Published in final edited form as:

Environ Res. 2016 October ; 150: 282–288. doi:10.1016/j.envres.2016.06.023.

Lactation History, Serum Concentrations of Persistent Organic Pollutants, and Maternal Risk of Diabetes

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Abstract

Objective—Lactation may help curb diabetes risk and is also known as an excretion route for some environmental pollutants. We evaluated associations of lifetime lactation history with serum concentrations of persistent organic pollutants (POPs) in the National Health and Nutrition Examination Survey 1999–2006, and examined whether potentially diabetogenic POPs account for associations between lactation and diabetes.

Research Design and Methods—Among 4,479 parous women, breastfeeding history was defined as the number of children breastfed ≥ 1 month. Diabetes was identified by self-report or hemoglobin A1c $>6.5\%$. Twenty-four POPs were measured in serum among subsamples of 668 to 1,073 participants.

Results—Compared with women without lactation history, odds ratios (95% confidence intervals) of having diabetes among those with 1–2 and ≥ 3 lactation periods were 0.83(0.61, 1.13) and 0.63(0.44, 0.91; $P_{\text{trend}}=0.03$). Lifetime lactation history was inversely associated with serum

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Competing financial interests declaration:

All authors declare that they received no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

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concentrations of 17 out of the 24 organochlorine pesticides, polychlorinated biphenyl congeners (PCBs), and perfluoroalkyl substances ($P_{\text{trend}} < 0.05$). Comparing the 3 lactations group with women without a lactation history, the relative reduction of POPs ranged from 12% (PCB-196) to 30% (oxychlordane). The inverse association between lactation and diabetes was slightly attenuated after adjustment for POPs. Age-stratified analyses showed that the inverse association between lactation periods and serum POP concentrations was observed primarily among participants <60 years, whereas age did not significantly modify the association between lactation history and diabetes prevalence.

Conclusions—Crudely-classified lifetime lactation history was inversely associated with concurrent serum POP concentrations and diabetes prevalence. Prospective studies are needed to clarify how lactation could complement diabetes prevention through decreasing the POP body burdens.

Keywords

Lactation; persistent organic pollutant; diabetes

INTRODUCTION

Lactation has been linked with a lower risk of chronic diseases,(Victora et al.) such as type 2 diabetes, although potential mechanisms remain to be explored.(Aune et al., 2014; Gunderson et al., 2015; Jager et al., 2014) Breast milk is known to contain environmental chemicals,(Massart et al., 2005; Needham et al., 2011) and lactation is an important excretion route for many of them,(LaKind et al., 2001; Massart et al., 2005; Needham et al., 2011) especially those with long elimination half-lives in humans.(LaKind et al., 2001; Needham and Wang, 2002) As many environmental chemicals are suspected of being diabetogenic,(Kuo et al., 2013; Thayer et al., 2012) the possibility exists that an apparent beneficial effect of lactation could be due to the elimination of diabetogenic chemicals.

Persistent organic pollutants (POPs) are resistant to degradation in the environment and highly persistent in the human body. These pollutants include organochlorine pesticides (OCP), polychlorinated dibenzo-p-dioxins (PCDD), polychlorinated dibenzofurans (PCDF), polychlorinated biphenyls (PCB), and perfluoroalkyl substances (PFASs).(Vallack et al., 1998) It has been found that lactation could lower the POP burden in mothers.(Hooper et al., 2007; Kostyniak et al., 1999; Mondal et al., 2014; Skaare and Polder, 1990; Thomsen et al., 2010; Wang et al., 2009) Although several studies have linked higher POP storage with diabetes risk,(Lee et al., 2006; Lind et al., 2014; Suarez-Lopez et al., 2015; Wu et al., 2013) it remains unclear whether potential long-term benefits of lactation on chronic disease risk in women could be attributed to the reduction in POP burden.

Among parous women participating in the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2006, we examined three hypotheses: 1) a lifetime lactation history is associated with lower serum POP concentrations, 2) a lactation history is associated with a lower diabetes risk, whereas higher POP concentrations are associated with a higher diabetes risk, and 3) a lactation history may lower diabetes risk through reducing serum POP concentrations.

METHODS

Study population

The continuous NHANES used a complex, multistage, probability sampling design to randomly select a nation-wide representative sample of non-institutionalized U.S. residents every two years.(CDC, 2013) The study protocol was approved by the institutional review board at the Centers for Disease Control and Prevention (Atlanta, GA, USA), and written informed consent was obtained from all participants. A total of 10,701 women aged 20 years were surveyed between 1999 and 2006. Among them, we excluded participants who 1) did not complete medical examination(n=919); 2) did not have a pregnancy resulting in a live birth (n=2,652), because nulliparous women in NHANES were much younger and their serum POP concentrations were much lower than the others, suggesting a different exposure history; 3) reported current pregnancy or breastfeeding (n=800); 4) reported diabetes diagnosed before last delivery (n=258), to ensure temporal relationship between lactation and diabetes onset; 5) had prevalent cardiovascular disease or cancer (n=1,211); or 6) had a missing body mass index (BMI, n=82), leaving 4,779 participants for analysis.

