDA (OR 0.71, 95% CI 0.48, 1.05). PFOS, PFOA and PFHxS concentrations (median PFOS 33 ng/mL, PFOA 4.6 ng/mL, PFHxS 2.01 ng/mL in the controls) were about twice as high as in this present study, while PFNA (0.61 ng/mL) and PFDA (0.16 ng/mL) were similar.

The preceding studies in general adult populations addressing glucose homeostasis indicators in relation to PFAS exposure also yielded inconsistent results and only one had a prospective design (Cardenas et al., 2017). Although most of the cross-sectional studies found no evidence of an association between PFAS and glucose homeostasis parameters (Lind et al., 2014; Fisher et al., 2013; Nelson et al., 2010), some reported positive (Lin et al., 2009) or inverse (Lin et al., 2009; Fleisch et al., 2017) associations. In the prospective study of adults at high risk of T2D (prediabetic cohort), the cross-sectional associations with insulin resistance and beta-cell function with PFAS were positive, while their prospective associations displayed null results (Cardenas et al., 2017).

Although human exposure to PFAS may occur through different pathways, dietary intake seems to be the main route of exposure to these compounds. Diet is a major factor in T2D aetiology and is, in addition, linked with lifestyle factors of concern. Therefore, potential confounding by diet or lifestyle factors associated with diet must be considered when associations between PFAS and T2D are interpreted (Tuomisto et al., 2016). Throughout the world, the origin, production, packaging and consumption of food differs between countries (Domingo and Nadal, 2017). Consequently, there are considerable differences in where PFAS are detected and at what concentrations. These differences on the dietary sources of PFAS, together with the different dietary habits among populations, might be an explanation (or

Table 3
Prospective associations between long-term PFAS plasma concentrations[a] and insulin resistance (HOMA2-IR) and beta-cell function (HOMA2-B%) in controls.

	Median (IQR)[b]	Controls (n = 184)	HOMA2-IR[c]	HOMA2-B%[d]
			β (95% CI)	β (95% CI)
Σ z-score PFAS				
Tertile 1		62	1 (ref)	1 (ref)
Tertile 2		61	−0.20 (−0.44, 0.04)	−1.95 (−14.17, 10.27)
Tertile 3		61	−0.26 (−0.52, −0.01)	−9.61 (−22.60, 3.39)
p for trend			0.04	0.14
1-SD $\log_{10}$-ΣPFAS[e]			−0.03 (−0.05, −0.01)	−0.72 (−1.93, 0.48)
PFOA				
Tertile 1	2.0 (1.7–2.2)	62	1 (ref)	1 (ref)
Tertile 2	2.8 (2.6–3.1)	64	−0.00 (−0.25, 0.24)	−0.24 (−12.61, 12.14)
Tertile 3	4.3 (3.9–4.8)	58	−0.12 (−0.39, 0.14)	−3.47 (−17.12, 10.17)
p for trend			0.32	0.59
1-SD $\log_{10}$-PFOA[e]			−0.08 (−0.18, 0.03)	−1.08 (−6.54, 4.39)
PFOS				
Tertile 1	11.5 (9.5–12.7)	62	1 (ref)	1 (ref)
Tertile 2	17.5 (16–19)	61	−0.13 (−0.38, 0.12)	−5.85 (−18.73, 7.03)
Tertile 3	25 (23–29.5)	61	−0.24 (−0.50, 0.02)	−5.34 (−18.77, 8.09)
p for trend			0.07	0.45
1-SD $\log_{10}$-PFOS[e]			−0.11 (−0.22, 0.00)	−1.33 (−7.02, 4.36)
PFHxS				
Tertile 1	0.69 (0.56–0.82)	63	1 (ref)	1 (ref)
Tertile 2	1.12 (1.0–1.25)	60	−0.24 (−0.50, 0.01)	−3.31 (−16.27, 9.65)
Tertile 3	1.60 (1.5–1.80)	61	−0.22 (−0.48, 0.03)	−6.07 (−19.33, 7.18)
p for trend			0.11	0.37
1-SD $\log_{10}$-PFHxS[e]			−0.07 (−0.17, 0.04)	−1.49 (−6.91, 3.92)
PFNA				
Tertile 1	0.47 (0.41–0.54)	63	1 (ref)	1 (ref)
Tertile 2	0.70 (0.64–0.75)	61	−0.18 (−0.43, 0.06)	7.53 (−4.99, 20.05)
Tertile 3	1.10 (0.96–1.53)	60	−0.25 (−0.51, 0.00)	−5.72 (−18.91, 7.47)
p for trend			0.06	0.28
1-SD $\log_{10}$-PFNA[e]			−0.06 (−0.17, 0.05)	−1.52 (−7.12, 4.08)
PFDA				
Tertile 1	0.17 (0.13–0.20)	63	1 (ref)	1 (ref)
Tertile 2	0.28 (0.27–0.31)	62	−0.35 (−0.58, −0.12)	5.15 (−6.80, 17.10)
Tertile 3	0.46 (0.38–0.59)	59	−0.41 (−0.65, −0.17)	−12.36 (−24.84, 0.12)
p for trend			< 0.01	0.03
1-SD $\log_{10}$-PFDA[e]			−0.16 (−0.26, −0.05)	−3.45 (−8.78, 1.88)
PFUnDA				
Tertile 1	0.08 (0.08–0.12)	64	1 (ref)	1 (ref)
Tertile 2	0.19 (0.17–0.24)	59	−0.29 (−0.53, −0.05)	−6.70 (−19.13, 5.74)
Tertile 3	0.38 (0.31–0.45)	61	−0.43 (−0.67, −0.19)	−15.31 (−27.79, −2.82)
p for trend			< 0.01	0.02
1-SD $\log_{10}$-PFUnDA[e]			−0.17 (−0.27, −0.07)	−5.80 (−11.15, −0.45)

