Longitudinal Associations of Exposure to Perfluoroalkylated Substances in Childhood and Adolescence and Indicators of Adiposity and Glucose Metabolism 6 and 12 Years Later: The European Youth Heart Study

Sidsel L. Domazet,[1] Anders Grøntved,[1] Amalie G. Timmermann,[2] Flemming Nielsen,[2,3] and Tina K. Jensen[2]

Diabetes Care 2016;39:1745–1751 | DOI: 10.2337/dc16-0269

OBJECTIVE

To investigate the long-term association of exposure to perfluoroalkylated substances, including perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), during childhood (9 years) and adolescence (15 years) on indicators of adiposity and glucose metabolism in adolescence (15 years) and young adulthood (21 years). Secondarily, we aim to clarify the degree of tracking of exposure from childhood into young adulthood.

RESEARCH DESIGN AND METHODS

Data derived from a large multicenter prospective cohort study, in which the same participants have been observed from childhood (*N* = 590), during adolescence (*N* = 444), and into young adulthood (*N* = 369). Stored plasma samples were analyzed for PFOS and PFOA. Indicators of adiposity comprising body height, body weight, sum of four skinfolds, and waist circumference, as well as indicators of glucose metabolism, comprising fasting blood glucose, triglyceride, and insulin levels, β-cell function, and insulin resistance, have been collected at all study waves. Multiple linear regression was applied in order to model earlier exposure on later outcome while controlling for baseline outcome levels, sex, age, and socioeconomic factors.

RESULTS

Childhood exposure to PFOS was associated with indicators of adiposity at 15 years of age that are displayed in elevated BMI, skinfold thickness, and waist circumference, as well as increased skinfold thickness and waist circumference at 21 years of age. PFOA exposure in childhood was associated with decreased β-cell function at 15 years of age. We did not observe associations between exposure during adolescence and indicators of adiposity and glucose metabolism in young adulthood.

CONCLUSIONS

This study found evidence for childhood exposure to PFOS and PFOA predicting adiposity at 15 and 21 years of age and impaired β-cell function at 15 years of age, respectively.

[1]Department of Sports Science and Clinical Biomechanics, Division of Exercise Epidemiology, Centre of Research in Childhood Health, University of Southern Denmark, Odense, Denmark
[2]Institute of Public Health, Department of Environmental Medicine, University of Southern Denmark, Odense, Denmark
[3]Institute of Public Health, Department of Clinical Pharmacology, University of Southern Denmark, Odense, Denmark

Corresponding author: Sidsel L. Domazet, sdomazet@health.sdu.dk.

Received 8 February 2016 and accepted 5 July 2016.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-0269/-/DC1.

The global pandemic of obesity and type 2 diabetes continues to affect populations of children and adults in all parts of the world (1–3). Although the etiology of obesity is partly explained by a long-term positive energy balance in addition to genetic predisposition (2), industrial chemicals with endocrine-disrupting properties used in the majority of today's households may also cause obesogenic effects on the human organism by targeting the endocrinological system (4,5). These chemicals may be involved in the development of impaired insulin secretion and sensitivity that may ultimately cause diabetes. Perfluoroalkylated substances (PFASs), including perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), have been suspected to cause obesogenic and diabetogenic effects in animals and humans (6). PFASs compose a group of chemicals, which are considered persistent organic pollutants because of their resistance to biodegeneration, direct photolysis, atmospheric photooxidation, and hydrolysis (7). These substances are mainly used as surfactants in a wide range of consumer products (e.g., paint and lacquers, carpets, impregnated outdoor clothing, food packaging) because of their water- and soil-repellent properties (7). In May 2009, PFOS was banned under the Stockholm Convention; however, the long half-lives of PFASs (5.4 years for PFOS and 3.8 years for PFOA in human serum) (8) and their bioaccumulation into food and drinking water ensure a continuing exposure risk (9).

Animal studies have suggested that intrauterine and perinatal exposure to PFOS may contribute to impaired glucose tolerance and abnormal lipid homeostasis in adulthood (10,11). In humans, prenatal exposure to PFASs has been considered a catalyst of later weight gain in longitudinal studies (12–14). Also cross-sectional studies have linked PFAS exposure to glucose homeostasis, and indicators of the metabolic syndrome in children (15), adolescents, and adults (16). However, we are unaware of prospective studies that have observed children over adolescence into young adulthood for PFAS exposure and indicators of adiposity and glucose metabolism. To clarify these long-term associations, our aim was to examine the exposure to PFOS and PFOA in childhood, adolescence, and young adulthood for indicators of adiposity and glucose metabolism 6 and 12 years later. Because childhood and adolescence is distinguished by marked changes in growth, sexual maturity, and hormonal secretion, the risk of endocrine disruption by extrinsic agents may be altered during these life phases. Considering this, we hypothesized that exposure to PFASs in childhood and adolescence during maturity and growth would have detrimental consequences on later adiposity and glucose metabolism.