Assessment of reproductive history

During medical examination, trained technicians performed private interviews of female participants aged 12 and above on reproductive history.(CDC, 2015) Women reported number of pregnancies resulting in live birth, age at last birth, number of parity (1–2, 3–4, and 5), whether they had breastfed any child (yes or no), and number of children breastfed for at least 1 month. Lactation history was categorized into 0 (no lactation), 1–2, or 3 based on the number of children breastfed for at least 1 month.

Assessment of serum concentrations of POPs

Procedures for blood collection and processing have been described elsewhere.(CDC, 2015) Serum POPs were measured in one thirds of participants who provided blood samples. OCPs, PCDDs, PCDFs, and PCBs were measured in survey years 1999–2004, using high-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry.(CDC, 2015) Concentrations were lipid-standardized through dividing POP concentrations by total serum lipids derived using the Philipps formula based on total cholesterol and triacylglycerol.(Zong et al., 2015) PFASs were measured in 1999–2000 and 2003–2006, using automated solid-phase extraction coupled to reverse-phase high-performance liquid chromatography/tandem mass spectrometry.(Kato et al., 2011) In this study, data on OCPs, PCDDs, PCDFs, and PCBs were available among 1,165 participants, whereas PFAS data were available from 1,029 participants. POP values below the limit of detection were replaced with limit of detection divided by the square root of 2, according to NHANES analysis recommendation.(Zong et al., 2015) In the current study, we focused on chemicals measured in 2 survey circles (to maintain reasonable sample size) and with 70% participants having values above the limit of detection (as a trade-off between the number of POPs included in the main analysis and a reasonable percentage of participants with values above the limit of detections to ensure adequate sample variability in POP values for analysis).(Zong et al., 2015) Twenty four POPs in the following groups were analyzed: 1) OCPs and their metabolites, including oxychlordane, trans-nonachlor, *p,p'*-dichlorodiphenyl

dichloroethylene (*p,p'*-DDE), and β -hexachlorocyclohexane (β -HCH); 2) PCDDs and PCDFs, including, 1,2,3,6,7,8-heptachlorodibenzo-p-dioxin (1,2,3,6,7,8-HxCDD), 1,2,3,4,6,7,8-octachlorodibenzodioxin (1,2,3,4,6,7,8-HpCDD), 1,2,3,4,6,7,8,9-heptachlorodibenzofuran (1,2,3,4,6,7,8,9-OCDD), and 1,2,3,4,6,7,8-Heptachlorodibenzofuran (1,2,3,4,6,7,8-HpCDF); 3) PCBs, including the dioxin-like PCB-118, PCB-126, and PCB-169, and the non-dioxin like PCB-074, PCB-138, PCB-153, PCB-170, PCB-180, PCB-187, PCB-194, PCB-196, and PCB-199; and 4) PFASs, such as perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA).

Assessment of diabetes

Diabetes was defined as self-report of physician-diagnosed diabetes, current use of insulin or oral diabetes medications, or hemoglobin A1c (HbA1c) $\geq 6.5\%$. (Kilpatrick et al., 2009) HbA1c concentrations were measured in whole blood using a high-performance liquid chromatography system by the Diabetes Diagnostic Laboratory at the University of Missouri-Columbia in NHANES 1999–2004 and by the Fairview Medical Center Laboratory at the University of Minnesota for 2005–2006. (Carson et al., 2010) HbA1c values were recalibrated for NHANES 2005–2006 to account for the differences in the assays used between laboratories. (Carson et al., 2010) Age at diabetes diagnosis was self-reported for participants with known diabetes, or current age for those diagnosed by abnormal HbA1c levels.

Assessment of covariates

Information on demography, lifestyle, and prevalent diseases was collected using survey questionnaires during in-person interviews. (CDC, 2015) Ethnicity was categorized into non-Hispanic white, non-Hispanic black, Mexican, and other ethnic groups including multi-ethnicity. Country of birth was classified as U.S. born and others. Educational attainment was grouped as high school or below, any college, and graduate school or beyond. Smoking status was classified as never smokers, past smoker, and current smokers. Alcohol consumption was divided into abstainers, 1–3 drinks/day, and ≥ 4 drinks/day. Regular moderate-to-vigorous physical activity and family history of chronic diseases (cardiovascular diseases or cancer) was defined as yes or no. (Zong et al., 2015) We further adjusted for survey years (1999–2000–2001–2002–2003–2004, and 2005–2006) to account for time trends in POP exposures in general populations.

