Patel, J. F., Hartman, T. J., Sjodin, A., Northstone, K., & Taylor, E. V. (2018). Prenatal exposure to polychlorinated biphenyls and fetal growth in British girls. *Environment International*, *116*, 116-121. https://doi.org/10.1016/j.envint.2018.04.007

Prenatal Exposure to Polychlorinated Biphenyls and Fetal Growth in British Girls

Jill P. Shah[1,2], Terryl J. Hartman[1,2,3], Andreas Sjodin[1], Kate Northstone[4,5], Ethel V. Taylor[1]

[1]Centers for Disease Control and Prevention, Atlanta, GA 30341
[2]Department of Epidemiology, Rollins School of Public Health, and [3]Winship Cancer Institute, Emory University, Atlanta, GA 30322
[4] The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West (NIHR CLAHRC West) at University Hospitals Bristol NHS Foundation Trust, UK
[5] School of Social and Community Medicine, University of Bristol, Bristol, UK

Corresponding author and person to whom reprint requests should be addressed:

Terryl J. Hartman, PhD, MPH, RD (corresponding author)
Professor of Epidemiology
Rollins School of Public Health
Winship Cancer Institute
Emory University
1518 Clifton RD NE, CNR 3035
Atlanta, GA 30322
tjhartm@emory.edu
404-727-8713 (phone)
404-727-8737 (fax)

Key words: polychlorinated biphenyls, endocrine disrupting chemicals, pregnancy, birthweight

Abstract

Polychlorinated biphenyls (PCBs) are synthetic chemicals that bioaccumulate in the food chain. PCBs were used primarily for industrial applications due to their insulating and fire retardant properties, but were banned in the 1970s in the United States and in the 1980s in the United Kingdom, as adverse health effects following exposure were identified. Previous studies of populations with high PCB exposure have reported inverse associations with birth weight and gestational length. Birth weight is a powerful predictor of infant survival, and low birth weight can predispose infants to chronic conditions in adult life such as diabetes and cardiovascular diseases.

Using data from the Avon Longitudinal Study of Parents and Children, we investigated the association between prenatal exposure to PCBs and fetal growth in a sample of 448 mother-daughter dyads. Concentrations of three common PCB analytes, PCB-118, PCB-153 and PCB-187, were measured in maternal serum collected during pregnancy, and fetal growth was measured by birth weight and birth length. Multivariable linear regression was used to examine the associations between PCB analytes and measures of fetal growth, after adjusting for parity, maternal age, pre-pregnancy BMI, educational status, tobacco use and gestational age of infant at sample collection. Birth length, ponderal index and gestational age were not associated with any of the PCB analytes. Mothers' educational status modified associations for PCB analytes with birthweight. We observed significant inverse associations with birth weight only among daughters of mothers with less education. Daughter's birth weight was 138.4g lower (95% CI: -218.0, —58.9) for each 10ng/g lipid increase in maternal serum PCB-118. Similarly, every 10ng/g lipid increase in maternal serum PCB-153 was associated with a 41.9g (95% CI: -71.6, -12.2) lower birth weight. Every 10ng/g lipids increase in maternal serum PCB-187, was associated with a -170.4g (95% CI: -306.1, -34.7) lower birth weight, among girls with mothers in the lowest education group.

Our findings suggest that prenatal exposure to PCBs is inversely associated with daughters' birth weight and that mothers' education, which is a possible marker for socioeconomic status, significantly modified the association between maternal PCB concentrations and birth weight in female newborns.

1. Introduction

Polychlorinated biphenyls (PCBs) are a family of synthetic organic chemicals, comprising 209 chemically related compounds that were used between 1930 and 1977 for various industrial applications because of their insulating and fire-retardant properties (1). PCBs were banned in the 1970s in the United States and in the 1980s in the United Kingdom, as adverse health effects following exposure were identified. PCBs are biphenyls with between one and ten chlorine atoms attached, and the degree of chlorination determines the stability and lipophilicity of the specific PCB analyte (2). PCBs with lower degrees of chlorination tend to be more rapidly excreted from the body, while more chlorinated PCB compounds (e.g., PCB 153) are retained for a longer period of time, many with biological half-lives in the order of years (3, 4). There are no known natural sources of PCBs (5) and once PCBs are released into the environment, they do not readily break down and can easily cycle between air, water and soil. Furthermore, they can be carried long distances and have been found in areas of snow and sea water far from the original release site (3).

