Socioeconomic Disparities and Sexual Dimorphism in Neurotoxic Effects of Ambient Fine Particles on Youth IQ: A Longitudinal Analysis

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Abstract

Mounting evidence indicates that early-life exposure to particulate air pollutants pose threats to children's cognitive development, but studies about the neurotoxic effects associated with exposures during adolescence remain unclear. We examined whether exposure to ambient fine particles ($PM_{2.5}$) at residential locations affects intelligence quotient (IQ) during pre-/early-adolescence (ages 9-11) and emerging adulthood (ages 18-20) in a demographically-diverse population (N = 1,360) residing in Southern California. Increased ambient $PM_{2.5}$ levels were associated with decreased IQ scores. This association was more evident for Performance IQ (PIQ), but less for Verbal IQ, assessed by the Wechsler Abbreviated Scale of Intelligence. For each inter-quartile (7.73 $\mu g/m^3$) increase in one-year $PM_{2.5}$ preceding each assessment, the average PIQ score decreased by 3.08 points (95% confidence interval = [-6.04, -0.12]) accounting for within-family/within-individual correlations, demographic characteristics, family socioeconomic status (SES), parents' cognitive abilities, neighborhood characteristics, and other spatial confounders. The adverse effect was 150% greater in low SES families and 89% stronger in males, compared to their counterparts. Better understanding of the social disparities and sexual dimorphism in the adverse $PM_{2.5}$–IQ effects may help elucidate the underlying mechanisms and shed light on prevention strategies.

Introduction

Intelligence is a broad collection of cognitive abilities including reasoning, problem solving, attention, memory, knowledge, planning, and creativity sub-served by different parts of the brain. Intelligence quotient (IQ), a global measure of intellectual development, is an

important determinant of national wealth and economic growth (1). It is estimated that a single point change of IQ could bring a gain of $55 billion to $65 billion (in year 2000 dollars) for a single birth cohort of US population (2). At the individual level, childhood IQ is a powerful predictor of later-life socioeconomic success (3). Although the brain size has reached 90% of adult size by age 5 (4), development of efficient brain structure and networks in early childhood continues into adolescence. There is an increasing recognition that IQ can change significantly during adolescence (5).

Adolescence, defined by the World Health Organization (6) as the period from ages 10 to 19 (after childhood and before adulthood), is a transition stage characterized by many significant biological and social changes. Human growth during adolescence is greatly influenced by changes in hormone production and neuroendocrine response (7) with the beginning of reproductive lifespan, while the developing brain is undergoing further remolding of gray matter (e.g., cortical thinning) (8) and white matter (e.g., continuing myelination of axons) (9). The growing adolescents start to disengage from their parents and exert more autonomous control on their own decisions and actions. These biological and social changes not only suggest that plasticity in IQ development continues with interactions among brain, behavior, and social context, but that adolescent brains are also vulnerable to environmental insults from various neurotoxins. As the brain network matures by the end of adolescence (4, 10), IQ is expected to remain relatively stable until the advent of aging during late adulthood.

Environment in general can explain up to 50% of individual difference in IQ, with its resulting influence depending on socioeconomic context (11) and age (12). Research on environment-mediated IQ effect is thus important as such knowledge may help identify potentially modifiable factors and develop timely intervention to reduce disparities in cognitive

development. While there has been extensive research on IQ development and social adversities in the family and school environments (13-15), influences of physical environments are understudied.

Exposure to ambient particulate air pollutants, including $PM_{2.5}$ (particulate matter [PM] with aerodynamic diameter <2.5 μm), has emerged as a novel environmental neurotoxin affecting brain development in children (16). The hypothesized link of child intellectual development with early-life PM exposures has been examined in several birth cohorts (17-27), including four based in the US and three from Poland, China, and Italy. Although most of the reported findings generally showed a negative association between PM exposure and IQ in children, each of these birth cohort studies included only one-time assessment on intellectual development. One small longitudinal study (28) compared children living in highly-polluted Mexico City (n=20) and the control group (n=10) from a clean-air area (matched on age and socioeconomic status), and reported in their post-hoc analyses the difference in IQ at baseline disappeared after one year of follow-up when the matched cohort became 8 years old. Therefore, it remains unclear whether PM exposure could still exert adverse effect on intellectual development during adolescence. The primary aim of our current study was to examine the adverse effect of $PM_{2.5}$ on IQ, using longitudinal data spanning a 12-year period. Because previous studies have been underpowered to assess the potential heterogeneity in the reported associations, our secondary aim was to evaluate whether the putative neurotoxic adverse effect on intellectual development during adolescence, if any, could vary by sex and family socioeconomic status (SES) based on a relatively large sample (N=1360).