Statistical analysis

Our analysis followed the survey-based design according to NHANES analytic guidelines whenever possible. (CDC, 2013) Odds ratio of diabetes according to lactation categories (0, 1–2, ≥ 3) were estimated using the SURVEYLOGISTIC procedure with adjustment for age (in years), survey year, BMI (kg/m^2), ethnicity, education, smoking status, alcohol drinking, family history of chronic diseases, and moderate-to-vigorous physical activity. For the trend analysis, we used the midpoint of each category, or median when data were highly skewed.

Since the number of missing data varied among the POPs, we utilized all non-missing data for each POP to preserve statistical power as much as possible. (Zong et al., 2015) Natural

log-transformation was performed to improve the normality of POP values before analysis. We calculated least squared means of POPs according to lactation categories in the SURVEYREG procedure after adjusting for the same covariates for the association between lactation and diabetes. Some adjacent groups of categorical covariates were collapsed due to the limited sample size, such as education (high school, >high school), smoking status (never smokers, ever smokers), and alcohol drinking (abstainers, drinkers). The adjusted means and standard errors of logarithmic values were transformed back to the original scale for presentation. We also repeated the association between lactation and diabetes among participants with POP data, and analyzed the association between POPs and diabetes after categorizing participants into tertiles of corresponding POPs. For each POP, when the inter-correlation between lactation history, concentrations of individual POPs, and diabetes were all at the two-sided $P < 0.10$ level, we further explored whether adjusting for POP concentrations attenuated the association between lactation and diabetes. We performed stratified analyses by age (< 60 years and ≥ 60 years) to better account for the effects of age on the associations of interest. In addition, we stratified analyses by BMI (<30 kg/m², ≥ 30 kg/m²), smoking (never smoked, ever smoked), number of parity (< 3, ≥ 3), and ethnicity (Non-Hispanic White, others). Analysis was performed in SAS, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Table 1 presents the baseline characteristics of study participants. Compared with those with no lactation history and those with ≥ 3 lactation periods, women with 1–2 lactation periods were younger and more likely to be non-Hispanic white, with higher education and physical activity, as well as a lower BMI ($P < 0.001$). In addition, women with more lactation periods tended to have lower alcohol consumption and were less likely to smoke cigarettes ($P < 0.001$). Diabetes was diagnosed, on average, 23.2 years (standard error=0.8) after the last delivery or 6.0 years (standard error=0.5) before serum POPs were measured.

We identified 401 diabetes cases diagnosed after the last delivery, which accounted for 5.5% of weighted samples (Table 2). Of these cases, 193 were identified through both self-report and HbA1c assessments, 112 by self-report only, and 96 by HbA1c only. Major characteristics, including age, ethnicity and family history of chronic diseases, did not significantly vary between these groups of patients (data not shown). In Model 1 adjusted for age and survey years, parous women who ever lactated had 26% lower risk of diabetes compared to those did not ($P = 0.02$). The association between number of lactation periods and diabetes did not reach statistical significance in model 1, but further adjustment for other covariates strengthened the association. In the fully-adjusted model (Model 3), odds ratios (95% confidence intervals) of diabetes were 0.84 (0.63, 1.13) and 0.61 (0.41, 0.89) for 1–2 and ≥ 3 lactation, respectively ($P_{\text{trend}} = 0.007$).

As shown in Table 3, the sample size for serum POP analysis ranged from 668 for oxychlordane to 1,073 for PCB187. In a multivariate-adjusted model, the total number of lactation periods was inversely associated with serum concentrations of most POPs, and the associations for 17 out of 24 pollutants reached statistical significance ($P_{\text{trend}} < 0.05$). Comparing the ≥ 3 lactation group to the no lactation group, serum concentrations were 26%

lower for oxychlordane, 27% for trans-nonachlor, 23% for β -HCH, 25% for 1,2,3,6,7,8-HxCDD, 19% for PCB-074, 14% PCB-118, 20% for PCB-138, 20% for PCB-153, 17% for PCB-169, 23% for PCB-170, 24% for PCB-180, 19% for PCB-194, 12% for PCB-196, 16% for PCB-199, 21% for PFOA, 20% for PFOS, and 13% for PFNA (all P values for between-group difference <0.05). In addition, lactation was non-significantly associated with lower serum concentrations of PCB-187 (P value for between-group difference <0.10). Between-group differences for the 1–2 lactation group and the no lactation group was significant only for PCB-170, PCB-180, and PFOA ($P<0.05$).