The most common sources of environmental exposure to these substances are dairy products, meat and especially fish (6). PCBs are stored mainly in human adipose tissue, and their poor metabolism results in elimination half-lives of approximately 10-15 years (7, 8). Animal and human studies have shown that PCBs cross the placenta (2) and the quantities of PCBs found in cord serum may be considerable relative to the size of the developing fetus (9). Endocrine pathways that are important for fetal development, such as thyroid hormone signaling, can be disrupted by PCBs, potentially leading to decreased *in utero* growth (5).

Birth weight is one of the most, if not the most, powerful predictors of infant survival (10), with low birth weight contributing to about 9.1 million infant deaths each year. Globally, 17% of total births are to low birth weight newborns (10). Low birth weight in early childhood can be associated with adiposity in adolescents and earlier pubertal maturation, and is a strong predictor of the development of obesity, hypertension and cardiovascular disease in adults (11). Additionally, low birth weight is a predictor for other adverse outcomes such as poor school performance, high blood pressure and cardiovascular diseases (12-15). Therefore, it is important to determine whether prenatal PCB exposure is associated with birth outcomes such as low birth weight. The objective of this study was to investigate the association between prenatal exposure to PCBs and fetal growth in a well-characterized British sample of mother-daughter dyads.

2. Methods

2.1 Population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective birth-cohort study designed to evaluate the influences of genetic and environmental factors on health. During the years 1990–1992, 14,541 pregnant women residing in Avon, Great Britain with an estimated delivery date between April 1991 and December 1992 were enrolled in the study. These (initial) pregnancies resulted in a total of 14,062 live births and 13,988 children alive at one year of age. An additional 713 eligible children were enrolled at approximately 7 years of age and their data are available for analyses when including variables collected from the age of seven and later. Details of recruitment methods are described in detail elsewhere (16, 17).

This study examined associations between maternal exposure to PCBs and fetal growth in girls in an ancillary study designed to look at the association between maternal serum concentrations of environmental exposures and daughter's puberty characteristics (18). To be considered, girls had to

have at least two pubertal assessments to allow for classification of age at menarche. The ancillary study included all girls with early menarche (<11.5 years; n=218) and a random sample of girls without early menarche ≥11.5 years (n=230)). Informed consent was provided at the time of enrollment by the mothers. Human subjects' protection and ethical approval were provided by the ALSPAC Law and Ethics Committee, the Local Research Ethics Committees, and the Centers for Disease Control and Prevention (CDC) Institutional Review Board. Please note that the study website contains details of all the data that are available through a fully searchable data dictionary, http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary.

2.2 Data Collection

Outcomes of interest included birth weight (in grams), birth length (in centimeters), and gestational age (in weeks) which were abstracted from medical records. Low birth weight was considered <2500 grams. Ponderal index was calculated using the following formula: (weight in grams/height in centimeters^3) x 100 (19). Self-reported data on maternal prenatal characteristics and behaviors were obtained from questionnaires completed during pregnancy. Data collection and methods have been described in detail elsewhere (20).

2.3 Laboratory Analyses

Blood samples were collected during pregnancy, processed and serum was stored frozen at -20°C. In 2008, samples were shipped to the National Center for Environmental Health's Division of Laboratory Sciences, Centers for Disease Control and Prevention where PCB-118, PCB-153 and PCB-187 were measured by gas chromatography isotope dilution high resolution mass spectrometry (GC-IDHRMS) (21). This analysis presents lipid-adjusted exposures and measurements recorded as 0 ng/g are noted as <LOD.

