Diabetologia
DOI 10.1007/s00125-013-3126-3

ARTICLE

Circulating levels of perfluoroalkyl substances and prevalent diabetes in the elderly

Lars Lind · Björn Zethelius · Samira Salihovic · Bert van Bavel · P. Monica Lind

Received: 29 August 2013 / Accepted: 12 November 2013

Abstract
Aims/hypothesis Several environmental contaminants, such as polychlorinated biphenyls, dioxins, bisphenol A and phthalates, have been linked to diabetes. We therefore investigated whether other kinds of contaminants, perfluoroalkyl substances (PFAS), also called perfluorinated compounds (PFCs), are also associated with diabetes.
Methods The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study investigated 1,016 men and women aged 70 years. Seven PFAS were detected in almost all participant sera by ultra-high performance liquid chromatograph/tandem mass spectrometry. Diabetes was defined as use of hypoglycaemic agents or fasting glucose >7.0 mmol/l.
Results 114 people had diabetes. In the linear analysis, no significant relationships were seen between the seven PFAS and prevalent diabetes. However, inclusion of the quadratic terms of the PFAS revealed a significant non-linear relationship between perfluorononanoic acid (PFNA) and diabetes, even after adjusting for multiple confounders (OR 1.96, 95% CI 1.19, 3.22, $p=0.008$ for the linear term and OR 1.25, 95% CI 1.08, 1.44, $p=0.002$ for the quadratic term). Perfluorooctanoic acid (PFOA) also showed such a relationship ($p=0.01$). PFOA was related to the proinsulin/insulin ratio (a marker of insulin secretion), but none of the PFAS was related to the HOMA-IR (a marker of insulin resistance) following adjustment for multiple confounders.
Conclusions/interpretation PFNA was related to prevalent diabetes in a non-monotonic fashion in this cross-sectional study, supporting the view that this perfluoroalkyl substance might influence glucose metabolism in humans at the level of exposure seen in the general elderly population.

Keywords Diabetes · Elderly · Environmental contaminants · Epidemiology · Insulin · Perfluoroalkyl substances

Abbreviations

L-PFOS	Linear isomer of perfluorooctane sulfonic acid
PCB	Polychlorinated biphenyl
PFAS	Perfluoroalkyl substances
PFBuS	Perfluorobutane sulfonic acid
PFC	Perfluorinated compound
PFDA	Perfluorodecanoic acid
PFDS	Perfluorodecane sulfonic acid
PFDoDA	Perfluorododecanoic acid
PFHpA	Perfluoroheptanoic acid
PFHxA	Perfluorohexanoic acid
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PFOSA	Perfluorooctane sulfonamide
PFPeA	Perfluoropentanoic acid
PFTrDA	Perfluorotridecanoic acid
PFUnDA	Perfluoroundecanoic acid

L. Lind · S. Salihovic
Department of Medical Sciences, Cardiovascular Epidemiology, Uppsala University, Uppsala, Sweden

B. Zethelius
Department of Public Health/Geriatrics, Uppsala University, Uppsala, Sweden

B. Zethelius
Medical Product Agency, Uppsala, Sweden

S. Salihovic · B. van Bavel
MTM Research Centre, Örebro University, Örebro, Sweden

P. M. Lind (✉)
Department of Medical Sciences, Occupational and Environmental Medicine, Uppsala University, 751 85 Uppsala, Sweden
e-mail: monica.lind@medsci.uu.se

PIVUS Prospective Investigation of the Vasculature in Uppsala Seniors
PPAR Peroxisome proliferator-activated receptor

Introduction

Perfluoroalkyl substances (PFAS), also denoted as perfluorinated compounds (PFCs), are high-volume chemicals that have been produced for more than 50 years [1]. Because the compounds have both hydrophobic and hydrophilic groups they have unique properties and are used in a number of applications, such as fire-fighting foams, impregnation agents for textiles, paper and leather, and in wax, polishes, paints, varnishes and cleaning products. PFAS are also used in the semiconductor industry and in multiple photolithography chemicals. Following oral exposure, PFAS accumulate in the circulation, liver and kidney [2], but not in the adipose tissue to a major degree [3]. Perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) are the two PFAS most commonly found in humans and in the environment, although a large number of other PFAS exist.