In the subsample with non-missing data on lactation, serum POPs, and diabetes status, using $P<0.10$ criterion, we found that trans-nonachlor, β -HCH, PCB-118, and PCB-169 were significantly associated with a higher prevalence of diabetes ($P<0.05$; Supplemental Table S1), whereas serum PCB-074 was associated with higher diabetes risk with marginal significance ($P<0.10$). When we adjusted for these five POPs, the association between lactation and diabetes was only slightly attenuated (Table 4). Results for the other POPs are shown in Supplemental Table S2. Associations between serum POPs and diabetes were slightly attenuated after adjusting for lactation history as well (Supplemental Table S1).

Age-stratified analyses were performed among subsamples with data on trans-nonachlor, β -HCH, PCB-074, PCB-118, and PCB-169. As shown in Supplemental Table S3 and Supplemental Table S4, participants aged 60 and above had higher prevalence of diabetes and higher serum concentrations of POPs. The association between lactation and diabetes was significant only in older participants (Supplemental Table S3), although the statistical test for interaction between age and lactation history was not significant (P for interaction=0.20). The association between lactation and serum POPs was significant only among younger participants for trans-nonachlor, PCB-074, PCB-118, and PCB-169 (P for interaction <0.05 , Supplemental Table S4). Lastly, adjusting for trans-nonachlor and β -HCH attenuated the significant association between lactation and diabetes among older participants (Table 5). In analyses stratified by BMI, smoking, number of parity, and ethnicity, in each stratum there was no significant change on the associations between lactation and diabetes after further adjusting for serum POPs (Supplemental Table S5).

DISCUSSION

In this cohort of parous women, we confirmed that the number of lactation periods ≥ 1 month was significantly associated with a lower diabetes risk and also lower serum concentrations of 17 select POPs. Although some POPs were also positively associated with diabetes, further adjustment for POPs did not significantly change the association between lactation history and diabetes.

Our findings were consistent with most previous studies that collectively demonstrated an inverse relationship between lactation and POP burden in women.(Agudo et al., 2009; Hooper et al., 2007; Skaare and Polder, 1990; Thomsen et al., 2010) For example, Thomsen *et al* analyzed changes of 18 POPs in milk samples of 70 Norwegian mothers over a year of lactation, with a 1.2–4.7% decrease for PFASs and PCBs per month of lactation.(Thomsen et al., 2010) Other studies demonstrated an inverse association between previous lactation

duration and concurrent maternal POP burden.(Kostyniak et al., 1999; Mondal et al., 2014; Wang et al., 2009) The C8 Science Panel study reported that each additional month of lactation was associated with 1% to 3% lower PFAS concentrations in maternal serum. (Mondal et al., 2014) In an early study of women (16–59 years) from NHANES 1999–2002, the number of lactation periods was associated with only two of the 12 lipophilic POPs, and a positive association with PCB-180 was observed.(Wang et al., 2009) These results might be influenced by the inclusion of younger and nulliparous women who had only background exposure of POPs, and the use of the highly skewed lactation period variable as a continuous variable. In the current study, lifetime lactation was inversely associated with 17 out of the 24 analyzed organic pollutants in the serum of parous women. Taken together, these findings highlighted the role of lactation in determining POP body burden and diabetes risk in women, particularly in light of the crude, retrospective classification of lactation.

POPs are excreted through lactation by passive transport. Coakley *et al* reviewed studies that compared lipophilic POP concentrations in maternal serum and milk, and found that the number of halogen substitutes, molecular weight, molar volume, and hydrophobicity are all associated with a lower serum/milk ratio of PCDDs, PCDFs, and PCBs,(Mannetje et al., 2012) suggesting that POPs with larger molecular size are less likely to be transferred. Unlike lipophilic POPs, PFASs bind to protein fractions (such as albumin) in the blood and possibly during their passage into breast milk.(Butenhoff et al., 2006; Jones et al., 2003) Among PFASs, PFOA and PFOS might be more efficiently transported to breast milk than, e.g., perfluorohexane sulfonic acid,(Mogensen et al., 2015) but the ratios of maternal blood and breast milk for PFASs are much lower than those of lipophilic POPs overall.(Liu et al., 2011) Moreover, the relative reduction of pollutants through lactation is also determined by mother's age, weight change, and baseline POP exposures.(Glynn et al., 2007; Glynn et al., 2003) These differences in toxicokinetics of POPs need to be considered in future studies.

