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Title

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Permalink

<https://escholarship.org/uc/item/68n7g91g>

Journal

Environmental Health Perspectives, 131(3)

ISSN

1542-4359

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Publication Date

2023-03-01

DOI

10.1289/ehp10812

Peer reviewed

# Cognitive Development and Prenatal Air Pollution Exposure in the CHAMACOS Cohort

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**BACKGROUND:** Because fine particulate matter [PM, with aerodynamic diameter  $\leq 2.5 \mu\text{m}$  ( $\text{PM}_{2.5}$ )] is a ubiquitous environmental exposure, small changes in cognition associated with  $\text{PM}_{2.5}$  exposure could have great societal costs. Prior studies have demonstrated a relationship between *in utero*  $\text{PM}_{2.5}$  exposure and cognitive development in urban populations, but it is not known whether these effects are similar in rural populations and whether they persist into late childhood.

**OBJECTIVES:** In this study, we tested for associations between prenatal  $\text{PM}_{2.5}$  exposure and both full-scale and subscale measures of IQ among a longitudinal cohort at age 10.5 y.

**METHODS:** This analysis used data from 568 children enrolled in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a birth cohort study in California's agricultural Salinas Valley. Exposures were estimated at residential addresses during pregnancy using state of the art, modeled  $\text{PM}_{2.5}$  surfaces. IQ testing was performed by bilingual psychometricians in the dominant language of the child.

**RESULTS:** A  $3\text{-}\mu\text{g}/\text{m}^3$  higher average  $\text{PM}_{2.5}$  over pregnancy was associated with  $-1.79$  full-scale IQ points [95% confidence interval (CI):  $-2.98, -0.58$ ], with decrements specifically in Working Memory IQ (WMIQ) and Processing Speed IQ (PSIQ) subscales [WMIQ  $-1.72$  (95% CI:  $-2.98, -0.45$ ) and PSIQ  $-1.19$  (95% CI:  $-2.54, 0.16$ )]. Flexible modeling over the course of pregnancy illustrated mid-to-late pregnancy (months 5–7) as particularly susceptible times, with sex differences in the timing of susceptible windows and in which subscales were most affected [Verbal Comprehension IQ (VCIQ) and WMIQ in males; and PSIQ in females].

**DISCUSSION:** We found that small increases in outdoor  $\text{PM}_{2.5}$  exposure *in utero* were associated with slightly lower IQ in late childhood, robust to many sensitivity analyses. In this cohort there was a larger effect of  $\text{PM}_{2.5}$  on childhood IQ than has previously been observed, perhaps due to differences in PM composition or because developmental disruption could alter the cognitive trajectory and thus appear more pronounced as children get older. <https://doi.org/10.1289/EHP10812>

## Introduction

Particulate matter (PM) exposure is ubiquitous in the United States, and newly available estimates of PM that combine ground-based measurements with remotely sensed data<sup>1</sup> allow for characterization of exposure of populations, especially in rural areas, for which such estimates were previously unavailable. This characterization of the PM in rural areas is important because the composition of PM can vary between urban and rural areas,<sup>2</sup> with the potential for differences in biologic effects.<sup>3</sup> Urban areas tend to have more combustion-related particles with a higher content of metals in comparison with rural areas, which have more PM from natural sources and less ultrafine PM.<sup>2</sup>

There are many known health effects of PM,<sup>4</sup> including increasing evidence for neurocognitive effects across the life course. Because childhood is a particularly critical period of rapid brain growth and neurodevelopment,<sup>5</sup> recent evidence linking fine PM [PM with aerodynamic diameter  $\leq 2.5 \mu\text{m}$  ( $\text{PM}_{2.5}$ )] exposure to decrements in childhood cognitive function is particularly concerning.<sup>6,7</sup> Yet, much of what we know about these

effects of  $\text{PM}_{2.5}$  exposure comes from studies in major metropolitan areas. For example, in a Los Angeles cohort, monthly  $\text{PM}_{2.5}$  levels averaged over the 1–3 y prior to the assessments were associated with increased risk of delinquent behavior in adolescents.<sup>8</sup> Using a combination of two German cohorts, a large population of adolescents in major cities was also found to have increased risk of hyperactivity and inattention at age 15 y associated with  $\text{PM}_{2.5}$  exposure estimated at their childhood (age 10 y) or current home addresses.<sup>9</sup> A large reanalysis of multiple European birth cohorts, mostly based in large population centers, did not find any relationship between *in utero*  $\text{PM}_{2.5}$  exposure and neurodevelopmental outcomes; however, their exposure data were back-extrapolated to dates many years prior, raising the possibility that exposure misclassification may have obscured a relationship.<sup>10</sup> Multiple studies have also shown that when comparing schools with higher roadway pollution exposure to those with lower, students in lower pollution–exposure schools perform better on cognitive testing even when controlling for socioeconomic status (SES).<sup>11,12</sup>

The prenatal period could be a particularly critical time for neurodevelopmental insults, given the rapid growth of brain structures during that period. A 2016 systematic review concluded that *in utero* exposure to urban air pollution was associated with decreases in measured intelligence in preschool-age children,<sup>6</sup> and noted that a few studies of air pollution's effect on neurodevelopment through the life course suggest a larger effect of air pollution exposure on boys in comparison with girls. Higher prenatal  $\text{PM}_{2.5}$  exposure levels have been associated with lower cognitive functioning in early childhood (ages 1–6 y),<sup>13–15</sup> as has prenatal exposure to larger PM (ages 2–6 y),<sup>16,17</sup> to polycyclic aromatic hydrocarbons (age 5 y),<sup>18,19</sup> to  $\text{NO}_2$  (age 7 y),<sup>20</sup> and to roadway proximity (age 7–8 y).<sup>20,21</sup> To our knowledge, no studies have assessed effects of prenatal exposures on cognitive function later in childhood.

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

Received 17 December 2021; Revised 19 January 2023; Accepted 26 January 2023; Published 13 March 2023.

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The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study is a birth cohort study conducted in an agricultural community in California with extensive exposure and health outcome characterization, including prenatal residential address data and detailed neurodevelopmental follow-up throughout childhood. Prenatal exposures to organochlorine pesticides<sup>22</sup> and organophosphate pesticides as measured by urinary metabolites,<sup>23</sup> ambient exposure to organophosphate pesticides and carbamates as well as other pesticides estimated near the prenatal residence,<sup>24</sup> organophosphate flame retardant exposure,<sup>25</sup> and polybrominated diphenyl ether (PBDE) flame retardant exposure<sup>26,27</sup> have been previously adversely associated with neurocognitive development in the cohort. In this study, our aim was to use PM<sub>2.5</sub> estimates—newly available for areas like Salinas with rural and small urban areas—to assign prenatal PM<sub>2.5</sub> exposures to CHAMACOS cohort members and assess the relationship with IQ at age 10.5 y, using the rich data available in the cohort on other exposures.

## Methods

### Study Population

This analysis uses data from the CHAMACOS study, a decades-long birth cohort study in California's agricultural Salinas Valley, which is part of the Center for Environmental Research and Community Health (CERCH) at the University of California Berkeley (UC Berkeley). Details of the cohort recruitment and follow-up have been previously reported in detail.<sup>22,28,29</sup> The CHAMACOS study is approved by the UC Berkeley Institutional Review Board, and informed consent was given by the participating parents on behalf of themselves and their children.