2.4 Statistical Analyses

Pearson correlation coefficients were used to assess the relationship between PCB analytes. Stratum-weighted linear models, which accounted for the nested case-control study design, were used to estimate the association between individual PCB concentrations (PCB-118, PCB-153, and PCB-187) and fetal growth markers (birth weight, birth length, gestational age, and ponderal index). To adjust for the original selection criteria for the nested case-control study, cases (all girls who attained menarche <11.5 years) and controls (girls who attained menarche $\geq$ 11.5 years) were assigned weights of 1 and 15.1, respectively. Each PCB analyte was examined individually in a stratum-weighted model for each birth outcome, and backwards elimination was used to identify potential covariates which appreciably contributed to model fit or interpretation. . Covariates considered included previous births (0/$\geq$1), maternal age (continuous), maternal race (white/non-white), pre-pregnancy BMI (continuous), educational status (categorical), tobacco use (binary), and gestational age when maternal serum sample was obtained (continuous).In this analysis, not attaining any General Certificates of Secondary Education (GCSEs, at 16 years of age) was coded as "< O" (low) educational level, obtaining GCSEs as "O" (medium) and completing GCSEs and/or vocational training with additional education (e.g., University or Advanced) was considered "> O level" (high). After backwards elimination, the remaining covariates for birth weight outcome included previous births, maternal BMI, race, education, tobacco use during pregnancy and gestational ages at sample collection.. For birth length, the confounders included in the model were parity and maternal BMI. The ponderal index model included the confounders, parity, maternal BMI, and tobacco use during pregnancy. For gestational age at birth, the only confounder remaining in the model was gestational age when serum sample was collected. Effect modification by maternal smoking and maternal education was also examined by testing appropriate interaction terms for statistical significance. SAS version 9.3 (SAS Institute Inc., Cary, NC) was used to conduct all analyses. All statistical tests were 2-tailed; a p-value of <0.05 was considered statistically significant.

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. The CDC Institutional Review Board also assessed and approved human subjects' protection. Informed consent was provided by the mothers at the time of enrollment.

3. Results

More than half of the mothers were 29 years of age or younger at delivery and reported having normal pre-pregnancy BMI. About half of the mothers had an educational level of less than or equal to O level and most mothers were white (94%) (Table 1). The median gestational age at serum sample collection was 15 weeks with an interquartile range of 10–28 weeks. Among 448 daughters included in the study population, mean birth weight (± SD) was 3396.7 (± 498.7) g; birth length was 50.4 (±2.2)cm; ponderal index was 2.7 (± 0.2) kg/m^3; and gestational age was 39.8 (±1.6) weeks (data not presented). Less than 4% of daughters were born preterm or weighed less than 2,500g.

PCB analytes were detected in greater than 98% of the samples tested. PCB-153 had the highest median maternal serum concentrations followed by PCB-118 and PCB-187 (Table 1). Median (min-max) concentration in maternal samples of PCB-153 was 64.5 (3.7-200.1) ng/g; PCB-118 was 14.9 (<LOD-90.9) ng/g; and PCB-187 was 11.3 (<LOD-41.6) ng/g. Pearson correlation coefficients showed high levels of correlation between PCB-118 and PCB-153 (r= 0.80) and PCB-118 and PCB-187 (r = 0.73), and a very high level of correlation between PCB-153 and PCB-187 (r = 0.90).

Birth length, ponderal index and gestational age were not associated with any of the PCB analytes in main effects' models (Table 2). There was significant effect modification between maternal education and PCB analytes (PCB-118, PCB-153, and PCB-187) for birth weight; therefore, results for birth weight were stratified by maternal education (Table 3). For all three analytes, we observed significant inverse associations with birth weight only among daughters of mothers with less than O-level (low) education. Daughter's birth weight was 138.4g lower (95% CI: -218.0, -58.9) for each 10ng/g

lipid increase in maternal serum PCB-118. Similarly, every 10ng/g lipids increase in maternal serum PCB-153 was associated with a 41.9g (95% CI: -71.6, -12.2) lower birth weight. Every 10ng/g lipids increase in maternal serum PCB-187, was associated with a 170.4g (95% CI: -306.1,-34.7) lower birth weight (Table 3), among girls with mothers in the lowest education group.

4. Discussion

In this analysis, we explored the associations between prenatal exposure to PCB-118, PCB-153 and PCB-187 and fetal growth markers; birth weight, birth length, ponderal index, and gestational age. Our findings suggest that prenatal exposure to PCBs is inversely associated with birth weight and that mother's education significantly modified the association between maternal PCB concentrations and birth weight in female newborns. Educational status may be a marker for socioeconomic status in this population; both education and socioeconomic status have positively associated with maternal diet quality and food security (22). This could in part contribute to the differences that we observed by mother's education.