The associations of self-reported lactation history and serum POPs with diabetes in our analysis were consistent with findings in previous studies. Aune *et al* reviewed six prospective cohort studies that analyzed total breastfeeding duration, breastfeeding duration per child, or lactation history (breastfeeding >3 months or not) and calculated a pooled diabetes risk of 0.68 (95%CI: 0.57, 0.82) associated with history of lactation.(Aune et al., 2014) Meanwhile, adverse effects of POPs on diabetes development are supported by both observational and experimental studies. Meta-analysis of prospective studies linking OCPs and PCBs with diabetes risk found total PCBs and hexachlorobenzene were associated with a higher risk of type 2 diabetes.(Wu et al., 2013) PFASs have recently been associated with long-term diabetes risk among Swedish seniors and young Americans.(Lind et al., 2014; Suarez-Lopez et al., 2015) Previous studies of the NHANES population reported positive associations of PCB-153, 1,2,3,4,6,7,8-HpCDD, oxychlordane, *p,p'*-DDE, and trans-nonachlor with prevalent diabetes,(Lee et al., 2006) and associations of PFOA and PFOS with deteriorated glucose homeostasis.(Lee et al., 2006) In experimental studies, lipophilic POPs have been shown to block insulin signals, promote pro-inflammatory gene expression, and act as endocrine disruptors by binding to estrogen receptors and peroxisome proliferator receptors.(Ngwa et al., 2015) PFASs also bind to peroxisome proliferator receptors,(Lau et al., 2007) and can influence thyroid hormone-responsive gene expression as well. (Vongphachan et al., 2011)

In our analysis, concurrent serum POP concentrations did not significantly explain the association of lactation with diabetes. Although the limitations of the cross-sectional study design may at least partially explain the null findings, other alternate mechanisms are worth considering. For example, lactation is associated with lower weight gain, higher insulin sensitivity and glucose tolerance, and improved lipid metabolism and inflammatory status, (Aune et al., 2014) which are all established factors predicting a lower diabetes risk.(Donath and Shoelson, 2011; Stern, 1995) In our study, the association between lactation history and POP concentrations was primarily found in younger women. Reproductive history was more recent in younger women than in older women, and thus may have a stronger impact on serum POP concentrations younger women, whereas current body POP burdens in older women were influenced more by subsequent lifestyle and physiological changes rather than remote lactation history. In support of this notion, Agudo et al reported that the inverse association between lactation and serum POP concentrations was restricted to women who had their last pregnancy within the previous 10 years.(Agudo et al., 2009) Verner et al simulated changes of POPs in the human body using physiologically based pharmacokinetic modeling, and found that differences in POP levels induced by lactation were attenuated later in life.(Verner et al., 2008) It is also worth mentioning that the serum concentrations of POPs are higher among older women, which has been attributed to higher past exposures when the use of these POPs was not yet restricted or banned, longer exposure duration, and possibly longer half-lives of POPs among older people.(Wolff et al., 2007; Zong et al., 2015) Therefore concurrent POPs are influenced by lactation in the past and ongoing accumulation of POPs through continuous background exposure. These considerations may further explain why the cross-sectional association between lactation history and diabetes risk was only slightly attenuated when the concurrent POP concentrations were adjusted. Thus a prospective study design is needed to establish whether changes of serum POP concentrations before/after lactation account for the benefits of lactation on mothers' health.

Transfer of pollutants from mothers to infants through lactation is likely. Despite the emerging concern regarding to the health impact of infant exposure to POPs through breastfeeding,(Mead, 2008; Mondal et al., 2014) existing studies have consistently suggested that, for diabetes, the long-term beneficial effects of breast milk outweighs the risk associated with POP exposures among offspring.(Owen et al., 2006; Sadauskaite-Kuehne et al., 2004) In addition, it has been shown that the body burden of many POPs in U.S. populations has steadily decreased in the past decades.(Kato et al., 2011; Nost et al., 2013) Therefore, any adverse impact of POPs transferred through lactation to children may decrease over time. Taken together, the current findings remain in line with the current recommendations encouraging breastfeeding.