PFAS have been show to bind to peroxisome proliferator-activated receptors (PPARs) [4]. These receptors are of major importance for lipid metabolism and fat storage and have therefore been a target for pharmaceutical drugs aimed at treating dyslipidaemia and diabetes. The glitazones are a family of compounds that are PPAR-γ agonists and are used clinically as oral glucose-lowering drugs. Since PFAS bind to the same receptor, investigation of the effects of PFAS on glucose metabolism is worthwhile, particularly since another group of environmental contaminants that similarly bind to PPAR receptors, the phthalates, have been linked to diabetes in epidemiological studies [5–7]. PFAS have also been linked to disturbances in lipid metabolism [8]. Gestational and lactational exposure to PFOS led to signs of impaired glucose tolerance and increased fat accumulation in rats [9], but epidemiological studies have yielded divergent results regarding PFAS exposure and diabetes [8, 10–12].

Since a number of other environmental contaminants, such as polychlorinated biphenyls (PCBs), organochlorine (OC) pesticides, bisphenol A and phthalates, have all been associated with diabetes [5–7, 13–18], we hypothesised that high levels of PFAS in humans might also be associated with the disease. To evaluate this hypothesis, we used data from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study in which we measured circulating levels of several PFAS in almost 1,000 elderly individuals. As a secondary objective, we also investigated whether PFAS levels were associated with markers of insulin secretion and resistance, two major determinants of glucose regulation.

Methods

Participants and sampling

All people aged 70 living in the community of Uppsala, Sweden were eligible for the PIVUS study [19]. Individuals invited to take part in the study were randomly chosen from the register of community living. A total of 1,016 individuals participated during 2001–2004, yielding a participation rate of 50.1%. The study was approved by the Ethics Committee of Uppsala University, and all participants gave their informed consent before the study.

Clinical examination

All participants attended the examination in the morning after an overnight fast. Since they were asked to fast from midnight and blood was drawn between 08:00 and 10:00 hours, the fasting period was at least 8 h. No medication or smoking was allowed after midnight. The participants were asked to answer a questionnaire about their medical history, education level, exercise habits, smoking habits and regular medication. Education level was divided into three groups: <9 years, 9–12 years, and >12 years. Exercise habits were divided into four groups: light exercise (no sweat) <2 times per week (none), light exercise ≥2 times per week (only light), heavy exercise (sweat) 1–2 times per week (moderate) and heavy exercise >2 times per week (athlete). Venous blood samples were collected and stored at −70°C until analysis. Lipid variables and fasting plasma blood glucose were measured using standard laboratory techniques [20].

The participants were asked if they had been diagnosed with diabetes by a physician (including diet-controlled diabetes). Diabetes was defined as a history of diabetes or a fasting glucose value >7.0 mmol/l. There were 119 participants with diabetes in the total sample. Of those, 88 had a history of diabetes (mean duration (±SD) of diabetes was 8.9±7.7 years). Only four participants reported a diabetes duration of >20 years.

Insulin and proinsulin measurements

Plasma proinsulin and insulin concentrations were determined at the laboratory of the Department of Public Health and Caring Sciences/Geriatrics, University Hospital, Uppsala, using the Proinsulin ELISA and the Insulin ELISA immunoassays (Mercodia, Uppsala, Sweden) on a Bio-Rad Coda Automated EIA Analyzer (Bio-Rad Laboratories, Hercules, CA, USA).

The ratio of fasting proinsulin/insulin was used as an index of insulin secretion, since this ratio increases with failing beta cell function [21, 22]. HOMA-IR was used as an index of insulin resistance and was calculated as described by Matthews et al [23].