Evidence from previous studies suggests prenatal exposure to PCBs has harmful effects on fetal growth (2, 23, 24). A meta-analysis of 12 European cohorts including 7,990 mother-child dyads and a pooled study of 9377 mother-child dyads from 11 European cohorts (15 studies) both observed inverse associations between fetal PCB-153 exposure and birth weight (25, 26). Compared to the maternal serum levels observed in other European studies, our median PCB-153 concentration (64.5 ng/g lipid), while not the lowest observed, does fall in the lower half of overall results (range of median PCB-153 across European studies 15.3-394.4 ng/g lipid)(26) . In contrast, Longnecker et al., in the U.S. Collaborative Perinatal Project of 1034 pregnant women enrolled between 1959-1965, found no associations between birth weight or gestational age and serum concentrations of 11 PCB analytes collected during the third trimester of pregnancy (27). Lignell et al., observed that breast milk

concentrations of PCB-138, PCB-153 and PCB-180 assessed within the first month post-delivery were positively associated with birth weight in a sample of first-time mothers in Sweden (n=411) (28) with stronger associations reported for males than females.

Inconsistent findings across studies may be related to multiple factors such as differences in study design, population charcteristics, sample sizes, timing or type of sample measured, and overall distribution of exposure (e.g., low v. high). PCB levels measured in breast milk collected after birth may not be representative of *in utero* exposure. Also, differences in the PCB analytes examined can lead to varied findings since PCB analytes vary in their ability to bioaccumulate and in level of toxicity (27, 29). PCBs with lower degrees of chlorination tend to be more rapidly excreted from the body; thus, may be poorer biomarkers of long-term exposure.

Although the possible mechanism of PCBs on birth weight is not known, it could be related to the endocrine-disrupting properties of PCBs (30). Estrogens promote fetal growth and PCBs have been found to have both estrogenic and anti-estrogenic roles (31). In animal models, a growing body of literature suggests that exposure to endocrine-disrupting chemicals can have a wide range of effects on metabolism such altering insulin metabolism and disrupting energy balance (1, 32). For example, PCB153 concentrations have been inversely associated with serum thyroxine levels in an animal model (33).

Our analysis was conducted on a sample of mothers and their daughters chosen from a nested case-control study for pubertal development. Although our results could be biased if the girls excluded from the analysis were different from girls who were included in the analysis, it is unlikely since mean values of maternal characteristics and fetal growth outcomes for the study sample are similar to those of the group of girls enrolled in the full cohort (19). These analyses were performed on a sample of girls because data on prenatal exposure to PCBs are not currently available for ALSPAC boys. It is unknown whether these results can be extrapolated to males. Additionally, PCB measurements are only available

for a single time point during pregnancy and daughters' PCB concentrations measured at birth are not available. The timing of specimen collection is important and in our analyses we controlled for gestational age at sample collection, because evidence suggests that concentrations decline from preconception to postnatally sensitive windows (34). Further analyses will explore the association between prenatal PCB exposure and postnatal growth in girls at other time points. Lastly, there is the possibility of residual confounding by unmeasured or poorly measured (e.g., maternal smoking) covariates.

5. Conclusions

Our results are consistent with results from other studies that show an association between higher prenatal PCB levels and lower birth weight (23, 25, 35). Birth weight is reflective of fetal development from conception to birth, and low birth weight is associated with negative health outcomes later in life. Pre-term or low birth weight infants are at a heightened risk for morbidities and chronic conditions, including cardiovascular diseases and adverse behavioral, cognitive and psychiatric outcomes (36). In our study, mother's education, a possible marker for socioeconomic status, significantly modified the association between maternal PCB concentrations and birth weight in female newborns. We observed significant inverse associations with birth weight only among daughters of mothers with less education (lower socioeconomic status). This relationship has not previously been identified and should be investigated in future research.

Table 1: Frequency distribution and lipid adjusted maternal serum concentrations (ng/g lipid) of selected polychlorinated biphenyl (PCB) analytes in a sample of British girls (n=448).