The strength of our investigation is the inclusion of a nation-wide representative sample of parous women with rich data of individual POPs in serum. On the other hand, a major limitation is the cross-sectional nature of NHANES study. The lack of a clear temporal relationship between lactation history, serum POP concentrations, and diabetes risk prevents us from drawing any causal inference from the observed associations, which should ideally be examined in prospective studies that longitudinally assess POP exposures before and after lactations and the subsequent diabetes incidence. A second limitation is due to using number of children breastfed 1 month, which led to a potential misclassification of the true overall

breastfeeding duration that may have weakened the association of breastfeeding with serum POPs and diabetes risk. Third, misclassification of diabetes status is possible in NHANES surveys, but it may introduce only minor bias toward the null, as the misclassification is unlikely to be related with lactation history or POP concentrations. Fourth, recall bias may have affected all self-reported data, especially for diabetes diagnosis and breastfeeding history, in particular among older participants. Fifth, since healthy women are more likely to have reproductive activities and a lower risk of chronic diseases, it is possible that an inverse association between lactation and diabetes onset could be influenced by the pre-existing health status of women. Sixth, we cannot exclude the role of chance in our findings. In particular, some of the associations may be driven by individuals assigned with large sampling weight due to the NHANES survey-based design. For example, when we ignored sampling weight in the data analyses, the association between number of lactation periods and diabetes risk was attenuated (data not shown). Finally, as we used non-missing values for each POP to maximize the statistical power, the analytic samples for each POP differed, thus making it difficult to directly compare between-individual associations and making mutual adjustments non-informative.

CONCLUSION

In conclusion, lifetime lactation history was inversely associated with both serum POP concentrations and the risk of having diabetes. However, adjustment for concurrent serum POP concentrations only weakly affected the association between lactation history and diabetes. These findings provide some support to the hypothesis that lactation may lower the subsequent diabetes risk, and that this may at least in part happen through reducing the maternal POP body burden due to the POP elimination through human milk. Well-designed prospective studies with repeat measurements of serum POP concentrations before and after lactation periods and long-term follow-up for incident diabetes are required to help establish causal inferences regarding the role of POP exposure in the relationship between lactation and adverse health conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding:

This research was supported by NIEHS-sponsored grants ES021372 and ES022981. Qi Sun was supported by a career development award, R00-HL-098459, from the National Heart, Lung, and Blood Institute. Philippe Grandjean is supported by an NIEHS grant (ES021447). Xiaobin Wang is supported by an NIEHS grant (ES022790).

GZ designed the study, analyzed the data, and drafted the manuscript; PG analyzed the data and critically revised the manuscript; XW analyzed the data and critically revised the manuscript; QS designed the study, analyzed the data, and critically revised the manuscript. All authors approved the final version for publication. GZ and QS are guarantors.

Abbreviations

POP	persistent organic pollutants
OCP	organochlorine pesticides
PCDD	polychlorinated dibenzo-p-dioxins
PCDF	polychlorinated dibenzofurans
PFAS	perfluoroalkyl substances
PCB	polychlorinated biphenyl
NHANES	National Health and Nutrition Examination Survey
<i>p,p'</i>-DDE	<i>p,p'</i> -dichlorodiphenyldichloroethylene
β-HCH	β -hexachlorocyclohexane
1,2,3,6,7,8-HxCDD	1,2,3,6,7,8-hexachlorodibenzo-p-dioxin
1,2,3,4,6,7,8-HpCDD	1,2,3,4,6,7,8- heptachlorodibenzodioxin
1,2,3,4,6,7,8,9-OCDD	1,2,3,4,6,7,8,9-octachlorodibenzodioxin
1,2,3,4,6,7,8-HpCDF	1,2,3,4,6,7,8-heptachlorodibenzofuran
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonic acid
PFHS	perfluorohexane sulfonic acid
PFNA	perfluorononanoic acid
HbA1c	hemoglobin A1c

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Highlights

- Number of lactation periods is inversely associated with persistent organic pollutants in serum.
- Lactation is inversely associated with subsequent diabetes risk.
- Certain pollutants are associated with an increased risk of diabetes.
- Serum pollutants do not fully explain the association between lactation and diabetes.

Table 1Characteristics of study population according to lactation^a

	Number of children breastfed 1 month			P value ^b
	0	1–2	3	
Number of participants	2158	1645	976	
Number of children breastfed 1 month	0	1.50±0.02	3.88±0.05	
Number of parity	2.40±0.03	2.17±0.03	4.06±0.06	<0.001
Age, years	49.0±0.4	45.8±0.4	51.1±0.5	<0.001
Body mass index, kg/m ²	28.8±0.2	27.9±0.2	28.4±0.3	<0.001
Ethnicity				<0.001
Non-Hispanic white	70%	73%	67%	
Non-Hispanic black	16%	9%	8%	
Mexican American	5%	7%	13%	
Other ethnic group	8%	11%	13%	
Born in the United States	91%	83%	76%	<0.001
Moderate to vigorous physical activity	56%	69%	64%	<0.001
Education				<0.001
High school or below	58%	37%	46%	
Any college	29%	34%	29%	
Graduate school	13%	29%	24%	
Alcohol use, drinks/day				<0.001
Abstainers	36%	29%	44%	
1–3	54%	64%	51%	
>4	10%	6%	5%	
Smoking status				<0.001
Never smoked	50%	60%	67%	
Past smoker	20%	22%	19%	
Current smoker	29%	18%	13%	
With family history of chronic diseases	70%	73%	67%	0.28

^aData are weighted means (standard errors) for continuous variables or weighted percentages for categorical variables;^bP value was tested using ANOVA for continuous variables and Chi-squared test for categorical variables.