Note: Estimations of individual PFAS are not mutually adjusted. Estimations adjusted for gender, age (< or ≥ 45 years at baseline) and sample year (1990–93, 1994–97, 1998–2003), body mass index (≤25, > 25–≤30, > 30 kg/m^2), red and processed meat intake (< 3, 3–4, 4–6, > 6 times/week) and fish intake (< 3, 3–5, 6–7, > 8 times/month). Abbreviations: **β**, mean difference compared with the first tertile or estimated slope coefficient; **CI**, confidence interval; **PFAS**, perfluoroalkyl substances; **PFOA**, perfluorooctanoic acid; **PFOS**, perfluorooctane sulfonate; **PFNA**, perfluorononanoic acid; **PFHxS**, perfluorohexane sulfonic acid; **PFDA**, perfluorodecanoic acid; **PFUnDA**; perfluoroundecanoic acid; **HOMA2-IR** computerized homeostatic model assessment of insulin resistance; **HOMA2-B** computerized homeostatic model assessment of beta-cell function

[a] Average of baseline and follow-up plasma PFAS concentrations.
[b] IQR, interquartile range (percentiles 25–75).
[c] n = 178 (6 missing values on glucose or insulin).
[d] n = 181 (3 missing values on glucose or C-peptide).
[e] β for a 1-SD increase in log transformed PFAS.

could partially contribute) to the dissonant results reported in the existing prospective studies (Karnes et al., 2014; Sun et al., 2018; Cardenas et al., 2017), including the present work.

Data from Chinese residents indicated important regional differences in dietary sources of PFAS (Zhang et al., 2011), where fish and seafood consumption could account from 7% to 84% of total PFOS intake depending on the region (Zhang et al., 2011). In Sweden, fish is the main contributor to the dietary exposure to PFAS (Vestergren et al., 2012) and fish were consumed on average 1–2 times per week in the present study. Accordingly, in an elderly Swedish population, the highest body burden of PFAS were found in individuals with high adherence to a Mediterranean-like diet characterized by high fish consumption (Sjogren et al., 2016). In contrast, in the referred prospective study conducted among US-nurses (Sun et al., 2018), a higher overall diet quality was associated with lower PFOS concentrations, higher popcorn intake was linked to higher PFOS concentrations (probably due to the use of some PFAS in paper-based containers used for hot fatty foods (Domingo and Nadal, 2017)) and more frequent seafood intake was only associated with higher PFNA concentrations.

In light of these observations and that dietary patterns are associated with both exposure to PFAS and the risk of T2D, any failure to fully account for this confounding by diet may lead to biased associations. In the present study, we adjusted for confounding related to fish and meat consumption, while the healthy diet score did not affect the estimates. Still we cannot rule out the possibility of residual or unmeasured confounding by a healthy diet.