Our secondary aim was to investigate the extent of the tracking of PFOS and PFOA during the 6- and 12-year study period. As we know, PFASs have long half-lives, so we would expect a certain degree of tracking at least within the life span of the substances. However, tracking analyses may provide more insight into the continued accumulation and decomposition of PFASs from childhood into young adulthood.

RESEARCH DESIGN AND METHODS

Participants and Sampling

This study originated from a large multicenter prospective cohort study, the European Youth Heart Study (EYHS), which was orchestrated by an international research group in the 1990s. The first study wave was conducted in Denmark in 1997 and recruited 9-year-old children from schools within the municipality of Odense. The children were randomly selected through a two-stage cluster sampling at 25 schools. The participants were invited for physical examination at intervals of 6 years in 2003 as 15-year-old adolescents and in 2009 as 21-year-old young adults. The examination was conducted according to a fixed protocol at all study waves, providing longitudinal measurements on sociodemographics, personal characteristics, anthropometry, blood sample, blood pressure, and physical fitness. Of a total of 771 invited participants, 590 children, 444 adolescents, and 369 young adults participated in the EYHS in 1997, 2003, and 2009, respectively (Supplementary Fig. 1). However, for the scope of this study the final sample comprised only those children who had submitted a blood sample and had enough stored plasma for PFAS analysis (n = 501). Because these analyses were expensive to perform, a random subsample of adolescents (n = 201) and young adults (n = 202) was selected for studying the longitudinal associations of exposure. Thus, the random subsample comprised subjects with sufficient plasma volume and repeated measurements. The sampling procedure, aims, and methods in the EYHS have been further described elsewhere (17).

PFAS Measurements

Analysis of PFASs was performed using the stored plasma samples at the Department of Environmental Medicine at the University of Southern Denmark. Five PFASs were detectable ($\geq$0.03 ng/mL) for most individuals, and PFOS and PFOA were detected at the highest median concentrations across all study waves. Within-batch and between-batch imprecision was $>$3.0% and $>$5.2%, respectively, for all analytes. Results with excellent accuracy were obtained in the regular comparisons organized by the German Society of Occupational Medicine. The methods have been described in detail elsewhere (18).

Anthropometry

Body height and body weight was measured following standard anthropometric procedures. Body height was measured to the nearest 0.1 cm, and body weight was measured to the nearest 0.1 kg. BMI was calculated as weight divided by height squared (kg/m^2). Age- and sex-adjusted cutoff points defining overweight in children and adolescents were applied (19). Waist circumference was measured twice with an anthropometric tape between the lower rib margin and the iliac crest at the end of a light expiration. The sum of four skinfolds was estimated from measuring positions at biceps, triceps, subscapular, and suprailiac sites with Harpenden calipers. Measurements were performed twice, and if the estimates differed by $>$2 mm, a third measurement was performed.

Metabolic Markers

Insulin, glucose, and triglyceride levels were extracted from a fasting blood sample taken in the morning from the antecubital vein. Blood samples were aliquoted and separated within 30 min of venipuncture and stored at -80°C. HOMA of β-cell function (HOMA-β) and HOMA of insulin resistance (HOMA-IR) were subsequently estimated using the HOMA (called "HOMA2") described by Levy et al. (20).

Questionnaire

Information on potential covariates related to the child's and adolescent's socioeconomic background (i.e., ethnicity,

parental education and income, and maternal parity) and perinatal life (i.e., birth weight and breast-feeding) was gathered from a parental questionnaire in 1997 and 2003. Information on diabetes was assessed indirectly in 1997 and 2003 by asking the parents whether their child/adolescent was eating an antidiabetic diet. In 2009, the questionnaire contained questions directly referring to having diabetes. Female participants were also asked whether they were pregnant at the physical examination in 2009. A matrix of the potential covariates and their relation to PFOS and PFOA in childhood, adolescence, and adulthood is found in Supplementary Table 1.

Ethics

The EYHS was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Scientific Ethical Committees for Southern Denmark in 1997, 2003, and 2009. Participants were informed of possible hazards, discomfort, or inconvenience related to the physical examination, and their allowance for withdrawing from the study at any time. Written informed consent was obtained from all participants prior to testing. Parents or legal guardians of minors received the information and signed the consent on their child's/adolescent's behalf.

Statistics

Sample characteristics were presented as the median with interquartile range because of non-normal distributed response variables. The difference in exposure levels between sexes was tested using an unpaired two-sample *t* test. Multiple linear regression models were performed to determine the associations between PFAS exposure at 9, 15, and 21 years of age, and indicators of adiposity (BMI, skinfold thickness, and waist circumference) and glucose metabolism (fasting glucose, insulin, and triglyceride levels, and HOMA-β and HOMA-IR) in adolescence and young adulthood.