Table 2

Associations between lactation and diabetes ^a

	Number of children breastfed			P _{trend}	Ever breastfeeding
	0	1–2	3		
Weighted sample of case	6.5%	4.4%	5.6%		
Model 1 ^b	Ref	0.73(0.55, 0.99)	0.75(0.53, 1.07)	0.07	0.74(0.58, 0.95) 0.02
Model 2 ^c	Ref	0.80(0.60, 1.07)	0.66(0.47, 0.93)	0.01	0.75(0.59, 0.96) 0.02
Model 3 ^d	Ref	0.84(0.63, 1.13)	0.61(0.41, 0.89)	0.007	0.75(0.58, 0.97) 0.02

^aData are odds ratio calculated in SURVEYLOGISTIC procedure.

^bModel 1: adjusted for age, and survey years;

^cModel 2: further adjusted for ethnicity, country of born, education, and family history of chronic diseases;

^dModel 3: further adjusted for smoking status, alcohol consumption, regular moderate to-vigorous physical activity, and BMI.

Table 3Adjusted means of serum persistent organic pollutants according to lactation groups ^{a-c}

	N	Number of children breastfed			P _{trend}
		0	1-2	3	
Oxychlordane, pg/g	668	17.6±1.0	15.8±1.1	13.0±1.1 ^{**}	0.005
Trans-nonachlor, pg/g	746	25.6±1.0	24.4±1.1	18.7±1.1 ^{**}	0.002
<i>p,p'</i> -DDE, pg/g	750	618.8±1.0	542.3±1.1	513.4±1.1	0.11
β-HCH, pg/g	736	15.0±1.0	16.3±1.1	11.6±1.1 [*]	0.02
1,2,3,6,7,8-HxCDD, pg/g	987	26.8±1.1	23.4±1.1	20.0±1.1 [*]	0.009
1,2,3,4,6,7,8-HpCDD, pg/g	985	42.5±1.0	43.0±1.1	42.6±1.1	0.97
1,2,3,4,6,7,8,9-OCDD, pg/g	981	380.8±1.0	375.6±1.0	372.7±1.1	0.69
1,2,3,4,6,7,8-HpCDF, pg/g	948	7.0±1.0	7.0±1.1	7.3±1.1	0.55
PCB-074, pg/g	1070	9.6±1.0	9.2±1.0	7.8±1.0 ^{***}	0.001
PCB-118, pg/g	1071	11.2±1.0	11.0±1.0	9.6±1.1 [*]	0.04
PCB-126, pg/g	983	23.4±1.1	24.1±1.1	24.3±1.1	0.73
PCB-138, pg/g	1069	25.6±1.0	24.2±1.0	20.5±1.1 ^{**}	0.004
PCB-153, pg/g	1070	35.6±1.0	33.5±1.0	28.4±1.1 ^{***}	<0.001
PCB-169, pg/g	981	15.8±1.0	14.7±1.0	13.1±1.0 ^{***}	0.001
PCB-170, pg/g	1044	10.6±1.0	9.7±1.0 [*]	8.2±1.0 ^{***}	<0.001
PCB-180, pg/g	1069	25.4±1.0	23.1±1.0 [*]	19.2±1.0 ^{***}	<0.001
PCB-187, pg/g	1073	7.6±1.0	7.5±1.0	6.9±1.0	0.07
PCB-194, pg/g	725	5.8±1.0	5.5±1.0	4.7±1.1 ^{**}	0.005
PCB-196, pg/g	733	5.1±1.0	4.8±1.0	4.5±1.0 [*]	0.05
PCB-199, pg/g	729	5.8±1.0	5.5±1.0	4.9±1.0 [*]	0.01
PFOA, ng/mL	1029	3.9±1.0	3.5±1.1 [*]	3.1±1.1 [*]	0.008
PFOS, ng/mL	1029	20.6±1.0	19.9±1.1	16.4±1.1 [*]	0.02
PFHxS, ng/mL	1029	1.5±1.1	1.5±1.1	1.3±1.2	0.36
PFNA, ng/mL	1029	0.8±1.1	0.8±1.1	0.7±1.1 [*]	0.05

Data are calculated in SURVEYREG procedure after adjustment of age, survey years, ethnicity, country of born, education, family history of chronic diseases, smoking status, alcohol consumption, regular moderate to-vigorous physical activity, and BMI;