	Frequency n (%)	PCB118 Median (min-max)	PCB153 Median (min-max)	PCB187 Median (min-max)
Overall	448 (100)	14.9 (<LOD[a]-90.9)	64.50 (3.70-200.10)	11.3 (<LOD-41.6)
Maternal pre-pregnancy BMI				
Underweight	18 (4.0)	14.2 (5.2-28.1)	79.7 (45.5-120.8)	14.0 (8.9-23.1)
Normal	290 (64.7)	15.2 (<LOD-52.4)	68.6 (3.7-184.7)	11.7 (<LOD-34.4)
Overweight	63 (14.1)	14.8 (5.7-58.6)	57.2 (25.1-152.9)	9.6 (<LOD-25.60)
Obese	31 (6.9)	18.1 (6.1-90.9)	57.3 (25.9-200.1)	9.6 (<LOD-41.60)
Missing	46 (10.3)	13.0(4.2-29.4)	58.7 (24.0-153.40)	10.4 (3.7-23.90)
Maternal age at delivery (years)				
<25	92 (20.5)	10.4 (4.2-34.20)	44.2 (22.10-141.10)	7.8 (<LOD-21.0)
25-29	164 (36.6)	14.5 (5.2-58.6)	59.8 (26.3-184.7)	10.3 (<LOD-34.4)
≥30	189 (42.2)	18.6 (<LOD-90.90)	81.9 (3.70-200.10)	14.5 (<LOD-41.6)
Missing	3 (0.7)	14.2 (10.9-19.2)	80.4 (63.4-94.0)	13.6 (11.2-23.1)
Maternal education[b]				
< O level (low)	89 (19.9)	13.3 (2.0-90.9)	57.3 (3.7-200.1)	10.5 (<LOD-41.6)
O level (medium)	140 (31.3)	13.3 (5.20-37.40)	55.9 (25.9-154.9)	9.6 (<LOD-28.1)
> O level (high)	200 (44.6)	18.1 (<LOD-52.4)	74.4 (11.8-184.7)	13.0 (<LOD-34.4)
Missing	19 (4.2)	12.8(5.2-35.2)	62.9 (32.60-163.90)	11.6 (5.5-32.5)
Maternal race				
White	423 (94.4)	14.9 (<LOD-90.90)	64.8 (3.70-200.10)	11.2 (<LOD-41.6)
Nonwhite	8 (1.8)	19.5 (2.8-35.3)	67.7 (11.80-140.10)	14.8 (3.7-24.2)
Missing	17 (3.8)	12.5 (5.2-35.2)	58.5 (32.60-125.90)	10.3 (5.5-23.10)
Previous births				
0	208 (46.4)	15.5 (4.2-41.40)	63.9 (22.10-184.70)	10.9 (<LOD-34.4)
≥ 1	211 (47.1)	14.9 (<LOD-90.9)	66.9 (3.7-200.1)	11.9 (<LOD-41.6)
Missing	29 (6.5)	11.7 (5.2-35.2)	59.7 (28.1-110.4)	11.2 (5.2-24.0)
Tobacco use during first 3 months				
Yes	102 (22.8)	13.0 (4.2-51.0)	60.8 (24.0-153.4)	10.5 (4.6-29.0)
No	328 (73.2)	16.5 (<LOD-90.90)	67.8 (3.7-200.10)	11.6 (<LOD-41.60)
Missing	18 (4.0)	10.9 (5.2-21.3)	59.7 (28.1-94.0)	10.5 (5.2-23.1)
Low birth weight (<2500 g)				
Yes	17 (3.8)	20.7 (5.9-90.9)	74.4 (26.9-200.1)	13.0 (4.9-41.6)
No	423 (92.4)	14.7 (<LOD-58.6)	63.7 (3.7-184.7)	10.9 (<LOD-34.4)
Missing	8 (1.8)	15.3 (10.90-27.30)	75.5 (59.3-130.8)	13.9 (10.5-23.1)
Preterm delivery (<37 weeks)				
Yes	14 (3.1)	16.7 (7.6-35.2)	69.7 (37.8-125.9)	12.0 (6.6-27.0)
No	431 (96.2)	14.8 (<LOD-90.9)	63.6 (3.7-200.10)	11.2 (<LOD-41.6)
Missing	3 (0.7)	14.2 (10.9-19.2)	80.4 (63.4-94.0)	13.6 (11.2-23.1)
Menarche (years)				
< 11.5	218 (51.3)	15.2 (2.0-58.6)	62.1 (3.7-163.9)	10.9 (<LOD-32.5)
≥ 11.5	230 (48.7)	14.8 (<LOD-90.9)	68.2 (22.1-200.1)	11.5 (<LOD-41.6)

[a] <LOD= Below limit of detection

[b] O–level of education is the qualification obtained at 16 years of age when obligatory schooling ends.