To obtain variance homogeneity and normally distributed residuals in the regression models, all outcome measures were transformed using the natural logarithm. Log-transformed regression coefficients were expressed as the percentage change in the geometric mean of the outcome for every 10 ng/mL change in the concentration of PFASs by exponentiation of the regression coefficients.

Associations between two time points were adjusted for sex, age, and outcome level at baseline. Additionally, estimates were adjusted for ethnicity, maternal income level, and maternal parity in 1997 because of their significant correlation with PFOS and PFOA. Socioeconomic inequality has previously been associated with the risk of type 2 diabetes (21) and obesity (22,23), suggesting that ethnicity, maternal income level, and maternal parity may also be related to indicators of adiposity and glycemic control. Estimates including waist circumference were adjusted for height in order to account for body size.

Six- and 12-year tracking of PFAS exposure was estimated by calculating standardized tracking coefficients from linear regression models adjusted for sex and age, which is equivalent to a Pearson correlation. Tracking can be defined as *1*) the overall stability of a given variable through time (T_1 to T_n) or *2*) the predictability of information regarding risk status at T_1 on risk status at T_n (24). The tracking coefficient lies within 0 and 1 (with 0 indicating no tracking and 1 indicating perfect tracking). Intraclass correlation coefficients (ICCs) from mixed-model regression on exposure from childhood to adulthood were calculated as well (Supplementary Table 2). The extent of tracking of PFASs for specific subgroups (sex, ethnicity, maternal income level, maternal parity, and overweight) was also estimated in order to define possible risk groups (Supplementary Tables 3 and 4). Sex interactions in the associations between PFAS exposure and indicators of adiposity were tested in the performed regression models adjusted for age.

Assumptions of normality and homoscedasticity of residuals were tested. Data were analyzed using Stata IC version 14.0 (StataCorp, College Station, TX) with a significance level of 0.05 (two-sided).

RESULTS

Sample Characteristics

Median levels of exposure and outcomes stratified by study wave are presented in Table 1. A total of 501 children had data on PFAS exposure in 1997, of whom 200 (40.0%) had repeated PFAS measurements in 2003 and 2009. There was moderate-to-strong correlation between both exposures (PFOS and PFOA) and indicators of adiposity (BMI, waist circumference, and skinfold thickness) with correlation coefficients ranging from $r = 0.31$ to $r = 0.77$ ($P < 0.01$) for exposure, and from $r = 0.59$ to $r = 0.85$ ($P < 0.01$) for adiposity. Correlations were strongest in childhood and weakest in adulthood. The prevalence of overweight comprising obesity according to sex- and age-adjusted BMI cutoffs was 14% in childhood, 10% in adolescence, and 30% in young adulthood. Five subjects were excluded from parts of the analysis because of putative or self-reported diabetes, low glucose level, or pregnancy. Two children reported eating an antidiabetic diet as a proxy for having diabetes, one adolescent had a glucose level that was too low (<3.5 mmol/L), one adult was pregnant, and one adult reported having diabetes.

Of potential covariates, being Caucasian and having higher maternal income level and lower maternal parity in 1997 were associated with higher levels of PFASs. Associations were most evident in childhood, although ethnicity and parity also appeared to be related to exposure level in adolescence. In young adulthood, only ethnicity was associated with PFOS exposure (Supplementary Table 1). Furthermore, ethnicity and maternal income level were also associated with indicators of adiposity (Supplementary Table 5). Males had a higher PFAS exposure level in childhood and adulthood relative to females ($P < 0.04$). No significant difference in exposure level was observed between sexes in adolescence.

Main Results

Results showed clear and consistent associations between early exposure to PFOS (9 years) and indicators of adiposity in adolescence displayed in elevated BMI, skinfold thickness, and waist circumference at 15 years of age (Fig. 1). Likewise, childhood PFOS exposure was associated with increased skinfold thickness and waist circumference in young adulthood (Fig. 2). PFOA exposure in childhood was associated with decreased β-cell function in adolescence (Fig. 1). We did not observe evident associations between later exposure (15 years) and indicators of adiposity and glucose metabolism in young adulthood (Fig. 3).