The inverse association between PFOA on T2D development is consistent with an animal study, which found that PFOA exposure

increased insulin sensitivity and inhibited hepatic glycogen synthesis (Yan et al., 2015). Further evidence of anti-diabetic effect of median chain length perfluorocarbons such as PFOA and PFNA comes from earlier studies in rodents (Kees et al., 1989; Kees et al., 1992). However, there are also some animal studies supporting a potential diabetogenic effect of PFAS in adult animals exposed in utero (Lv et al., 2013).

The underlying biological mechanisms linking environmentally relevant PFAS exposure concentrations to the development of T2D are unknown. Nonetheless, PFAS possess endocrine-disrupting properties (Kraugerud et al., 2011; Pedersen et al., 2016) and activate the isoforms α and γ of the PPAR (Takacs and Abbott, 2007; Vanden Heuvel et al., 2006; Shipley et al., 2004), which are involved fundamentally in regulating gene expression for lipid and glucose metabolism, inflammation, adipocyte differentiation as well as atherosclerosis (Berger et al., 2005; Staels and Fruchart, 2005). PPARs are therapeutic targets for treating metabolic diseases. The insulin-sensitizing antidiabetic thiazolidinediones, which are used in the treatment of T2D, are high-affinity PPARγ ligands, whose beneficial effects include improvement of glycaemic control, dyslipidaemia, atherogenesis or inflammatory responses (Gurnell, 2007). Likewise, synthetic PPARα agonist, such as fibrates, are clinically used to treat dyslipidaemia and have shown to exert anti-inflammatory effects both in the vascular wall and the liver (Zandbergen and Plutzky, 2007; Yu et al., 2015).

Limitations of the present study are the potential of chance findings and bias arisen from residual or unmeasured confounding, for example by lifestyle and/or diet. Another limitation regarding the accuracy of exposure measurement when assessing the T2D risk is that PFAS were measured only once at baseline, and therefore, there is a possibility of misclassification of PFAS long-term exposure concentrations, which would bias the results toward null. However, the long elimination half-life in humans and the expected continuous exposure to PFAS in the general population (through diet, drinking water, consumer products) – supported by the high ICCs of repeated measurements – speaks for a limited impact of this limitation. Specifically for PFDA and PFUnDA, several measurements were < LOQ; however, we expect the estimates to be reliable in the relative ranking of participants' exposures. The overall low exposure levels may be accompanied by a low exposure contrast that, together with the limited sample size, might compromise the ability to find significant associations. Finally, having given blood samples twice to the biobank was required for inclusion in this nested T2D case-control study. In the unlikely situation that there were differences between the members of the cohort who gave two samples (selected) and those who had only one (not selected), this selection criteria was applied for both cases and controls.

This study, however, stands out for the methodological strengths that maximizes the internal validity of the results, which include: 1) the prospective study design where data is repeatedly collected on cohort members, which avoids reverse causation bias and takes into account long-term PFAS exposure; 2) the standardized collection and measurement of plasma PFAS, the high quality analytical techniques used and high ICC, which decrease the possibility of exposure misclassification; 3) the stringent clinical diagnosis of T2D, which decrease the possibility of outcome misclassification; 4) the systematic procedure to identify T2D cases via linkage with registries, avoiding medical surveillance bias; 5) the available data on diet, anthropometric measurements and clinical parameters as well as the individual case-control matching by age, gender and sampling date, which allowed us to properly account for confounding by these factors.

5. Conclusion

The present study did not indicate any adverse effect of PFAS on diabetes risk, if anything, our findings may suggest a lower risk of type 2 diabetes with increasing exposure to PFAS. We also found that higher plasma concentrations of long-term PFAS were associated with improved trajectories of insulin resistance during up to 10 years of follow-up in diabetes-free individuals. Diet as a common cause of both PFAS exposure and outcome, is likely an underestimated confounding factor that may contribute to the conflicting results observed in earlier prospective studies. If, despite our concern about possible confounding by dietary patterns, there was a true inverse association, it would imply interference with glucose homeostasis at the exposure concentrations found in the general population. Such associations should be regarded as an uncontrolled and undesirable pharmacological intervention on the whole population, including small children and pregnant women. Thus, the potential impact of the exposure to these perfluoroalkyl substances on glucose metabolism warrants attention, and understanding the biology underlying this observed PFAS-mediated metabolic effect is required for accurate risk evaluation.

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Financial interest's declaration

The authors declare they have no actual or potential competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.12.026.

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