Materials and Methods

Participants

Participants were drawn from the University of Southern California (USC) Risk Factors for Antisocial Behavior (RFAB) twin study. RFAB is a prospective longitudinal study of the interplay of genetic, environmental, social, and biological factors on the development of antisocial behavior from pre-adolescence to early adulthood. Participating families were recruited from communities in Los Angeles and surrounding counties, with the resulting sample representative of the socio-economically-diverse multi-ethnic population residing in the greater Los Angeles area (29). To date, five waves of data have been collected from 780 twin pairs (N=1,569 in total including triplets). Study protocols were approved by the USC Institutional Review Board. Informed consents were obtained from all participants (after reaching adulthood) or their parents/guardians (during pre-adolescence).

The current study utilized IQ data collected from the RFAB cohort during pre-/early-adolescence (aged 9-11) and emerging adulthood (aged 18-20). Our analytic sample was limited to participants with at least one valid IQ score and a corresponding estimate of air pollution exposure, plus complete data on major sociodemographic characteristics (including age, gender, race/ethnicity and family SES). A total of 1,360 subjects (from 687 families) were retained in the main analyses, including 810 tested during pre-/early- adolescence only, 170 during emerging adulthood only, and 380 at both age periods. These three groups did not differ in the distributions by sex, race/ethnicity, or family SES (S1 Table). Subjects tested with higher IQ scores at baseline were more likely to participate in the follow-up, but their IQ scores were no different from those only tested during the emerging adulthood. The $PM_{2.5}$ exposure 1-year before the baseline testing was slightly lower among subjects tested twice, as compared to those not participating in the second testing (20.28 ± 2.82 vs. 20.59 ± 2.53; p = .06), but there was no

statistically significant difference in the $PM_{2.5}$ exposure estimate at the follow-up between the two groups assessed during emerging adulthood.

Assessment of IQ

IQ was measured using the Wechsler Abbreviated Scale of Intelligence (WASI) (30). The WASI provides a quick and reliable assessment of an individual's verbal, nonverbal, and general cognitive functioning. The WASI yields two standardized scores: Verbal IQ and Performance IQ. Verbal IQ (VIQ) is based on subtests Vocabulary and Similarities, whereas Performance IQ (PIQ) is based on subtests Block Design and Matrices. Correlations between PIQ and VIQ ranged from 0.48 (pre-/early- adolescence) to 0.56 (emerging adulthood) in the current study. The six-month test-retest reliability (n = 60) was satisfactory for both PIQ (r = 0.79) and VIQ (r = 0.78).

Estimation of Particulate Matter Exposure

Residential Location Data and Geocoding. Residential addresses for RFAB families were prospectively collected through self-reports every 2 to 3 years. Addresses were geocoded using services of the USC Spatial Sciences Institute, which successfully matched residences by exact parcel locations or specific street segments for 98.6% of participating families. The remaining addresses were checked for correctness using Google Earth and thereafter geocoded.

Spatiotemporal modeling for $PM_{2.5}$. Daily $PM_{2.5}$ (PM with aerodynamic diameters < 2.5μm) concentrations were obtained from U.S. EPA Technology Transfer Network for the years 2000 to 2014. A spatiotemporal model based on the measured $PM_{2.5}$ concentrations was constructed (with 10-fold cross-validation R^2=0.74-0.79) to estimate monthly average $PM_{2.5}$ concentrations for each subject's geocoded residential location (see the A2 in S1 File for more details). A time series of monthly $PM_{2.5}$ concentrations for the 2000-2014 period was constructed

and monthly estimates were aggregated to represent $PM_{2.5}$ exposure 1-, 2-, and 3-years preceding each IQ assessment.