Analysis of PFAS

The analytical method employed for all plasma samples was successfully validated in terms of recovery, accuracy and precision [24]. Briefly, 150 μl serum extracts were analysed using an automated column-switching ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS) method for determination of the perfluorocarboxylic acids perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorotridecanoic acid (PFTrDA), and the perfluoroalkyl sulfonic acids perfluorobutane sulfonic acid (PFBuS), perfluorohexane sulfonic acid (PFHxS), linear isomer of perfluorooctane sulfonic acid (L-PFOS), perfluorodecane sulfonic acid (PFDS) and perfluorooctane sulfonamide (PFOSA). The analytical procedure involves rapid protein precipitation using 96-well plates followed by analysis on an Acquity UPLC coupled to a Quattro Premier XE HPLC-MS/MS system (Waters, Milford, MA, USA) with an atmospheric electrospray interface operating in a negative ion mode system by injecting a 250 μl aliquot of the sample onto a C18 (2.1×20 mm, 2.5 μm) trap column connected to a C18 (2.1×100 mm, 1.7 μm) analytical column operated by a six-port column switch valve. Quantitative analysis of the PFAS was performed using the internal standard method; all standards (i.e. internal standards, recovery standards and native calibration standards) were purchased from Wellington Laboratories (Guelph, ON, Canada). The method detection limits ranged from 0.01 to 0.17 ng/ml depending on the analyte.

Statistics

Among the 14 PFAS measured at baseline, seven PFAS (PFPeA, PFHxA, PFDA, PFDoDA, PFTrDA, PFBuS and PFDS) with detection rates <90% were not included in the final analyses. All seven PFAS included (PFHpA, PFHxS, L-PFOS, PFOA, PFNA, PFOSA, PFUnDA), as well as the indices of insulin secretion and resistance, were skewed towards high levels, but were normally distributed following $\log_e$ transformation.

Relationships between PFAS and prevalent diabetes were evaluated by logistic regression models, first using the PFAS as linear variables, and thereafter using the squared form of the PFAS to search for non-linear effects. For the continuous analysis, two steps of adjustments were used. First, adjustment for sex only, and second, multiple adjustment for sex, serum cholesterol and triacylglycerol, BMI, smoking, exercise habits, energy and alcohol intakes, and education level. For confounding variables we imputed missing data with the median, since missing data were only present for <1% of the participants.

A similar approach was used when relating PFAS to either the proinsulin/insulin ratio or to HOMA-IR, but in this case, linear regression models were used. Only non-diabetic participants were included in this analysis.

In all analyses, we first investigated whether a sex vs PFAS interaction was present for each of the outcomes including a sex × PFAS variable in the models.

In the primary analysis, relating PFAS to prevalent diabetes, we investigated seven PFAS, and therefore the level of significance was set at 0.05/7=0.0071 using Bonferroni correction. The secondary analysis vs the proinsulin/insulin ratio or the HOMA-IR index was considered exploratory, and therefore $p<0.05$ was used to indicate significance.

Predictive margins were used to graphically illustrate the shape of the relationship between PFNA and prevalent diabetes. Stata 12 (Stata, College Station, TX, USA) was used for the calculations.

Results

The basic characteristics of study participants and the medians and 25th and 75th percentiles of the PFAS are given in Table 1.

Primary analysis

PFAS vs prevalent diabetes In the logistic regression analysis, no significant relationships were observed between the seven PFAS and prevalent diabetes, neither when adjusted for sex only nor when adjusted for multiple confounders (see Table 2 for details). However, an analysis of the quadratic terms of the PFAS revealed a significant non-linear relationship between PFNA and diabetes, even after adjusting for the multiple risk factors (OR 1.96, 95% CI 1.19, 3.22, $p=0.008$ for the linear term and OR 1.25, 95% CI 1.08, 1.44, $p=0.002$ for the quadratic term). Thus, the risk of prevalent diabetes was mainly seen for the highest values of PFNA (see Fig. 1, using non-$\log_e$-transformed data at the x-axis for easier interpretation of the relationship). PFOA also showed such a relationship; however, it was not significant following strict Bonferroni adjustment for the seven PFAS tested (OR 0.62, 95% CI 0.37, 1.07, $p=0.08$ for the linear term and OR 1.42, 95% CI 1.08, 1.86, $p=0.01$ for the quadratic term following adjustment for multiple risk factors).