Neither did we find cross-sectional associations between exposure and outcomes in adolescence to be significant. However, cross-sectional associations in

Table 1—Distribution of PFOS and PFOA and indicators of adiposity and glucose metabolism in childhood, adolescence, and young adulthood

	Childhood (1997)				Adolescence (2003)				Adulthood (2009)			
	Males		Females		Males		Females		Males		Females	
	N	Median (IQR)	*N*	Median (IQR)	*N*	Median (IQR)	*N*	Median (IQR)	*N*	Median (IQR)	*N*	Median (IQR)
Age (years)	279	9.7 (9.4; 10.0)	311	9.6 (9.3; 9.9)	193	15.8 (15.6; 16.0)	251	15.7 (15.4; 16.0)	171	21.8 (21.6; 22.1)	198	21.8 (21.4; 22.0)
PFOS (ng/mL)	236	44.5 (35.4; 55.7)	265	39.9 (34.3; 49.3)	91	22.3 (16.5; 25.1)	110	20.8 (15.9; 24.7)	92	11.9 (9.2; 15.2)	110	9.1 (7.0; 10.8)
PFOA (ng/mL)	236	9.7 (7.7; 12.1)	265	9.0 (7.4; 11.2)	91	3.7 (2.7; 4.4)	110	3.4 (2.8; 4.5)	92	3.1 (2.5; 3.9)	110	2.7 (2.1; 3.4)
BMI (kg/m^2)	279	16.9 (15.7; 18.4)	311	16.7 (15.4; 18.6)	193	20.7 (19.1; 22.1)	251	20.7 (19.4; 22.9)	171	24.1 (22.1; 26.3)	198	22.5 (20.9; 25.4)
Skinfold thickness (mm)	268	28.8 (23.0; 38.9)	305	33.2 (26.4; 46.0)	193	27.5 (22.6; 37.1)	251	49.2 (39.9; 61.7)	171	44.3 (35.5; 64.8)	195	66.3 (52.5; 80.9)
Waist circumference (cm)	272	58.0 (55.3; 61.5)	311	57.0 (54.3; 60.8)	192	74.4 (70.1; 78.2)	251	71.0 (68.3; 75.7)	171	82.8 (75.0; 89.8)	198	75.0 (70.2; 80.5)
Insulin (pmol/L)	245	41.5 (28.5; 56.4)	274	48.4 (36.6; 64.6)	190	53.2 (39.7; 71.3)	244	60.1 (43.8; 75.2)	167	35.2 (23.0; 52.8)	195	45.9 (36.0; 65.9)
HOMA-β	245	73.7 (61.0; 91.0)	274	88.2 (71.3; 103.7)	190	89.6 (75.6; 107.2)	244	105.0 (86.9; 128.7)	167	68.2 (53.7; 88.8)	194	90.8 (79.3; 106.8)
HOMA-IR	245	0.8 (0.5; 1.1)	274	0.9 (0.7; 1.2)	190	1.0 (0.7; 1.3)	244	1.1 (0.8; 1.4)	167	0.7 (0.4; 1.0)	194	0.9 (0.7; 1.2)
Glucose (mmol/L)	247	5.2 (4.9; 5.4)	278	5.0 (4.8; 5.3)	190	5.2 (4.9; 5.4)	244	4.9 (4.6; 5.1)	169	5.2 (4.8; 5.4)	195	4.9 (4.6; 5.2)
Triglyceride (mmol/L)	247	0.7 (0.6; 0.9)	278	0.8 (0.6; 1.1)	190	0.7 (0.5; 0.9)	244	0.7 (0.5; 1.0)	169	1.1 (0.7; 1.4)	195	1.1 (0.9; 1.4)

IQR, interquartile range.

young adulthood found that higher PFOA level was negatively related to waist circumference (−11.11% change; 95% CI −19.89586, −1.36191; $P = 0.03$).

Even though exposure levels were higher among males relative to females, we found no indication of interactions by sex in the association between PFAS exposure and indicators of adiposity.

Tracking of PFOS and PFOA

Tracking coefficients and ICCs (Supplementary Table 2) showed a moderate-to-good tracking (stability) of PFOS (0.43–0.69), especially indicated in the 6-year tracking coefficient from 15 to 21 years of age. Relative to PFOS, tracking of PFOA was weaker (0.07–0.50). In general, coefficients were weaker for 12-year correlations and ICC adjusted for sex, age, and socioeconomic factors (ethnicity, maternal income level, and maternal parity), when compared with 6-year correlations or ICCs adjusted only for sex and age.

According to the subgroup analysis of tracking, PFOS and PFOA exposure was suggested to track more strongly among males than females, although a statistically significant sex interaction appeared only in the tracking of PFOS from adolescence into young adulthood (P = 0.01). Differences in tracking among other subgroups were not consistent (Supplementary Tables 3 and 4).

CONCLUSIONS

To our knowledge, this is the first prospective study to find that exposure to PFOS during childhood was associated with increased adiposity in adolescence and young adulthood. Although we did not find the same evidence for associations between PFOA and indicators of adiposity, we observed a relatively large decrease in β-cell function in adolescence, with higher levels of PFOA at 9 years of age. We did not find evidence for associations of exposure in adolescence with later risk of adiposity and glucose metabolism at 21 years of age.