Enrollment into the cohort occurred in two phases. In the first phase ("CHAM1"), pregnant women were recruited from community clinics between October 1999 and October 2000. Inclusion criteria included: being over 18 y of age, being <20 wk pregnant, speaking Spanish or English, qualifying for low-income health insurance, and planning to deliver at the (single) county hospital. The initial CHAM1 cohort included 601 women enrolled in 1999–2000 while the CHAMACOS participant(s) were *in utero*, of whom 537 live-born infants were followed to delivery. Enrollment into the second phase ("CHAM2") occurred in 2009–2011, when the original cohort was 9–10 y of age, with an additional 305 9-y-old children recruited, using inclusion criteria to closely match the original cohort. Children recruited into CHAM2 had mothers who: were 18 y old or older at the time of the child's birth, were

Spanish- or English-speaking, were eligible for low-income health insurance at the time of delivery, and were residents of the Salinas Valley at birth (they did not necessarily deliver at the county hospital, though approximately 70% of these mothers did). By the time of the assessment for this study (roughly age 10.5 y), the participants from the two subcohorts have very similar demographics with the participants from the CHAM2 cohort being slightly younger, more male, and of lower SES (Table 1). CHAM1 participants who remained in the cohort for analysis of these outcomes at age 10.5 y were very similar to those lost to follow-up; one area of difference is children whose mothers smoked during pregnancy (or were exposed to smoke during pregnancy) were slightly more likely to be lost to follow up (see Table S1, "Characteristics of the CHAM1 Cohort remaining at 10.5 y").

Study visits were conducted repeatedly every year or two throughout childhood and adolescence. For this study, we use data from the visits at age 10.5 y and included 611 participants, who had no history of neurodevelopmental disease (e.g., down syndrome, hydrocephalus), and underwent cognitive testing at age 10.5 y (320 CHAM1 participants and 291 CHAM2 participants). Of these, we excluded 24 with no prenatal residential history data, 17 born at <36-wk gestation and two full-term infants who were from twin births in which the twin with the lower assigned ID number was selected for this analysis. Gestational age was based on last menstrual period (when that had been reported by the mother AND the resulting gestational age was within 2 wk of that listed in the medical record) or directly from the medical record. The final sample size for the analysis at 10.5 y was 568 children.

We conducted sensitivity analyses using cognitive outcomes at age 7 y on 310 CHAM1 participants, who had no history of neurodevelopmental disease, sat for neurodevelopmental testing at age 7 y, and had additional prenatal and early-life exposure data that were not available on the CHAM2 cohort. We excluded 11 children who were born at <36-wk gestation and two full-term infants who were from twin births in which the twin with the lower assigned ID number was selected for this analysis. Thus, the sample size for the 7-y-old sensitivity analysis was 297 children.

### Exposure Assessment

The date of conception was estimated from the child's birth date and estimated gestational age at the time of birth. Information on prenatal residential history was collected prospectively for CHAM1 and at 9-y and 16-y visits for CHAM2. Though every

**Table 1.** Characteristics of the CHAMACOS cohort in the Salinas Valley, California, at the 10.5-y analysis (2010–2013, *n* = 568).

	Full cohort ( <i>n</i> = 568)	Missing	CHAM1 ( <i>n</i> = 286)	CHAM2 ( <i>n</i> = 282)
<b>Demographics</b>				
Age (y)	10.52 (0.18)	0	10.62 (0.18)	10.42 (0.11)
Female	291 (51.2%)	0	152 (53.1%)	139 (49.3%)
Primarily Spanish speaking	181 (31.9%)	0	92 (32.2%)	89 (31.6%)
Household above the poverty level	156 (27.5%)	0	83 (29.0%)	73 (25.9%)
Mother born in Mexico	489 (86.4%)	2	247 (86.4%)	242 (86.4%)
Mother has seventh grade education or higher	327 (57.6%)	0	164 (57.3%)	163 (57.8%)
Maternal Peabody Picture Vocabulary test score	91.6 (19.4)	13	92.8 (18.8)	90.4 (20.0)
<b>Exposures</b>				
HOME score at age 10.5 ( <i>z</i> -scores)	0.01 (1.01)	0	0.00 (1.05)	0.01 (0.96)
Mother smoked during pregnancy	12 (2.1%)	2	9 (3.1%)	3 (1.1%)
Mother exposed to smoke (secondhand) during pregnancy	54 (9.5%)	2	21 (7.3%)	33 (11.8%)
<b>Outcomes</b>				
Full-scale IQ score	89.56 (11.09)	2	90.58 (11.04)	88.53 (11.06)
Verbal Comprehension subscale	86.96 (12.37)	1	87.37 (12.73)	86.53 (12.00)
Perceptual Reasoning subscale	92.65 (13.93)	0	94.10 (13.90)	91.19 (13.84)
Working Memory subscale	91.04 (12.00)	0	92.01 (11.96)	90.05 (11.98)
Processing Speed subscale	98.48 (11.97)	1	98.61 (12.26)	98.35 (11.69)

Note: All cells contain either mean (SD) or number (%).

effort was made to ensure accurate and complete residential histories, there is a somewhat higher likelihood of exposure misclassification among CHAM2 participants because parents may be less likely to remember exactly the month in which they moved in or out of a particular address during their child's gestation. Average PM<sub>2.5</sub> exposure was calculated as a continuous variable for each month of gestation at each residential location, rounding to the nearest calendar month because of the availability of pollutant data in calendar months (e.g., if the pregnancy started 5 January, the first month exposure was estimated using the January PM<sub>2.5</sub> spatial surface; however, if the pregnancy started 25 January, the first month exposure was estimated using the February PM<sub>2.5</sub> surface). Exposures were estimated through the ninth month of gestation (i.e., the 36th wk), because even among full-term infants there may not be a full 10th month of gestation.

We estimated annual ground-level PM<sub>2.5</sub> at each residential address from the publicly available data sets provided by the Atmospheric Composition Analysis Group at Washington University in St. Louis, Missouri (the "ACAG data sets"),<sup>1</sup> which combine remotely sensed data from satellites, chemical transport models, and ground-based measurements in a geographically weighted regression model. The ACAG data sets include monthly average estimates for PM<sub>2.5</sub> across North America beginning in January 2000, at roughly 1-km resolution. Because some infants in the cohort were *in utero* for a portion of 1999, we needed to calculate monthly surfaces for 1999. Using explained variability from regression models and prior knowledge, we chose to classify areas by whether they are goods movement corridors, have major nongoods movement corridor roadways, or are not characterized by either type of roadway because these differences are known to impact California PM<sub>2.5</sub> concentrations.<sup>30</sup> After we calculated exposure surfaces for 1999, we applied our method to the year 2000 and compared our calculated 2000 data set to the known ACAG data sets for that year. When comparing our 2000 data to the ACAG 2000 data, our model was highly correlated with the ACAG data ( $R^2 = 0.8$ ). Testing the method over an additional 10-y period (2000–2010) the  $R^2$  was 0.7. We are thus confident that the modeled PM<sub>2.5</sub> surfaces for 1999 capture most of the variability in the true values (more detail is available in the Statistical Analysis Plan in the Supplemental Material, Part A, section 6a). A total of 87 children had some prenatal exposure time in the year 1999; out of 5,112 exposure-months in the cohort, 284 (6%) occurred in 1999.