Relevant Covariates

To control for potential confounding, four groups of covariates were examined: (A) age, gender, race/ethnicity, family SES, and parents' cognitive abilities; (B) parent-reported neighborhood quality, neighborhood SES (nSES), traffic density and neighborhood greenspace; (C) CALINE4-estimated total annual nitrogen oxides (NO_x) and temperature/humidity; (D) parent-level risk factors (operationalized as maternal smoking during pregnancy and parental perceived stress). Covariates (A) and (B) were considered as the most relevant confounders as they were known to predict IQ and also likely influence where people chose to reside (and thus their exposure to ambient $PM_{2.5}$). More details about the selection and measurement of covariates are available in A3 of S1 File.

Statistical Analyses

Three-level mixed-effects models regressing IQ scores (Full-Scale IQ, VIQ and PIQ separately) at each assessment on the corresponding $PM_{2.5}$ exposures and accounting for both within-family (random intercepts and slopes of $PM_{2.5}$ effects by families) and within-individual (random intercepts by individual) covariance were constructed as the base models. These models were then adjusted for two sets of covariates incrementally: (1) individual and family characteristics—age (as a continuous variable or dichotomized as pre-/early- adolescence vs. emerging adulthood), sex, race/ethnicity, family SES, and parental cognitive abilities; and (2) neighborhood characteristics—nSES, neighborhood greenspace (1000m radius buffer, 1-year preceding test), traffic density (300m radius buffer), and parent-reported neighborhood quality. We conducted further sensitivity analyses by adding the following covariates to the fully

adjusted models: ambient temperature and humidity (1-year preceding); total annual NO_x; and parental risk factors.

Three separate pre-planned moderation analyses were conducted to examine whether the putative $PM_{2.5}$ effects on IQ varied by age (pre-/early- adolescence vs. emerging adulthood), sex, and SES levels (continuous), based on the interaction term between exposure and the putative moderator, each entering the fully adjusted model one by one. All the analyses were implemented using SAS 9.4.

Results

Descriptive Statistics

Participants' IQ scores were on average 101.62 (VIQ, SD = 17.93) and 100.25 (PIQ, SD = 17.98) during pre-/early- adolescence (9.59 ± 0.58 years); 104.47 (VIQ, SD = 16.01) and 102.71 (PIQ, SD = 16.01) during emerging adulthood (19.44 ± 1.07 years). About 99% of participants during pre-/early- adolescence and 78% during emerging adulthood were exposed to $PM_{2.5}$ (1-year preceding the IQ assessment) levels exceeding the EPA annual standard ($12ug/m^3$).

Population characteristics by quartiles of $PM_{2.5}$ (Table 1) and Full-Scale IQ (Table 2) at the study baseline (i.e., the first valid IQ assessment) were examined. The decrease of quartiles of $PM_{2.5}$ exposure across age reflected the higher ambient $PM_{2.5}$ levels in earlier years of testing. Compared to their counterparts, those with relatively higher $PM_{2.5}$ exposures were mostly Hispanics and Blacks, from lower quality neighborhoods (characterized by lower nSES, lower greenness, more negative perception of neighborhood quality and higher annual NOx), residing in locations with higher temperature and relative humidity, and children whose parents reported maternal smoking during pregnancy, displayed poorer cognitive abilities, and perceived more

stress. On the other hand, children with lower IQ score at baseline were more likely to be Hispanics, Black, and mixed racial/ethnicities; grow up in lower SES households; have parents perceiving more stress, smoking during pregnancy and demonstrating lower cognitive abilities; and reside in locations with lower neighborhood qualities and higher relative humidity. For population characteristics by quartiles of VIQ and PIQ, please refer to S2 and S3 Tables.

Main-effect of $PM_{2.5}$ on IQ Scores

In the base models, higher one-year average $PM_{2.5}$ predicted lower scores in the full-scale IQ, VIQ, and PIQ (Table 3). Although $PM_{2.5}$ exposures were still negatively associated with full-scale IQ and VIQ in the adjusted analyses, none of these associations reached statistical significance. However, the observed adverse $PM_{2.5}$ effects on PIQ were evident in the adjusted models. For each inter-quartile (7.73 $\mu g/m^3$) increase in 1-year $PM_{2.5}$, the average PIQ score decreased by 3.08 points (95% CI = [-6.04, -0.12]) in the mixed-effect model accounting for within-family/within-individual correlations, demographic characteristics, family SES, parents' cognitive abilities, perceived neighborhood quality, nSES, traffic density, and measure of greenspace (Adjusted Model-II). The observed adverse $PM_{2.5}$-PIQ effect remained robust in sensitivity analyses with further statistical adjustment for temperature and humidity (Sensitivity Model-1), total annual NO_x (Sensitivity Model-II), and parental stress and maternal smoking during pregnancy (Sensitivity Model-III).