No significant interactions were seen between PFAS and sex regarding prevalent diabetes.

Secondary analysis

PFAS vs the proinsulin/insulin ratio After adjusting for sex, only PFOSA was inversely related to the proinsulin/insulin ratio, while a tendency for a positive association was found for

Table 1 Basic characteristics and major cardiovascular risk factors in the sample (n = 1,016)

Variable	n	Value
Age (years)	1,016	70.1±0.1
Women (%)	1,016	50.2
Height (cm)	1,015	169±9.1
Weight (kg)	1,015	77±14
Waist circumference (cm)	1,014	91±12
BMI (kg/m^2)	1,015	27.0±4.3
Systolic BP (mmHg)	1,009	150±23
Diastolic BP (mmHg)	1,009	79±10
Serum cholesterol (mmol/l)	1,010	5.4±1.0
LDL-cholesterol (mmol/l)	1,009	3.3±0.88
HDL-cholesterol (mmol/l)	1,008	1.5±0.42
Serum triacylglycerol (mmol/l)	1,010	1.3±0.60
Fasting blood glucose (mmol/l)	1,013	5.3±1.6
Current smoking (%)	1,009	11
Exercise habits (%)	1,010[a]	
None		12
Only light		59
Moderate		22
Athlete		7
Education level (%)	1,008[a]	
<9 years		57
9–12 years		18
>12 years		25
Alcohol intake (g/day)	1,007	2.5±2.9
Energy intake (kJ/day)	1,007	7,911±2,114 (1,890±505 kcal/day)
PFHpA (ng/ml)	1,010	0.05 (0.03–0.09)
PFHxS (ng/ml)	1,011	2.1 (1.6–3.4)
L-PFOS (ng/ml)	1,011	13.2 (10.0–17.8)
PFOA (ng/ml)	1,010	3.3 (2.5–4.4)
PFNA (ng/ml)	1,010	0.7 (0.5–1.0)
PFOSA (ng/ml)	1,011	0.11 (0.07–0.17)
PFUnDA (ng/ml)	1,011	0.3 (0.2–0.4)

[a] In total

Data are presented as percentages, means ± SD or medians (25th to 75th percentiles)

PFNA (p = 0.05, see Table 3 for details). Following adjustment for multiple confounders, none of the two above-described relationships were significant, but at this stage the association between PFOA and the proinsulin/insulin ratio was of borderline significance (p = 0.04).

No non-linear relationships between the seven PFAS and the proinsulin/insulin ratio were disclosed by including a quadratic term in the models. No significant interactions were seen between PFAS and sex regarding the proinsulin/insulin ratio.

Table 2 Relationships between seven different PFAS (all $\log_e$ transformed) and prevalent diabetes

Variable	Sex-adjusted		Multiple-adjusted	
	OR (95% CI)	p value	OR (95% CI)	p value
PFHpA	1.07 (0.83, 1.38)	0.60	1.02 (0.77, 1.34)	0.90
PFHxS	0.87 (0.67, 1.13)	0.29	1.00 (0.74, 1.35)	0.98
L-PFOS	1.17 (0.79, 1.73)	0.42	1.43 (0.94, 2.16)	0.09
PFOA	0.77 (0.53, 1.13)	0.18	0.97 (0.61, 1.53)	0.88
PFNA	1.24 (0.85, 1.80)	0.25	1.30 (0.85, 1.97)	0.22
PFOSA	0.83 (0.60, 1.15)	0.25	1.07 (0.75, 1.53)	0.71
PFUnDA	0.74 (0.50, 1.09)	0.12	0.95 (0.59, 1.52)	0.81