### Outcome Assessment

Children's cognitive abilities were assessed at ages 7 and 10.5 y, using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) English or Spanish versions as appropriate.<sup>31</sup> All assessments at age 7 y were conducted by a single bilingual psychometrician; two bilingual psychometricians conducted the assessments at age 10.5 y. All psychometricians were trained and supervised by a pediatric neuropsychologist. Scores for four domains were calculated based on the following subtests<sup>31</sup>: Verbal Comprehension (VCIQ, composed of Vocabulary and Similarities subtests), Perceptual Reasoning (PRIQ, Block Design and Matrix Reasoning subtests), Working Memory (WMIQ, Digit Span and Letter-Number Sequencing subtests), and Processing Speed (PSIQ, Coding and Symbol Search subtests). All subtests were administered in the dominant language of the child, which was determined through administration of the Oral Vocabulary subtest of the Woodcock-Johnson/Woodcock-Muñoz Tests of Cognitive Ability in both English and Spanish at the beginning of the assessment.<sup>32</sup> The psychometrician was blinded to PM<sub>2.5</sub> exposure status. Full-Scale IQ (FSIQ) as well as subscale scores were used for each testing time point, standardized against U.S. population-

based norms for English- and Spanish-speaking children. Note that during the first 3 months of assessments at age 7 y, two subtests were not administered, meaning that 27 children are missing working memory and processing speed subscales, and thus FSIQ as well.<sup>25</sup>

### Missing Data

Only children who had at least one prenatal residential address recorded and underwent neurodevelopmental assessments were included in analyses. However, because of some missing residential addresses due to moves during pregnancy, we used multiple imputation by chained equations for missing PM<sub>2.5</sub> values for 531 of 5,112 exposure-months (roughly 10% of the months).<sup>33</sup> We imputed these using predictive mean matching with 5 donors, for each month of pregnancy. The whole-pregnancy mean was then calculated as an average of the full set of months, once each missing month had been imputed. We also used multiple imputation for missing covariate data.

### Statistical Analyses

All analyses were done in accordance with a prespecified analysis plan that was posted to *Open Science Framework* prior to the start of any exposure-outcome analyses (prespecified analysis plan with versioning and comments is available at [https://osf.io/zwbgs/?view\\_only=a01c321901024b4ab7bbc9e82920d025](https://osf.io/zwbgs/?view_only=a01c321901024b4ab7bbc9e82920d025); the most recent version is also Part A in the Supplemental Material).

The tidyverse implemented in R (version 3.6.3, codenamed "Holding the Windsock"; The R Foundation for Statistical Computing)<sup>34</sup> was used for all exposure modeling and the analysis of the exposure-outcome relationship (see Supplemental Material, Part A, section 6).

Confounder selection was prespecified based on subject matter knowledge and encoded in a directed acyclic graph (Figure S1, "Directed Acyclic Graph"); all recoding of variables was also prespecified. The analyses included the following covariates to block backdoor confounding pathways: maternal verbal intelligence (assessed when the children were 9 y of age), maternal education (dichotomized into  $\geq$  seventh grade education, or sixth grade education and lower), household poverty (dichotomized to less than or equal to the poverty level vs. above the poverty level, at the time of the neurocognitive testing, but as a proxy for lifetime poverty) and Home Observation for Measurement of the Environment (HOME) inventory<sup>35,36</sup> (assessed at the time of the neurocognitive testing but as a proxy for lifetime HOME). In addition, we included age, sex assigned at birth (binarized into female and male), language of assessment, and smoke exposure *in utero* (binary variables for whether the mother smoked and whether she was exposed to smoking during pregnancy) because these are expected to be strongly associated with the outcome variable.

Rothman and Greenland recently suggested that study design decisions should be based on precision rather than power,<sup>37</sup> because precision estimates do not change based on the alternative hypothesis considered. Power and precision analyses were calculated for the 10.5-y assessment (Supplemental Material, Statistical Analysis Plan Part A, section 3b, and Figure S2, "Power for analyses using Distributed Lag Models"). Because of variable degrees of correlation between the exposure at the various months of gestation, the power to detect a 3-point difference in IQ score with a 3- $\mu\text{g}/\text{m}^3$  difference in PM<sub>2.5</sub> ranged between  $\sim 20\%$ – $99\%$ , with most months of gestation having  $>80\%$  power. Thus, we also calculated the precision expected at each month of gestation (e.g., the full width of the confidence interval); these ranged from 2.2 to 6.0 IQ points for a 3- $\mu\text{g}/\text{m}^3$  increase in PM<sub>2.5</sub> (Supplemental Material, Part A, section 3b). A



3- $\mu\text{g}/\text{m}^3$  increase in the  $\text{PM}_{2.5}$  exposure was chosen because this is approximately the interquartile range (IQR) of the whole pregnancy average in this sample.

The main analyses were done using distributed lag models (DLM), which allowed us to include all the monthly exposure lags in a single analysis, thereby controlling for exposure during all other months.<sup>38–40</sup> We assumed that the relationship between  $\text{PM}_{2.5}$  and IQ was linear across our range of  $\text{PM}_{2.5}$  values, but we allowed the shape of the time-lag dimension to vary flexibly. We examined multiple options for smoothing functions (including allowing nonlinearity in the exposure dimension) and examined the Akaike Information Criteria (AIC).<sup>41</sup> The model specification with the best model fit (lowest AIC) in both the 7-y and 10.5-y analyses used b-splines for the smoothing functions (Table S2, “Akaike Information Criteria for Various Smoothing Functions”). Linear models were also used to associate whole-pregnancy average  $\text{PM}_{2.5}$  exposure with IQ and subscales, and assumptions were checked.

Even though the power and precision analyses were conducted for the larger, 10.5-y cohort, we made the decision *a priori* to also analyze the 7-y data, which consisted of only CHAM1 participants ( $n = 297$ ), because there are more early-life variables available for sensitivity analysis. To assess for changes in our results based on misclassification of covariates used at the time of assessment, HOME score and poverty category assessed at age 6 months instead of at the time of assessment were used together to perform a sensitivity analysis. Presence of a gas stove while the child was *in utero* (with or without a working range hood) could be associated with IQ (but not ambient prenatal  $\text{PM}_{2.5}$  exposure) and thus could affect the precision of our estimate. A separate sensitivity analysis was performed to assess for meaningful changes in the precision of our estimates after adding a variable for gas stove presence. Finally, exposure to pesticides and other environmental contaminants can vary seasonally, and multiple chemicals have previously been associated with neurodevelopmental outcomes in the CHAMACOS cohort. Thus, to assess for potential confounding by these environmental exposures, these variables were added (one at a time) to further sensitivity analyses: mean dialkyl phosphate metabolites (DAPs) measured in parental urine during pregnancy,<sup>23</sup> mean organophosphate flame retardants measured in maternal urine during pregnancy,<sup>25</sup> and prenatal polybrominated diethyl ether (PBDE) concentrations in nanograms per gram lipid measured during pregnancy<sup>26</sup> or estimated from mothers’ levels when children were 9 y of age.<sup>27,42</sup> The intent of this set of sensitivity analyses at the 7-y assessment was to look for major discrepancies in the pattern of associations between  $\text{PM}_{2.5}$  exposure and IQ between the 7-y and 10.5-y analyses and to identify other exposures that may bias the results in the analysis of the children at age 10.5 y. To achieve this goal, we also performed a post hoc sensitivity analyses on the data collected at age 10.5 y, restricted to the CHAM1 participants only ( $n = 286$ ).

Prespecified sensitivity analyses with the 10.5-y IQ measurements from both CHAM1 and CHAM2 included the addition (one at a time) of prenatal organophosphate and carbamate pesticide exposure estimated as described previously<sup>24,43</sup> from the California Department of Pesticide Regulation pesticide use reporting (PUR) data available with both spatial (1 square mile) and temporal (daily) resolution. We also added each of prenatal concentrations of PBDEs and DDE and DDT in nanograms per gram lipid measured during pregnancy or estimated from maternal levels when their children were 9 y of age. These analyses were performed to assess for potential confounding of the relationships by pesticides that have previously been shown to related to neurodevelopmental outcomes in the CHAMACOS cohort.

Additional post hoc sensitivity analyses compared a) results between the entire 10.5-y cohort and only those children whose entire *in utero* period was in 2000; b) results excluding the younger of 14 pairs of siblings; and c) results accounting for either duration of schooling or season of birth as covariate.

The only planned subgroup analysis was in the 10.5-y data, where we analyzed the  $\text{PM}_{2.5}$ –IQ relationship stratified by fetal sex.