Altogether, these findings suggest that PFAS exposure in childhood is critical in relation to obesity and β-cell dysfunction later in life, and confirm the notion that childhood represents a juncture in life that is particularly sensitive to endocrine disruption. Our hypothesis that early exposure to PFASs during maturity and growth may have detrimental consequences on later risk of developing

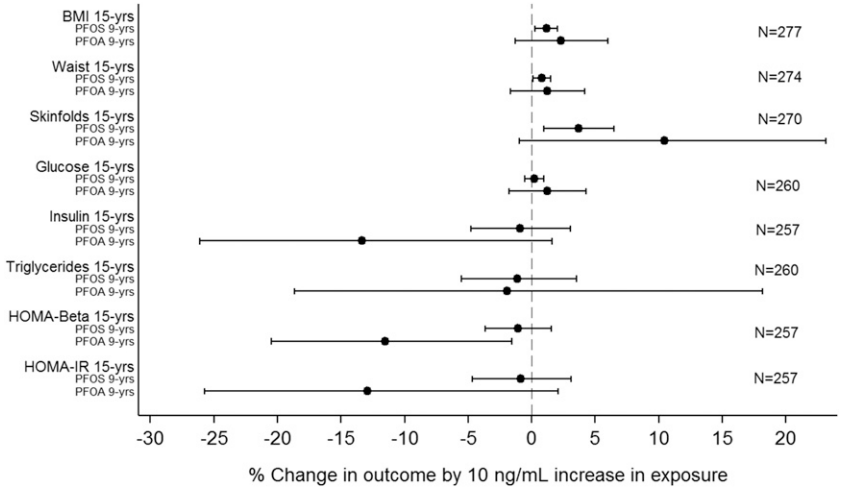

Figure 1—Associations between PFOS and PFOA exposure at 9 years of age, and indicators of adiposity and glucose metabolism at 15 years of age. Estimates were adjusted for sex, age, and outcome levels at baseline (9 years of age), and ethnicity, maternal parity, and maternal income in 1997 (9 years of age). Waist circumference was adjusted for height in order to account for body size.

overweight and insulin resistance were confirmed, at least for PFOS and indicators of adiposity, and PFOA in relation to impaired β-cell function.

A recently published study on the risk of diabetes in working-aged Taiwanese adults (25) showed a similar discrepancy between PFOS and PFOA in relation to glucose metabolism. High PFOS exposure was associated with a higher and steeper postload glucose trajectory, a greater tendency toward glucose intolerance, and a 3.4 times higher prevalence of diabetes, whereas an opposite relationship was found for other congeners of PFASs (PFOA, perfluorononanoic acid, and perfluoroundecanoic acid) (25). Previously published longitudinal studies (12–14,26,27) have relied on prenatal or perinatal exposure; however, long elimination half-lives of the substances from the human organism pave the way for using childhood PFAS exposure as a proxy for prenatal and postnatal exposure. Previous studies (12–14) have indicated that exposure to different congeners of PFASs in utero may cause permanent physiological changes, predisposing subjects to later weight gain. However, other longitudinal studies have not found any relationship between prenatal exposure and anthropometry at 7 years of age (26) or early life exposure and risk of overweight and obesity in adulthood (27).

Fundamentally, this highlights the fact that we are currently unaware of which time period or developmental phase is the most vulnerable for endocrine disruption in humans. It may be the antenatal phase, as previously proposed (12–14), or it may differ according to the health outcomes under observation. In relation to obesity, the time around growth spurts or the adiposity rebound may be particularly vulnerable windows for endocrine disruption in children. Thus far, we can conclude that exposure in adolescence did not predict later adiposity or glycemic control, at least in this cohort.

Previously published cross-sectional data on 9-year-old children from the Danish EYHS showed no link between PFASs and indicators of adiposity and glycemic control among normal-weight children, whereas high PFAS concentrations were associated with higher insulin and triglyceride concentrations and increased insulin resistance and β-cell function among overweight children (15). This may foster a hypothesis that early-life exposure to PFASs impairs the long-term health profile in all children, whereas the immediate response is displayed only among physiologically predisposed or susceptible subgroups.

Our cross-sectional findings in adulthood revealed lower waist circumference with higher PFOA exposure. This finding was contrary to our longitudinal associations on waist circumference and earlier cross-sectional findings in 9-year-old children (15). This might be a chance finding due to multiple comparisons or a result of unknown or residual (positive or negative) confounding. Specifically, it might be a matter of confounding from positive health behaviors, suggesting that leaner young adults are more exposed to PFASs compared with their less lean counterparts due to certain health habits. A possible exposure source may be sports and outdoor clothing, which have previously been reported to contain PFASs (28), besides reflecting an active and healthy lifestyle.