Relationships are given both for gender-adjusted and multiple-adjusted (sex, serum cholesterol and triacylglycerol, BMI, smoking, exercise habits, energy and alcohol intake, and education level) analyses. The ORs are for the linear models

PFAS vs HOMA-IR As can be seen in Table 3, a number of the PFAS were negatively associated with HOMA-IR. However, after adjusting for multiple confounders, none of these relationships remained significant. Further analysis showed that there was a negative relationship between several of the PFAS and BMI that induced the negative relationships vs HOMA-IR in the sex-adjusted models.

No non-linear relationships between the seven PFAS and the HOMA-IR index were disclosed by including a quadratic term in the models. No significant interactions were seen between PFAS and sex regarding HOMA-IR.

Discussion

The present cross-sectional study showed that PFNA was related to prevalent diabetes. PFOA showed a similar relationship, but this association was not significant following strict correction for multiple testing. PFOA was related to the

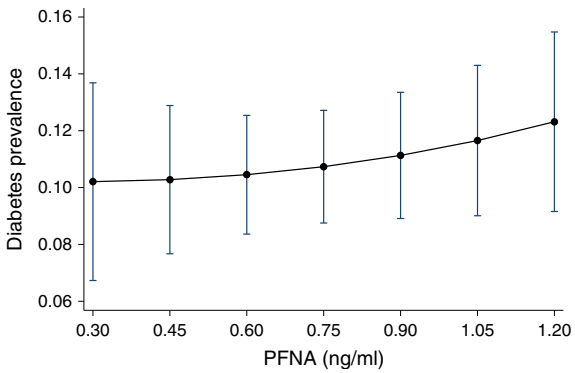

Fig. 1 The predictive margins (and 95% CI) for prevalent diabetes were calculated for given values for PFNA and fitted to a second-order model

Table 3 Relationships of seven different perfluoroalkyl substances (PFAS, all $\log_e$-transformed) with the proinsulin/insulin ratio and HOMA-IR

	Sex-adjusted		Multiple-adjusted	
Variable	β (95% CI)	*p* value	β (95% CI)	*p* value
Proinsulin/insulin ratio				
PFHpA	0.023 (−0.023, 0.063)	0.35	0.019 (−0.025, 0.063)	0.39
PFHxS	0.017 (−0.026, 0.059)	0.44	0.029 (−0.015, 0.073)	0.20
L-PFOS	0.007 (−0.058, 0.072)	0.84	0.026 (−0.042, 0.093)	0.46
PFOA	0.055 (−0.013, 0.123)	0.11	0.071 (0.001, 0.14)	0.048
PFNA	0.056 (−0.002, 0.113)	0.057	0.043 (−0.015, 0.102)	0.15
PFOSA	−0.079 (−0.13, −0.027)	0.0028	−0.047 (−0.102, 0.008)	0.094
PFUnDA	0.014 (−0.056, 0.085)	0.70	0.026 (−0.048, 0.1)	0.49
HOMA-IR				
PFHpA	0.015 (−0.04, 0.07)	0.59	0.014 (−0.033, 0.061)	0.56
PFHxS	−0.085 (−0.14, −0.03)	0.0025	−0.026 (−0.073, 0.022)	0.29
L-PFOS	−0.031 (−0.114, 0.053)	0.47	0.025 (−0.048, 0.097)	0.51
PFOA	−0.132 (−0.22, −0.045)	0.0031	−0.05 (−0.125, 0.026)	0.20
PFNA	−0.015 (−0.088, 0.058)	0.69	0.004 (−0.059, 0.066)	0.90
PFOSA	−0.082 (−0.147, −0.017)	0.013	−0.053 (−0.111, 0.004)	0.070
PFUnDA	−0.179 (−0.267, −0.091)	0.00012	−0.04 (−0.118, 0.038)	0.32

Relationships are given both for sex-adjusted and multiple-adjusted (sex, serum cholesterol and triacylglycerol, BMI, smoking, exercise habits, energy and alcohol intake, and education level) analyses. The regression coefficients (β) are for the linear models

proinsulin/insulin ratio, a marker of insulin secretion, but none of the PFAS analysed were related to HOMA-IR following proper adjustment.