## Results

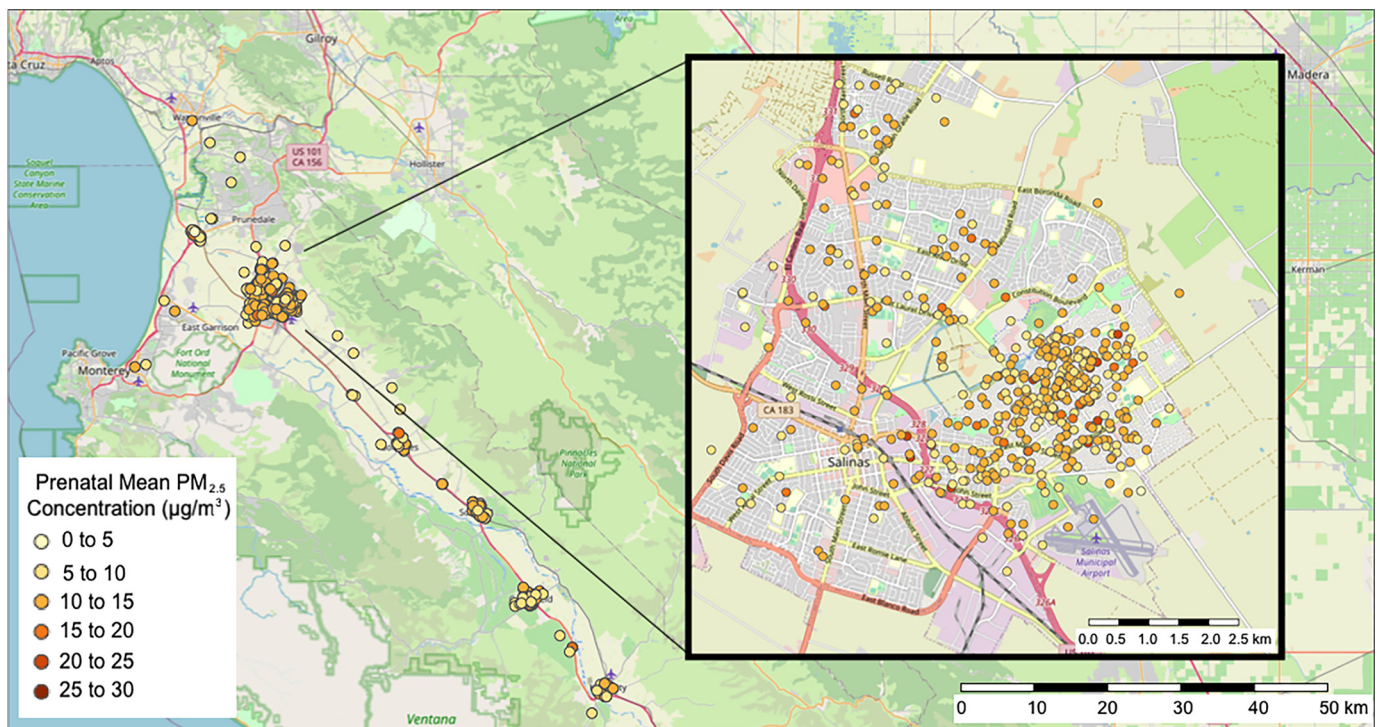
This cohort has many children of Mexican mothers (86% of mothers were born in Mexico) (Table 1). The cohort is low-income (72.5% of households at or below the poverty line), and nearly 40% of mothers had less than a seventh grade education. Though a large majority of recruited mothers (91% in CHAM1) primarily spoke Spanish as their dominant home language, by age 10.5 y roughly two-thirds of children had transitioned to English as their dominant academic language, meaning that they tested higher in English than Spanish on the screener and thus completed IQ testing in English. Mothers lived at 1.3 different addresses on average during pregnancy, and prenatal  $\text{PM}_{2.5}$  exposure averaged 10.6  $\mu\text{g}/\text{m}^3$  (Table 2), less than the current annual U.S. Environmental Protection Agency standard for fine particles (12  $\mu\text{g}/\text{m}^3$ ).<sup>4</sup>

Addresses where the mothers lived while pregnant with the cohort children are mapped (Figure 1). Though prenatal addresses are located throughout the Salinas Valley, many are clustered in the city of Salinas. As the map indicates, the presence of disparate ambient exposure levels at very similar residential locations (without a clear spatial pattern) makes clear that there is a substantial temporal component to the  $\text{PM}_{2.5}$  exposure received while *in utero* (i.e., seasonal variability), even though there is minimal seasonal variation in temperature in this area.

Linear models associating whole-pregnancy  $\text{PM}_{2.5}$  exposure with IQ at age 10.5 y demonstrated lower FSIQ [–1.79 IQ points (95% CI: –2.98, –0.58)] and WMIQ [–1.72 (95% CI: –2.98, –0.45)] associated with 3- $\mu\text{g}/\text{m}^3$  higher  $\text{PM}_{2.5}$  (3  $\mu\text{g}/\text{m}^3$  is roughly the IQR difference in this sample). Inverse associations were also observed with

**Table 2.** Exposure summary for the CHAMACOS cohort in the Salinas Valley, California, at the 10.5-y analysis (2011–2012,  $n = 568$ ).

Exposure window	Ambient $\text{PM}_{2.5}$ ( $\mu\text{g}/\text{m}^3$ )			Missing
	Mean (SD)	25th, 50th, 75th percentiles		
Overall <i>in utero</i>	10.63 (2.25)	8.94, 10.62, 12.53		246
First month of pregnancy	8.85 (4.89)	5.64, 6.47, 9.47		230
Second month of pregnancy	9.91 (5.45)	6.04, 7.69, 11.83		78
Third month of pregnancy	10.11 (5.61)	6.08, 7.95, 13.02		64
Fourth month of pregnancy	10.58 (5.70)	6.14, 8.32, 13.72		55
Fifth month of pregnancy	10.83 (5.75)	6.26, 8.40, 14.59		51
Sixth month of pregnancy	10.92 (5.92)	6.36, 8.36, 14.89		45
Seventh month of pregnancy	10.93 (5.67)	6.35, 8.92, 13.69		44
Eighth month of pregnancy	11.09 (5.74)	6.84, 8.99, 13.66		42
Ninth month of pregnancy	11.48 (6.36)	6.91, 8.90, 14.10		94



**Figure 1.** Map of prenatal addresses for the CHAMACOS cohort ( $n=568$ ). The larger map shows the entire Salinas Valley, and in the inset is the city of Salinas. The locations of CHAMACOS households are indicated with dots; these are shaded to represent the mean ambient  $PM_{2.5}$  exposure that an *in utero* CHAMACOS participant received at this address (with all *in utero* periods occurring between 1999–2002). All residential locations have had a small amount of random noise added to their location to protect participant privacy (i.e., have been jittered). This addition is the reason for a few implausible residential locations, such as in agricultural fields and on the airport runway. One address is not shown; that address was in the Los Angeles Valley and associated with a prenatal  $PM_{2.5}$  exposure between 25 and  $30 \mu\text{g}/\text{m}^3$ . Base map and data from OpenStreetMap and OpenStreetMap Foundation (<https://www.openstreetmap.org/>). Note: CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas.