As expected, we observed a high degree of tracking, which can be explained by the long half-lives of PFASs as well as sustained habits and environment over

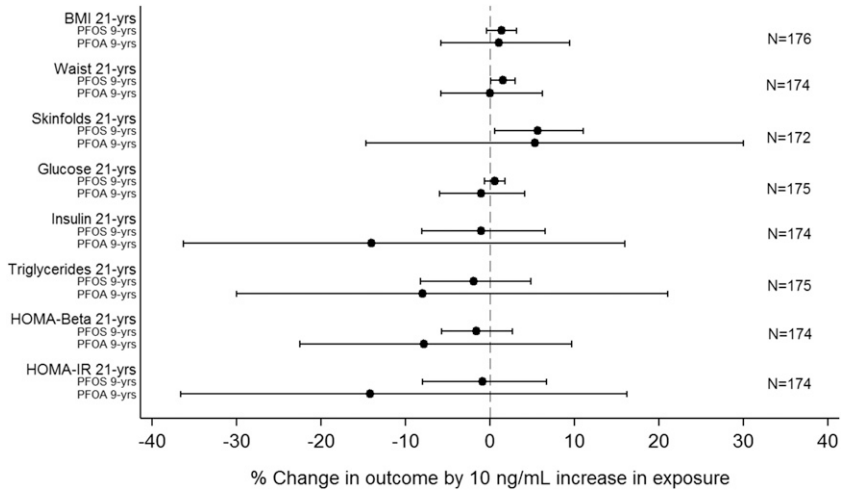

Figure 2—Associations between PFOS and PFOA exposure at 9 years of age, and indicators of adiposity and glucose metabolism at 21 years of age. Estimates were adjusted for sex, age, and outcome levels at baseline (9 years of age), and ethnicity, maternal parity, and maternal income in 1997 (9 years of age). Waist circumference was adjusted for height in order to account for body size.

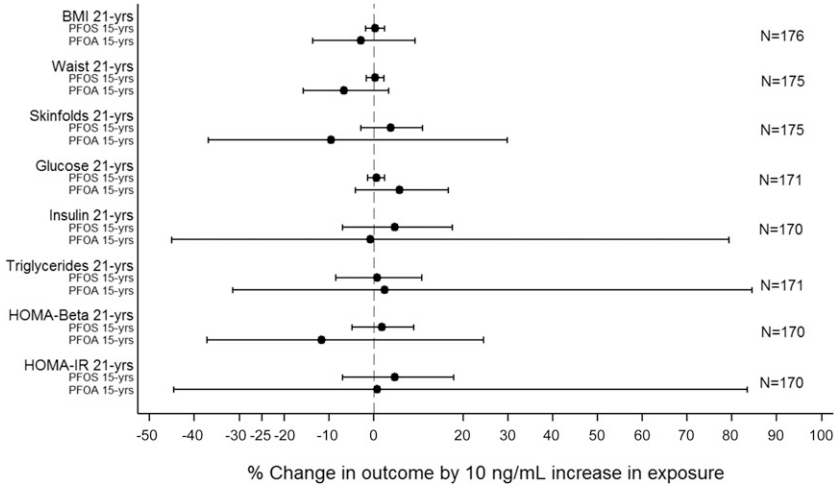

Figure 3—Associations between PFOS and PFOA exposure at 15 years of age, and indicators of adiposity and glucose metabolism at 21 years of age. Estimates were adjusted for sex, age, and outcome levels at baseline (15 years of age), and ethnicity, maternal parity, and maternal income in 1997 (9 years of age). Waist circumference was adjusted for height in order to account for body size.

time. The 6-year tracking was higher compared with the 12-year tracking, which is likely explained by the notion that habits and ways of living change more in 12 years than in 6 years. Interestingly, compared with female participants, we found stronger tracking among males, which suggests a more persistent PFAS exposure environment from childhood to young adulthood among males. Male participants also had higher levels of PFASs in childhood and young adulthood compared with females, which could indicate that the PFAS-associated health burden may be largest among young Danish males. However, we did not observe sex interactions between PFAS exposure and indicators of adiposity, which indicate comparable vulnerability to the hazards of PFASs between males and females. Other previous research (12) has shown sex differential effects of PFAS in relation to BMI, waist circumference, and serum insulin, leptin, and adiponectin concentrations. Thus, additional studies are needed to clarify any sex-discordant relationships.

The observed median concentrations of PFOS and PFOA were comparable with North American concentrations in human plasma and serum of nonoccupational populations within the same period, which are considered to be slightly higher than those found in European, Asian, and Australian study populations (29).