Comparison with the literature

Very few studies have evaluated the role of PFAS in diabetes. Although a study in workers exposed to PFOA reported an increased risk of diabetes mortality [10], other studies on the general population have not found any consistent relationships between PFAS and diabetes or insulin resistance [8, 11, 12]. Death from diabetes is not an optimal way of investigating incident diabetes in these kinds of epidemiological studies, since diabetes mortality is most often seen in type 1 diabetes with very poor metabolic control.

Potential mechanisms of action

PFAS are known to be ligands for PPARα and PPARγ [4]. PPAR activation has been shown to be involved in different steps of glucose homeostasis. For example, it has been shown to influence insulin resistance [25] insulin secretion [26], circulating levels of lipids [26] and the amount of visceral and subcutaneous fat [27, 28]. As PPAR ligands, PFAS are similar to the phthalates, a group of environmental contaminants previously linked to diabetes by our group and others [5–7]. PFAS have also been shown to alter thyroid gland function [29, 30] and to induce alterations in the immune system [30] – two other factors that could be involved in diabetogenic action of PFAS. It should be pointed out, however, that PFAS might exert their effects via an alternative mechanism, since a recent publication highlighted that PFAS might be protective against dementia in diabetic individuals [31].

In the present study no associations between PFAS and insulin resistance, evaluated by HOMA-IR, could be found following adjustment for BMI and other potential confounders. Furthermore, only PFOA was positively related to the proinsulin/insulin ratio, a marker of insulin secretion. Thus, the exact mechanism that links PFNA to diabetes is unknown.

Non-monotonic response

As could be seen in the figure, the effect of PFNA on diabetes was not evident for the lowest levels of PFNA, but was mainly apparent for the highest PFNA levels in the present sample. This is not the typical non-monotonic, low-dose response that has previously been observed regarding the relationship between PCBs and some metabolic disturbances [15].

Limitations

This study was performed in a sample of elderly individuals of European descent. Thus, we cannot extrapolate these findings to other ethnic or age groups. This was a cross-sectional study, and the risk of reverse causality cannot be fully disregarded. In addition, we cannot rule out the possibility that some glucose-lowering drugs were still present in the participants despite the fasting period, and this might have had an effect on the PFAS levels. Thus, the present findings have to be confirmed in prospective studies.

The participation rate in this study was moderate. We have previously reported an analysis of the non-participants and found the prevalence of some chronic disorders, including diabetes, to be slightly higher in the non-participants compared with the participants (16.9% vs 8.7% in participants for self-reported diabetes) [19]. However, the implications of this difference regarding the present findings are not known.

In conclusion, the perfluorinated compound PFNA was related to prevalent diabetes in non-monotonic fashion in this cross-sectional study, supporting the view that this perfluoroalkyl substance might influence glucose metabolism in humans at the level of exposure seen in the elderly population in general.

Funding This study was supported by the Swedish Research Council (VR) and the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning (FORMAS).

Duality of interest The authors declare that there is no duality of interest associated with this manuscript. No potential conflicts of interest relevant to this article were reported. BZ is employed by the Medical Products Agency (MPA), Uppsala, Sweden, and the views of the present study are not necessarily official views of the MPA.

Contribution statement PML conceived the project and contributed to critical revision of the manuscript for important intellectual content. BZ was responsible for laboratory analyses of insulin and proinsulin measurements. LL performed data analysis. Also, LL is principal investigator of PIVUS and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SS and BvB performed the analysis of the PFAS. LL wrote the first draft of the manuscript. All authors contributed to critical revision of the manuscript and approved the final version of the manuscript.

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