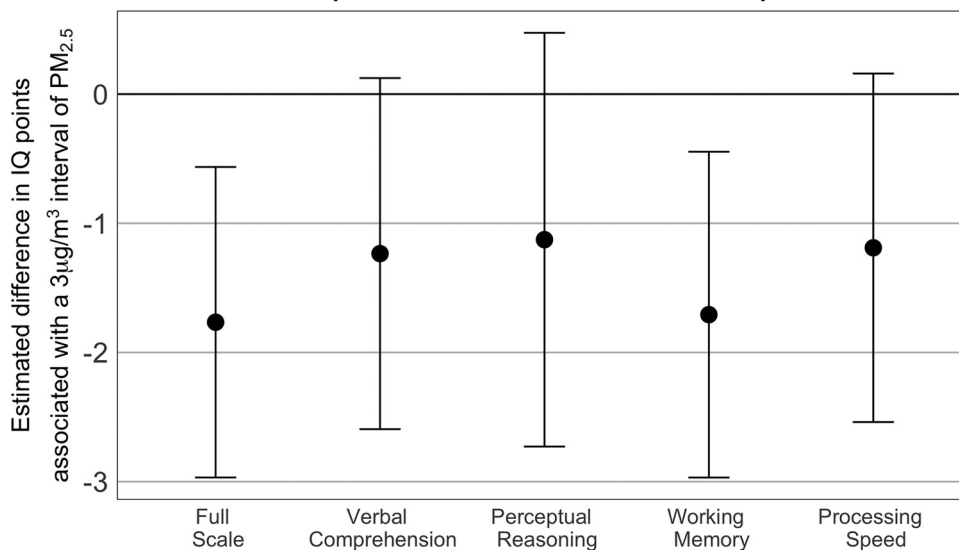
VCIQ [−1.25 (95% CI: −2.61, 0.11)], PRIQ [−1.14 (95% CI: −2.74, 0.46)], and PSIQ [−1.19 (95% CI: −2.54, 0.16)], though the CI crossed the null for these indices (Figure 2).

DLMs allowed the relationship between  $PM_{2.5}$  and IQ to vary over gestation, and the period from the fifth to seventh months of gestation emerged as the most susceptible window of exposure for potential effects of  $PM_{2.5}$  exposure on FSIQ [Figure 3; Table S3, “Main Distributed Lag Model Results for Full Scale IQ (age 10.5)”]. The figure presents the point estimate for IQ points per  $3\text{-}\mu\text{g}/\text{m}^3$  higher average ambient  $PM_{2.5}$  at each month of gestation (the solid line), with the 95% CI for those estimates in the shaded gray area. For example, at the sixth month following conception, a  $3\text{-}\mu\text{g}/\text{m}^3$  higher average ambient  $PM_{2.5}$  at the residential address is associated with a 2.4-point lower FSIQ at age 10.5 y (95% CI: −4.0, −0.8).

The pattern between  $PM_{2.5}$  and the subscales show different patterns over the course of gestation [Figure 4; Table S4, “Main Distributed Lag Model Results for IQ Subscales (age 10.5)”]. The Verbal Comprehension and Working Memory indices show a pattern similar to that of FSIQ; Verbal Comprehension and Working Memory scores are also lower with higher  $PM_{2.5}$ , with the largest effects seen at mid- to late gestation (5–7 months for VCIQ and 4–8 months for WMIQ). The patterns are less clear in Perceptual Reasoning and Processing Speed (with CIs that cross the null for all of gestation). Results were robust to the exclusion of the participants for whom a portion of the *in utero* period occurred in the year 1999 and also to the exclusion of children who had a sibling in the cohort (Table S5; Figure S3, “Sensitivity Analyses using LM and DLM models excluding children who: (a) had prenatal exposure time in 1999” and “(b) had a nontwin sibling in the cohort”).

When considering the exposure–outcome relationship based on the binary sex of the fetus (female vs. male), there are different patterns in the effects of  $PM_{2.5}$  on IQ subscale scores in childhood (Figure 5). A  $3\text{-}\mu\text{g}/\text{m}^3$  higher whole-pregnancy  $PM_{2.5}$  is associated with lower scores in Verbal Comprehension and Working Memory for males [in males, VCIQ −2.16 (95% CI: −4.28, −0.05); WMIQ −2.54 (95% CI: −4.50, −0.59)] in comparison with females [in females, VCIQ −0.32 (95% CI: −2.07, 1.44); WMIQ −1.24 (95% CI: −2.89, 0.42)], whereas females show larger decrements in PSIQ in comparison with males [female −2.42 (95% CI: −4.14, −0.69); male 0.20 (95% CI: −1.96, 2.35)]. CIs for sex by  $PM_{2.5}$  interaction terms for these three subscales (VCIQ, WMIQ, PSIQ) crossed the null, though the majority of the confidence band is below zero for VCIQ and WMIQ and above zero for PSIQ [per  $3 \mu\text{g}/\text{m}^3$  for males in comparison with females, there was an additional difference of −1.95 (95% CI: −4.70, 0.78) for VCIQ; −1.45 (95% CI: −4.00, 1.09) for WMIQ; 2.50 (95% CI: −0.21, 5.22) for PSIQ]. Lower IQ associated with  $PM_{2.5}$  exposure was similar in males and females for both FSIQ and PRIQ [male FSIQ −1.95 (95% CI: −3.85, −0.04); female FSIQ −1.56 (95% CI: −3.10, −0.01); male PRIQ −0.90 (95% CI: −3.40, 1.60); female PRIQ −1.09 (95% CI: −3.18, 1.01)]. Differences between males and females are also present in the time patterning of exposure (Figure 6; Table S6, “Distributed Lag Model Results for Full Scale IQ (age 10.5), stratified by sex”), with females showing a pattern of increasing difference in IQ associated with  $PM_{2.5}$  exposure throughout gestation, whereas males do not show a clear pattern and have a suggestion of a peak difference earlier in gestation (third–fourth months). A similar difference is present across all four subscales, with female fetuses having a steady decrease in IQ associated with  $PM_{2.5}$  exposure across gestation and male fetuses having a nonsignificant nadir around the fourth month

## Estimated change in IQ at age 10.5y (Full-Scale and Subscales)



**Figure 2.** Estimated difference in FSIQ and subscale IQ at age 10.5 y associated with  $3\text{-}\mu\text{g}/\text{m}^3$  higher  $\text{PM}_{2.5}$  exposure averaged over all of pregnancy for the CHAMACOS cohort in the Salinas Valley, California, at the 10.5-y analysis (2010–2013,  $n = 568$ ). Note: CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; FSIQ, full-scale IQ.

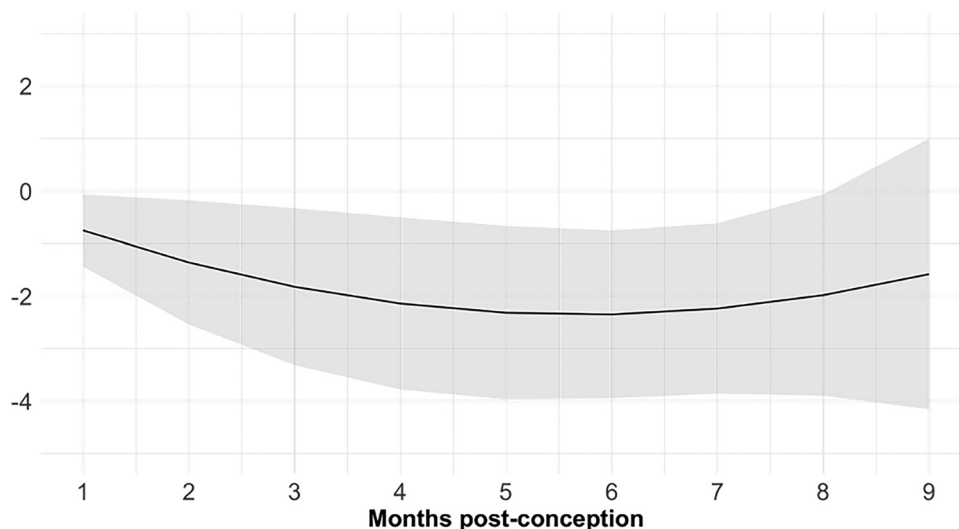
of gestation (Figure S4, “Sex Differences in the time patterning of  $\text{PM}_{2.5}$  effects on IQ across the different subscales,” and Table S7, “Distributed Lag Model Results for IQ subscales, stratified by sex”).