A limitation to this study was the risk of selection bias due to participants lost to follow-up and the extract of a random subsample in adolescence and adulthood, whose blood samples have not been analyzed for PFASs. However, included versus excluded participants did not differ in means of outcome measures except that participants lost to follow-up had a higher fasting triglyceride level compared with participants with follow-up data ($P = 0.02$). A struggle we might as well be facing is the complexity and lack of understanding of the interplay between exposure to endocrine-disrupting chemicals and personal characteristics, such as behavior and individual pharmacodynamics. An example within this field is the consumption of junk food, which is likely to increase both adiposity and exposure level. PFASs are widely used in junk food packaging because of their oil- and grease-repellant surface, from where they leach into the food, thus acting as a confounding factor as well as a key source of PFAS exposure (30). Another example is the consumption of seafood and predatory fish, which are considered to contain high doses of health-hazardous substances including PFASs (31). At the same time, fish intake has been related to weight loss in randomized trials (32). Generally, seafood and fish are perceived as a more exclusive and expensive alternative to other sorts of meat thus consumed more frequently by individuals of higher socioeconomic strata. Although these individuals may have higher accumulated doses of undesirable substances, their health profile and lifestyle are generally superior to those of individuals of lower socioeconomic strata (22). This provides a very complex interplay among adiposity, PFASs, sources of PFASs, and the socioeconomic profile of the participants, and, as a consequence, we cannot rule out the possibility of both positive and negative confounding, that are unaccounted for in our study. The EYHS had information on dietary habits; however, in this sample data were presumed to be crudely classified and to pose a risk of biasing our estimates.

Using clinically relevant outcomes (e.g., prediabetes, metabolic syndrome, obesity) would have been preferable; however, because of the few cases in our sample, this was not an option and resulted in low statistical power.

A major strength of this study was the prospective longitudinal design, which enables a conceivable prediction of a possible causal link between PFAS exposure and indicators of adiposity and glucose metabolism. Furthermore, having available repeated PFAS exposure levels from childhood through adolescence into adulthood provided us with the possibility of comparing the influence of PFASs in early and later periods of life. A further strength was the unique data on endocrine-disrupting chemicals and indicators of adiposity and glucose metabolism during growth and maturation, where body composition and metabolism are altered because of the transition from child to adult.

Because of a confined sample size, our findings need to be replicated in larger populations in order to consolidate the conception of childhood exposure to PFOS increasing gains in adiposity in adolescence and young adulthood, and to rule out the possibility that the general lack of association with glucose metabolism is explained by modest statistical power. However, this study found evidence for childhood exposure to PFOS and PFOA predicting later adiposity at 15 and 21 years of age and impaired β-cell function at 15 years of age, respectively. From a public health perspective, childhood exposure to PFOS may be considered when policies and strategies

in relation to obesity prevention are formed.

Acknowledgments. The authors thank all participants and families for their valuable contribution to the European Youth Heart Study. The authors also thank former and present researchers in the European Youth Heart Study for their dedicated work in disseminating and sustaining the study over the years. In addition, the authors thank Vibeke Kvist Pedersen and Annette Zeberg from the Department of Environmental Medicine, University of Southern Denmark, for performing and assisting with the chemical analysis.

Funding. The study was funded by the Danish Council for Strategic Research, Programme Commission on Health, Food, and Welfare (grant 95-103-21990).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. S.L.D. wrote the manuscript and performed the statistical analysis. A.G. collected data in 2009 and reviewed and edited the manuscript. A.G.T. and T.K.J. reviewed and edited the manuscript. F.N. performed the chemical analysis and reviewed the manuscript. S.L.D. is the guarantor of this work and, as such, 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.