POP values were log-transformed before analysis and back transformed to present in geometric means and standard error;

C Between-group difference compared to participants without children breastfed 1 month:

* P<0.05;

** P<0.01;

*** P<0.001.

Table 4

Associations between lactation and diabetes before and after adjustment of persistent organic pollutants^a

	N	Number of children breastfed					1 month		
		Multivariate model			P _{trend}	0	Further adjusted for POP		P _{trend}
		Missing/0/1-2/ 3	0	1-2	3		1-2	3	
Transnonachlor	419/221/234/291	Ref	0.79 (0.27,2.25)	0.29 (0.09,0.90)	0.03	Ref	0.87 (0.28,2.70)	0.33 (0.11,1.03)	0.07
β-HCH	415/175/202/373	Ref	0.79 (0.28,2.25)	0.28 (0.09,0.91)	0.04	Ref	0.67 (0.25,1.84)	0.33 (0.10,1.14)	0.08
PCB-074	429/187/195/354	Ref	0.91 (0.44,1.86)	0.33 (0.13,0.84)	0.03	Ref	0.92 (0.45,1.89)	0.36 (0.14,0.90)	0.04
PCB-118	178/325/297/365	Ref	0.91 (0.44,1.87)	0.33 (0.13,0.88)	0.04	Ref	0.90 (0.44,1.85)	0.35 (0.13,0.93)	0.05
PCB-169	180/279/312/394	Ref	1.06 (0.48,2.35)	0.33 (0.13,0.88)	0.05	Ref	1.08 (0.49,2.41)	0.40 (0.15,1.03)	0.09

^aData are odds ratio calculated in SURVEYLOGISTIC procedure after adjustment age, survey years, ethnicity, country of born, education, family history of chronic diseases, smoking status, alcohol consumption, regular moderate to-vigorous physical activity, and BMI.

Table 5
Age-stratified analysis on associations between lactation and diabetes before and after adjustment of persistent organic pollutants^a

	N	Number of children breastfed					1 month				
		Multivariate model			P trend	0	Further adjusted for POP			P trend	0
		Missing/0/1-2/3	0	1-2			0	1-2	3		
Transnonachlor	269/173/162/170	Ref	1.15 (0.22,6.11)	0.36 (0.03,5.07)	0.55	Ref	1.42 (0.25,8.20)	0.42 (0.02,10.5)	0.70		
β-HCH	275/147/139/213	Ref	1.15 (0.22,6.10)	0.36 (0.03,5.07)	0.55	Ref	1.03 (0.23,4.68)	0.33 (0.02,6.51)	0.53		
PCB-074	57/265/229/223	Ref	0.99 (0.35,2.82)	0.42 (0.12,1.51)	0.26	Ref	1.01 (0.37,2.78)	0.49 (0.14,1.71)	0.35		
PCB-118	56/259/223/236	Ref	0.99 (0.35,2.82)	0.42 (0.12,1.51)	0.26	Ref	1.10 (0.39,3.09)	0.47 (0.12,1.82)	0.36		
PCB-169	122/256/201/195	Ref	1.24 (0.39,3.97)	0.34 (0.07,1.63)	0.22	Ref	1.30 (0.41,4.15)	0.42 (0.09,2.04)	0.34		
Transnonachlor	150/73/80/88	Ref	0.56 (0.10,2.97)	0.27 (0.08,0.93)	0.04	Ref	0.79 (0.13,5.01)	0.43 (0.15,1.24)	0.12		
β-HCH	154/60/69/108	Ref	0.58 (0.11,3.03)	0.26 (0.07,0.95)	0.04	Ref	0.59 (0.12,2.77)	0.35 (0.10,1.25)	0.11		
PCB-074	38/124/106/123	Ref	0.73 (0.25,2.13)	0.35 (0.12,0.99)	0.05	Ref	0.79 (0.26,2.36)	0.35 (0.12,1.03)	0.06		
60 years	38/107/120/126	Ref	0.73 (0.25,2.13)	0.36 (0.13,1.04)	0.06	Ref	0.68 (0.23,2.03)	0.35 (0.12,1.00)	0.05		
PCB-169	62/120/97/112	Ref	0.85 (0.24,2.95)	0.35 (0.12,1.00)	0.06	Ref	0.88 (0.24,3.16)	0.35 (0.12,0.99)	0.05		

^aData are odds ratio calculated in SURVEYLOGISTIC procedure after adjustment of age, survey years, ethnicity, country of bom, education, family history of chronic diseases, smoking status, alcohol consumption, regular moderate to-vigorous physical activity, and BMI.