Analyses of the smaller, CHAM1-only cohort at age 7 y showed a similar pattern of results in both linear and nonlinear models, though CIs were wider, as expected (Figure S5 and Table S8, “Linear model results for IQ (full and subscales) testing at age 7”; Figure S6 and Table S9, “DLM model results for IQ (full and subscales) testing at age 7”). The subcohort present at age 7 y was similar to those tested at 10.5 y, except that more

children were using Spanish as their primary language at age 7 y than at age 10.5 y. (see Table S10, “Characteristics of the Cohort at the 7 y analysis”).

Sensitivity analyses using the CHAM1 data and IQ at age 7 y generally showed minimal differences in the  $\text{PM}_{2.5}$ –IQ association after adjusting for other exposures (Figure S7; Table S11, “Sensitivity Analyses, DLM, among CHAM1 participants only, age 7”).  $\text{PM}_{2.5}$  was associated with a larger IQ difference in the later months of pregnancy after adjusting for urinary DAPs or for the income and HOME score assessed in infancy rather than at

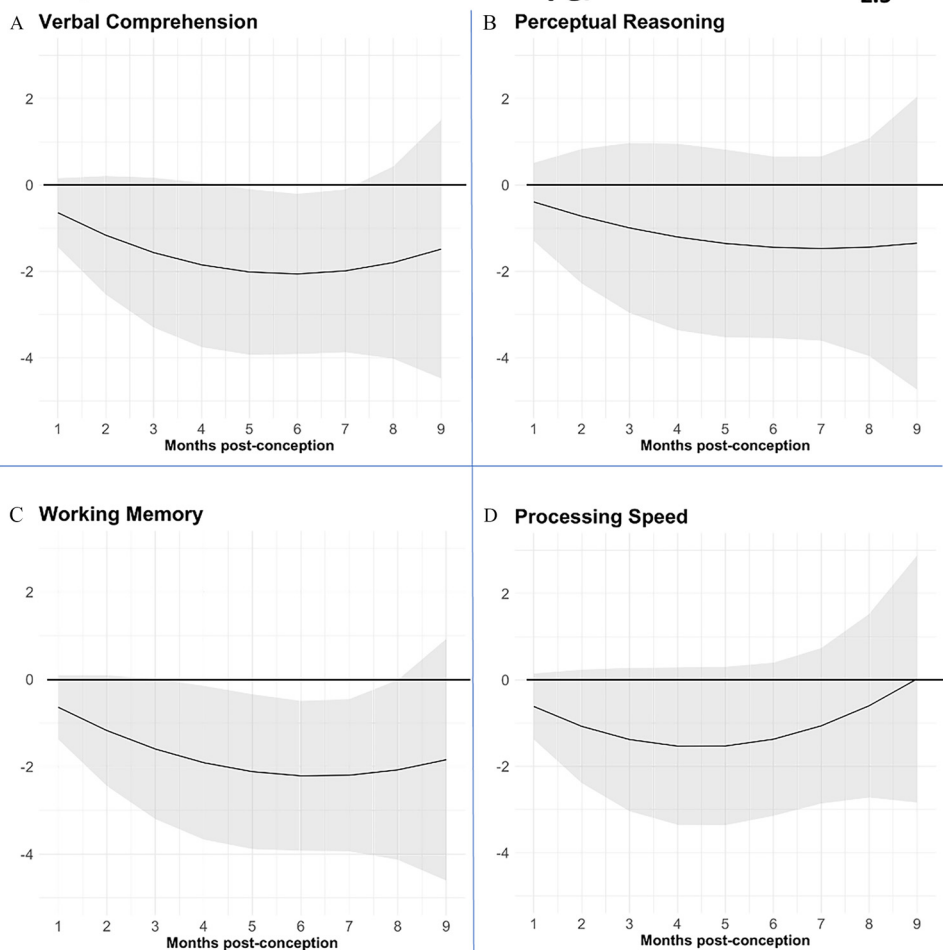
## Full-scale IQ difference associated with $3\text{ mcg}/\text{m}^3$ interval in $\text{PM}_{2.5}$



**Figure 3.** Estimated difference in FSIQ points at age 10.5 y associated with  $3\text{-}\mu\text{g}/\text{m}^3$  higher  $\text{PM}_{2.5}$  exposure each month of gestation, controlling for exposure at other months and flexibly modeling in the time dimension. These are calculated from the CHAMACOS cohort in the Salinas Valley, California, at the 10.5-y analysis (2010–2013,  $n = 568$ ). The solid line is the point estimate for the difference in IQ points at each month from distributed lag models, with the shaded area representing the 95% confidence interval of the estimate. Note: CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; FSIQ, full-scale IQ.



## IQ difference associated with a 3 $\mu\text{g}/\text{m}^3$ interval in $\text{PM}_{2.5}$



**Figure 4.** Estimated difference in IQ subscales at age 10.5 y associated with 3- $\mu\text{g}/\text{m}^3$  higher  $\text{PM}_{2.5}$  exposure each month of gestation, controlling for exposure at other months, and flexibly modeling in the time dimension. These are calculated from the CHAMACOS cohort in the Salinas Valley, California, at the 10.5-y analysis (2010–2013,  $n = 568$ ). The solid line is the point estimate for the difference in IQ points at each month from distributed lag models, with the shaded area representing the 95% confidence interval of the estimate. (A) VCIQ (B) PRIQ (C) WMIQ and (D) PSIQ. Note: CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; PRIQ, perceptual reasoning IQ; PSIQ, processing speed IQ; VCIQ, verbal comprehension IQ; WMIQ, working memory, IQ.

the time of neurodevelopmental testing. In addition, the association between  $\text{PM}_{2.5}$  and Processing Speed was moved toward the null once organophosphate flame retardants were added to the model, but the point estimate for the  $\text{PM}_{2.5}$ -Processing Speed association was near null regardless.

Based on findings in the sensitivity analyses from the CHAM1 cohort, the PUR estimate of nearby agricultural pesticide use was added as a sensitivity analysis at the 10.5-y assessment for CHAM1 and CHAM2. The sensitivity analysis using organophosphate and carbamate pesticide exposure as estimated with PUR data was unremarkable, and there were also minimal changes in the  $\text{PM}_{2.5}$ -IQ relationships seen after adjusting for maternal serum PBDEs, DDE, or DDT (Figure S8; Table S12, “Sensitivity Analyses, DLM, among full cohort at age 10.5”).

Sensitivity analyses using the CHAM1 data and IQ at age 10.5 y also generally showed minimal differences in the  $\text{PM}_{2.5}$ -IQ association after adjusting for other exposures (Figure S9; Table S13, “Sensitivity Analyses, DLM, CHAM1, age 10.5”).  $\text{PM}_{2.5}$  in late in pregnancy was associated with even lower FSIQ after adjusting for gas stoves in the home and when using the income and HOME score assessed in infancy rather than at the time of neurodevelopmental testing. In addition, the association between  $\text{PM}_{2.5}$  and processing speed was moved toward the positive once organophosphate flame retardants were added to the models (it moved

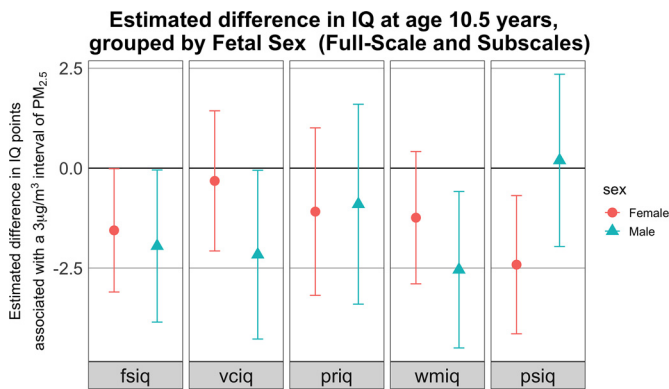
the estimate from negative to the null for most months, but from null into the positive for the last month of pregnancy), but the association between  $\text{PM}_{2.5}$  and processing speed were near null regardless.