References

1. Lobstein T, Baur L, Uauy R; IASO International Obesity TaskForce. Obesity in children and young people: a crisis in public health. Obes Rev 2004;5(Suppl. 1):4–104
2. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet 2011;378:804–814
3. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet 2011;378:31–40
4. Kelishadi R, Razaghi EM, Gouya MM, et al.; CASPIAN Study Group. Association of physical activity and the metabolic syndrome in children and adolescents: CASPIAN Study. Horm Res 2007;67:46–52
5. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 2009;30:293–342
6. White SS, Fenton SE, Hines EP. Endocrine disrupting properties of perfluorooctanoic acid. J Steroid Biochem Mol Biol 2011;127:16–26
7. U.S. Department of Health and Human Services; Public Health Service. *Toxicological profile for Perfluoroalkyls. (Draft for Public Comment)*. Atlanta, GA, Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, 2009
8. Olsen GW, Burris JM, Ehresman DJ, et al. Half-life of serum elimination of perfluorooctanesulfonate,perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 2007;115:1298–1305
9. Trudel D, Horowitz L, Wormuth M, Scheringer M, Cousins IT, Hungerbühler K. Estimating consumer exposure to PFOS and PFOA. Risk Anal 2008;28:251–269
10. Lv Z, Li G, Li Y, et al. Glucose and lipid homeostasis in adult rat is impaired by early-life exposure to perfluorooctane sulfonate. Environ Toxicol 2013;28:532–542
11. Wan HT, Zhao YG, Leung PY, Wong CK. Perinatal exposure to perfluorooctane sulfonate affects glucose metabolism in adult offspring. PLoS One 2014;9:e87137
12. Halldorsson TI, Rytter D, Haug LS, et al. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study. Environ Health Perspect 2012;120:668–673
13. Maisonet M, Terrell ML, McGeehin MA, et al. Maternal concentrations of polyfluoroalkyl compounds during pregnancy and fetal and postnatal growth in British girls. Environ Health Perspect 2012;120:1432–1437
14. Braun JM, Chen A, Romano ME, et al. Prenatal perfluoroalkyl substance exposure and child adiposity at 8 years of age: the HOME study. Obesity (Silver Spring) 2016;24:231–237
15. Timmermann CAG, Rossing LI, Grøntved A, et al. Adiposity and glycemic control in children exposed to perfluorinated compounds. J Clin Endocrinol Metab 2014;99:E608–E614
16. Lin CY, Chen PC, Lin YC, Lin LY. Association among serum perfluoroalkyl chemicals, glucose homeostasis, and metabolic syndrome in adolescents and adults. Diabetes Care 2009;32:702–707
17. Riddoch CJ, Bo Andersen L, Wedderkopp N, et al. Physical activity levels and patterns of 9- and 15-yr-old European children. Med Sci Sports Exerc 2004;36:86–92
18. Jensen TK, Andersen LB, Kyhl HB, Nielsen F, Christesen HT, Grandjean P. Association between perfluorinated compound exposure and miscarriage in Danish pregnant women. PLoS One 2015;10:e0123496
19. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240–1243
20. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care 1998;21:2191–2192
21. Agardh E, Allebeck P, Hallqvist J, Moradi T, Sidorchuk A. Type 2 diabetes incidence and socioeconomic position: a systematic review and meta-analysis. Int J Epidemiol 2011;40:804–818
22. Lynch JW, Smith GD, Kaplan GA, House JS. Income inequality and mortality: importance to health of individual income, psychosocial environment, or material conditions. BMJ 2000;320:1200–1204
23. Hoffmann R, Eikemo TA, Kulhánová I, et al. Obesity and the potential reduction of social inequalities in mortality: evidence from 21 European populations. Eur J Public Health 2015;25:849–856
24. Twisk JW, Kemper HC, van Mechelen W. Tracking of activity and fitness and the relationship with cardiovascular disease risk factors. Med Sci Sports Exerc 2000;32:1455–1461
25. Su T-C, Kuo CC, Hwang JJ, Lien GW, Chen MF, Chen PC. Serum perfluorinated chemicals, glucose homeostasis and the risk of diabetes in working-aged Taiwanese adults. Environ Int 2016;88:15–22
26. Andersen CS, Fei C, Gamborg M, Nohr EA, Sørensen TI, Olsen J. Prenatal exposures to perfluorinated chemicals and anthropometry at 7 years of age. Am J Epidemiol 2013;178:921–927
27. Barry V, Darrow LA, Klein M, Winquist A, Steenland K. Early life perfluorooctanoic acid (PFOA) exposure and overweight and obesity risk in adulthood in a community with elevated exposure. Environ Res 2014;132:62–69
28. Danish Environmental Protection Agency, Ministry of the Environment and Food of Denmark. Survey and environmental/health assessment of fluorinated substances in impregnated consumer products and impregnating agents [Internet], 2008. Copenhagen, Denmark, Ministry of the Environment and Food of Denmark. Available from http://mst.dk/service/publikationer/publikationsarkiv/2008/okt/survey-and-environmentalhealth-assessment-of-fluorinated-substances-in-impregnated-consumer-products-and-impregnating-agents. Accessed 25 October 2015
29. Fromme H, Tittlemier SA, Völkel W, Wilhelm M, Twardella D. Perfluorinated compounds—exposure assessment for the general population in Western countries. Int J Hyg Environ Health 2009;212:239–270
30. Trier X, Granby K, Christensen JH. Polyfluorinated surfactants (PFS) in paper and board coatings for food packaging. Environ Sci Pollut Res Int 2011;18:1108–1120
31. Danish Environmental Protection Agency, Danish Ministry of the Environment. Perfluoroalkylated substances: PFOA, PFOS and PFOSA, 2015. Copenhagen, Denmark, Danish Ministry of the Environment. Available from http://www2.mst.dk/Udgiv/publications/2015/04/978-87-93283-01-5.pdf. Accessed 25 October 2015
32. Bender N, Portmann M, Heg Z, Hofmann K, Zwahlen M, Egger M. Fish or n3-PUFA intake and body composition: a systematic review and meta-analysis. Obes Rev 2014;15:657–665