Table 2. Adjusted Regression coefficients (β)[a] for associations between prenatal growth measures[b] and maternal serum concentrations of PCB-118, PCB-153, and PCB-187 in a sample of British girls.

	PCB-118	p-value	PCB-153	p-value	PCB-187	p-value
Birth length [c](cm) (n=363)						
Unadjusted β (95% CI)	0.12 (-0.16, 0.41)	0.39	-0.04 (-0.12, 0.04)	0.30	-0.34 (-0.72, 0.05)	0.09
Multivariate β (95% CI)	0.08 (-0.21, 0.36)	0.60	-0.04 (-0.12, 0.04)	0.29	-0.33 (-0.73, 0.06)	0.10
Ponderal Index [d](n=357)						
Unadjusted β (95% CI)	-0.03 (-0.06, 0.01)	0.10	-0.01 (-0.01, 0.00)	0.24	-0.02 (-0.07, 0.02)	0.30
Multivariate β (95% CI)	-0.03 (-0.06, 0.01)	0.10	0.00 (-0.01, 0.01)	0.97	0.00 (-0.04, 0.05)	0.91
Gestational age[e] (wks) (n=444)						
Unadjusted β (95% CI)	0.02 (-0.15, 0.18)	0.85	-0.01 (-0.06, 0.04)	0.72	-0.12 (-0.37, 0.13)	0.35
Multivariate β (95% CI)	0.02 (-0.15, 0.18)	0.82	-0.01 (-0.06, 0.04)	0.80	-0.11 (-0.36, 0.14)	0.38

[a] per 10 unit (ng/g lipid) increase in analyte. In multivariate models maternal pre-pregnancy BMI, and gestational age at maternal sample collection were entered as continuous variables (rather than categorical as presented in table 1).

[b]. For birthweight, significant interactions were observed with educational status; thus, final stratified results for birthweight are provided in Table 3.

[c] Adjusted for sampling design, previous births and maternal pre-pregnancy BMI

[d]Adjusted for sampling design, previous births, maternal pre-pregnancy BMI, maternal tobacco use during pregnancy

[e] Adjusted for sampling design, gestational age at maternal s sample collection

Table 3. Regression coefficients (β)[ab] for birth weight (g) and maternal serum concentration of PCB-118 , PCB-153, PCB-187 stratified by maternal education level (low, medium, high) in a sample of British girls

Education level	PCB-118 β (95% CI)	p-value	PCB-153 β (95% CI)	p-value	PCB-187 β (95% CI)	p-value
< O level (low)						
(n=89)	-138.43 (-218.0,-58.9)	0.0009	-41.90 (-71.63, -12.17)	0.0006	-170.40 (-306.10, -34.70)	0.01
O level (medium)						
(n=140)	-7.92 (118.3, 102.5)	0.89	0.51 (-30.77, 31.78)	0.97	8.30 (-151.16, 167.76)	0.92
> O level (high)						
(n=200)	-24.51 (--56.1, 105.1)	0.55	-2.43 (-24.38, 19.52)	0.83	-8.30 (-114.60, 97.99)	0.88

[a] per 10 unit (ng/g lipid) increase in analyte. In multivariate models maternal pre-pregnancy BMI, and gestational age at sample collection age were entered as continuous variables (rather than categorical as presented in table 1). P-interactions = 0.02 (PCB-118); 0.02 (PCB-153); 0.03 (PCB-187)

[b] adjusted for sampling design, previous births, maternal pre-pregnancy BMI, maternal tobacco use during pregnancy, gestational age at sample collection and maternal race)

Acknowledgements

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support for ALSPAC. This research was specifically funded by the US Centers for Disease Control and Prevention (CDC). KN is funded by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care (NIHR CLAHRC) West at University Hospitals Bristol NHS Foundation Trust. This publication is the work of the authors and they will serve as guarantors for the contents of this paper.

The findings and conclusions do not necessarily represent views of the CDC, the NHS, the NIHR or the Department of Health. Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the U.S. Department of Health and Human Services. The authors declare they have no actual or potential competing financial interests.

Author Disclosure Statement

The authors declare no conflicts of interest.

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