Finally, sensitivity analyses exploring the effect of season of birth on the  $\text{PM}_{2.5}$ -IQ association suggest that the pattern of the relationships appear to also be robust to the inclusion multiple different markers for seasonality, though in some cases the results are attenuated. These analyses included explicitly controlling for season of birth and adjusting for schooling using the best estimate of schooling available to us [parent-reported grade at testing (Figure S10; Table S14, “Sensitivity Analyses, LM and DLM, accounting for schooling and season of birth”).

### Discussion

In this large, well-characterized cohort of preteens living in a rural to semirural agricultural community, we found lower WISC FSIQ and some subscales associated with average *in utero* exposure to fine PM. Using models that varied flexibly in the time dimension, we demonstrated that childhood IQ was particularly associated with  $\text{PM}_{2.5}$  exposure in mid- to late pregnancy (months 5–7). These results were robust to multiple sensitivity analyses.





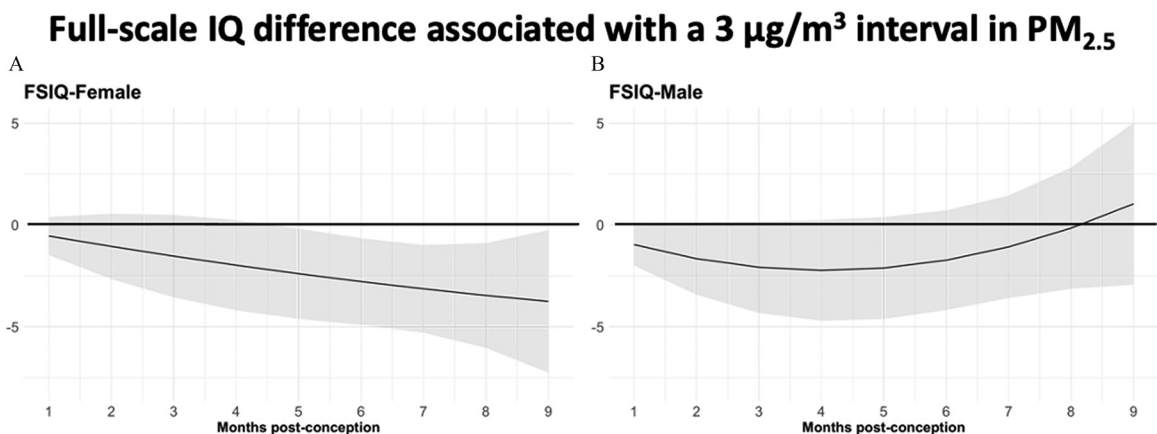
**Figure 5.** Estimated difference in FSIQ and subscale IQ at age 10.5 y associated with  $3\text{-}\mu\text{g}/\text{m}^3$  higher  $\text{PM}_{2.5}$  exposure averaged over all of pregnancy, stratified by assigned sex of the fetus, dichotomized as female vs. male. These are calculated from the CHAMACOS cohort in the Salinas Valley, California, at the 10.5-y analysis (2010–2013,  $n = 568$ ). Note: CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; FSIQ, full-scale IQ.

An interesting finding was that the  $\text{PM}_{2.5}$ –IQ relationship may be modified by the sex of the fetus, with males having lower verbal comprehension and working memory associated with average prenatal exposure to  $\text{PM}_{2.5}$ , and females having lower processing speed, though all had lower FSIQ. The prenatal period with highest susceptibility also seemed to vary between male and female fetuses: The lowest childhood IQ– $\text{PM}_{2.5}$  association occurred earlier in those assigned male at birth than in those assigned female. However, these differences between the association for male and female fetuses may also reflect some random variability in the exposures and outcomes within the sample.

Several other cohort studies have found decrements in cognition associated with prenatal  $\text{PM}_{2.5}$  exposure, though these have been in younger children and in more urban environments. A birth cohort in Mexico City found that prenatal  $\text{PM}_{2.5}$  exposure was negatively associated with cognitive and language development at multiple testing points through age 2 y, with the largest difference seen for exposure in the third trimester.<sup>14</sup> A birth cohort in multiple Spanish cities demonstrated a negative association between prenatal  $\text{PM}_{2.5}$  exposure and cognition at age 15 months<sup>15</sup> as well as with measures of memory at age 4–6 y,

but the latter only among children identified as male.<sup>44</sup> A recent study in New York assessed the relationship between prenatal  $\text{PM}_{2.5}$  exposure and IQ at age 6.5 y in a birth cohort that, like CHAMACOS, was low-income and largely Hispanic, but which was smaller and located in an urban area.<sup>13</sup> Using a flexible modeling strategy that was similar to ours, those investigators also showed a pattern of lower IQ score associated with higher  $\text{PM}_{2.5}$  exposure late in gestation (after approximately 30 wk). We were intrigued to see that their pattern for changes in FSIQ with late-pregnancy  $\text{PM}_{2.5}$  exposure suggested a larger difference in children identified as boys (with a 1–2 point lower FSIQ associated with a  $10\text{-}\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$ ), whereas we found a larger effect in those identified as female at birth with late gestation exposure. In a birth cohort in Italy, no significant relationships were found between prenatal  $\text{PM}_{2.5}$  exposure and IQ at age 7 y, though there was a trend toward lower Perceptual Reasoning and Processing Speed subscales [a  $10\text{-}\mu\text{g}/\text{m}^3$  higher average pregnancy  $\text{PM}_{2.5}$  was associated with 3.1-point lower perceptual organization (95% CI:  $-9.5, 3.4$ ) and a 4.0 lower processing speed (95% CI:  $-10, 2.4$ )].<sup>20</sup> A prospective birth cohort in urban and suburban Massachusetts found that prenatal traffic-related pollution exposure was associated with lower cognition at age 8 y but did not find a specific relationship with  $\text{PM}_{2.5}$  exposure.<sup>45</sup>

Sensitivity analyses suggest that our results are robust to consideration of a variety of other chemicals to which this population has been exposed, as well as to excluding portions of the cohort. As suggested by the sensitivity analysis using the HOME score and poverty data from infancy (among those cohort members for whom it was available), the use of these variables from the time of testing may have introduced some misclassification that biased our results to the null. Thus, the use of these variables from late childhood may mean that we are *underestimating* the effects of prenatal  $\text{PM}_{2.5}$  on IQ. Though explicitly accounting for season in the model moves the estimates toward the null, there is still a pattern of decreases in IQ scores associated with  $\text{PM}_{2.5}$  exposures. Moreover, because the exposure is seasonal, including seasonality in the model may be an overadjustment, adjusting away some of the true relationship between  $\text{PM}_{2.5}$  and IQ. The fact that the pattern of decreases in IQ remains, even with potential overadjustment, suggests that there may be a true relationship between  $\text{PM}_{2.5}$  and IQ, acknowledging that it may be only one factor among a seasonal milieu of factors that affect IQ.



**Figure 6.** Estimated difference in FSIQ at age 10.5 y associated with  $3\text{-}\mu\text{g}/\text{m}^3$  higher  $\text{PM}_{2.5}$  exposure each month of gestation, controlling for exposure at other months and flexibly modeling in the time dimension. These are calculated from the CHAMACOS cohort in the Salinas Valley, California, at the 10.5-y analysis (2010–2013,  $n = 568$ ). The solid line is the point estimate for the difference in IQ points at each month from distributed lag models, with the shaded area representing the 95% confidence interval of the estimate. (A) results for those assigned female at birth and (B) results for those assigned male at birth. Note: CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; FSIQ, full-scale IQ.

Though we are not aware of any other studies associating prenatal PM<sub>2.5</sub> exposure with cognitive function in preteen years/late childhood, a recent neuroimaging study demonstrated white matter changes in 9–12 y old children was associated with PM<sub>2.5</sub> exposure *in utero*,<sup>46</sup> providing further support for neurocognitive effects later in childhood, as we have found. Thus, to our knowledge, our study is the first in a cohort of preteens outside a major metropolitan area, and we found a somewhat larger effect of PM<sub>2.5</sub> on childhood IQ than has previously been seen. Because less-urbanized settings have more PM<sub>2.5</sub> from sources not related to traffic or power generation, such as biomass burning and windblown dust, and fewer combustion-related particles,<sup>2</sup> these differences in effect could be the result of differences in PM composition, or that developmental disruption causes effects that alter the cognitive trajectory and thus appear more pronounced as children get older.

Recently demonstrated effects of PM<sub>2.5</sub> on neurodevelopment using laboratory and animal data provide a strong scientific premise for an association between PM<sub>2.5</sub> exposure and neurodevelopment in children.<sup>47</sup> PM is directly toxic to human neurons,<sup>48</sup> can change neuron gene expression,<sup>49,50</sup> and may have a role in central nervous system myelination as well.<sup>51</sup> These direct effects are problematic, given that PM (especially the ultrafine particulate fraction, those <0.1 microns in diameter) can enter the systemic circulation, can cross the blood–brain barrier, and has been found in the brain parenchyma.<sup>47</sup> In addition to potential direct effects of PM, increases in inflammation and oxidative stress secondary to air pollution exposures have long been associated with cardiovascular and lung diseases but are increasingly recognized as contributors to central nervous system pathology as well.<sup>52</sup> Rodents have demonstrated increases in neuroinflammation following exposure to fine particles, including prenatal exposure.<sup>53–55</sup> In particular, prenatal diesel exhaust exposure, which has a large PM component,<sup>47</sup> induced long-term changes in the microglia, the resident immune cells in the brain, into adulthood.<sup>53</sup> Rodents exposed to PM have also shown deficits on tests of memory.<sup>56,57</sup> Furthermore, young people from urban centers in Mexico who died accidentally had more neuroinflammation on autopsy than those from smaller cities, a finding the authors ascribe to long-term air pollution exposure, mirroring the animal studies.<sup>58</sup> It is known that the functional connectivity of the human fetal brain increases substantially in the second half of pregnancy,<sup>59,60</sup> meaning this is a period that could be particularly susceptible to environmental insults.

How brain growth and development relate to biologic sex is incompletely understood, with potential roles for hormonal modifications, direct effects of genes on sex chromosomes, and epigenetic differences.<sup>61,62</sup> Studies in transgender people, which often show structural brain patterns more congruent with their experienced gender than with their assigned sex, highlight how much there is to learn in this area.<sup>63</sup> Yet, studies using binary categorizations of sex into male and female suggest that fetal brain development has some differences associated with fetal sex, including differences in neuronal connectivity,<sup>64</sup> which could differentially affect susceptibility to environmental insults. Animal studies have also demonstrated sex differences in critical windows of PM exposure; for example in a group of rats exposed to ultrafine particles, the male rats had increased impulsivity when exposed during the period of neurodevelopment, whereas female rats had these effects when exposed in adulthood.<sup>56</sup> As mentioned above, microglial cells are thought to play a key role in priming of the neurological system by air pollution,<sup>65</sup> and sex differences in the activation of microglial cells have been noted, with larger effects seen in male rodents. Thus, sex differences in the effects of PM<sub>2.5</sub> exposure on neurodevelopment and cognition are entirely plausible. Our

results suggest that the effects are somewhat different depending on the subscale considered, and that differences in the timing of exposure could be relevant.

Small changes in cognition associated with air pollution would be particularly important to understand because of the ubiquity of the exposure. Studies of other environmental exposures, such as lead, have indicated a large social cost to the loss of IQ points.<sup>66</sup> For example, a Belgian study estimated that in a population of adolescents from 2003 to 2004, among those with elevated lead there was an average IQ loss of 1.67 points per individual, and that this had a social cost of 1.8 billion Euros per 100,000 people.<sup>66</sup>

Strengths of this study include the use of a well-characterized cohort in which we were able to conduct many sensitivity analyses to look for changes in the PM<sub>2.5</sub>–IQ relationship associated with coexposures. We also have robust neuropsychological testing in the primary language of the child, whether Spanish or English. The use of newly available pollution surfaces that provide good spatial variability in rural areas allowed us to assess a cohort that previously had no such exposure assessment available. In addition, the flexible modeling strategy allowed us to evaluate exposures at multiple time points in a conservative manner, such that each month's exposure–response relationship controlled for exposure at the other months and allowed for identification of a susceptible window (5–7 months) that might not have been apparent if using the common trimester periods. If the body of literature were able to clearly establish susceptible windows, these could be used to counsel pregnant people to especially minimize air pollutant exposure during those periods.

Although the unique features of this cohort (including rural and semirural location and older children with prenatal exposure data) add a new dimension to the extant literature, these features also limit the generalizability of findings from the cohort, meaning that the findings may not generalize to the entire population of children in the United States, especially those living in more urban environments. It would be valuable to have further study in a more representative cohort, especially one large enough to analyze births occurring within a single season. Because residential history was incomplete for some of the cohort, we had to impute data for those exposures; uncertainty due to the multiple imputation has been included in the results.

In summary, in this large, well-characterized cohort of rural preteens growing up in an agricultural area, we have found that slightly higher outdoor PM<sub>2.5</sub> exposure *in utero* was associated with small decrements in IQ in late childhood. Though a 1- or 2-point change in IQ is unlikely to be meaningful for an individual, shifting the entire distribution of IQ down by a point or two could greatly change the number of individuals that qualify for intervention services. Because air pollution exposures are inequitably distributed, with low-income communities and communities of color exposed to higher levels of air pollution,<sup>67</sup> shifting the entire distribution of IQ down for these populations could have important implications, further contributing to systemic injustices. Our findings suggest that, at levels allowable within current U.S. EPA air quality standards, small fluctuations in exposure to fine PM might have enduring changes on childhood cognition.

## Acknowledgments

The authors thank K. Long and S. Rauch, the CHAMACOS data managers, for their prompt replies to queries and unending patience as we worked through this analysis. Eternal gratitude to the CHAMACOS families for allowing us snapshots of their lives and, in doing so, helping to teach us all.

The collection of data used in this analysis was supported by the following grants: National Institute of Environmental Health

Sciences (NIEHS) P01-ES009605, NIEHS R01-ES015572, NIEHS R01-ES017054, U.S. EPA RD 83171001, U.S. EPA RD 82670901, U.S. EPA RD 83451301, National Institute for Occupational Safety and Health R01 OH007400. This analysis did not receive any specific support from funding agencies in the public, commercial, or not-for-profit sectors.

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This manuscript is based on a chapter of a dissertation published by the University of California Berkeley in partial fulfillment of S.M.H.'s doctoral degree, but that dissertation is currently embargoed and not publicly available.

These data (de-identified) and associated documentation/metadata will be made available to others in the scientific community by the principal investigator of the study, under a data-sharing agreement consistent with both the University of California and NIH data-sharing policies.

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