Additional analyses on 2- and 3-year average $PM_{2.5}$ exposure effects on IQ (full-scale; VIQ; PIQ) revealed a fairly similar pattern of associations across different temporal scales of exposure (S1 Fig). Post-hoc analyses were also conducted to explore the possibility of differential impact of $PM_{2.5}$ on each component score of PIQ (Block Design; Matrix Reasoning)

Table 1. Population Characteristics in Relation to the Overall[a] $PM_{2.5}$ Exposure 1-Year Prior to IQ Assessment

Population Characteristics at Baseline[b]	N[c]	Quartile of $PM_{2.5}$ 2.14-16.08 Median=13.55 (N=339)	16.09-18.67 Median=17.56 (N=341)	18.68-21.13 Median=20.16 (N=340)	21.14-25.36 Median=22.76 (N=340)	p-value[d]
Age	1360	16.18 ± 3.12	12.76 ± 2.56	10.11 ± 1.73	9.63 ± 0.62	<0.0001
Gender						0.0970
Male	690	169 (24.49%)	192 (27.83%)	169 (24.49%)	160 (23.19%)	
Female	670	170 (25.37%)	149 (22.24%)	171 (25.52%)	180 (26.87%)	
Ethnicity						<0.0001
Caucasian	378	147 (38.89%)	83 (21.96%)	80 (21.16%)	68 (17.99%)	
Hispanic	504	81 (16.07%)	128 (25.40%)	129 (25.6%)	166 (32.94%)	
Black	188	31 (16.49%)	46 (24.47%)	57 (30.32%)	54 (28.72%)	
Asian	58	12 (20.69%)	21 (36.21%)	17 (29.31%)	8 (13.79%)	
Other or Mixed	232	68 (29.31%)	63 (27.16%)	57 (24.57%)	44 (18.97%)	
Household socioeconomic status	1360	45.35 ± 11.21	42.22 ± 11.19	41.80 ± 12.03	39.70 ± 11.07	<0.0001
Neighborhood socioeconomic status	1360	0.31 ± 0.93	-0.10 ± 0.90	-0.07 ± 1.07	-0.39 ± 0.85	<0.0001
Neighborhood quality[e]	1344	26.18 ± 9.09	26.68 ± 9.41	28.97 ± 10.70	29.52 ± 11.85	<0.0001
Maternal smoking during pregnancy						0.0037
No	1216	309 (25.41%)	312 (25.66%)	288 (23.68%)	307 (25.25%)	
Yes	84	16 (19.05%)	13 (15.48%)	34 (40.48%)	21 (25.00%)	
Parental WJ Score – Letter Word	1099	59.96 ± 9.88	54.23 ± 7.43	52.49 ± 5.81	54.07 ± 6.78	<0.0001
Parental WJ Score – Word Attack	1099	25.52 ± 5.30	23.08 ± 5.14	23.11 ± 4.74	22.82 ± 5.16	<0.0001
Parental Stress	1346	30.52 ± 8.14	31.88 ± 8.40	32.94 ± 8.54	32.99 ± 8.25	0.0002
NDVI 1-year prior in 1000m area	1360	0.33 ± 0.08	0.33 ± 0.07	0.32 ± 0.09	0.30 ± 0.07	<0.0001
Traffic density in 300m area	1360	73.95 ± 146.78	90.6 ± 138.17	87.38 ± 139.30	84.37 ± 127.64	<0.0001
Temperature 1-year prior (°C)	1360	17.25 ± 0.81	17.50 ± 0.68	17.42 ± 0.79	17.58 ± 0.56	<0.0001
Relative humidity 1-year prior (%)	1360	58.85 ± 7.60	61.08 ± 6.08	63.49 ± 5.95	62.85 ± 4.22	<0.0001
Total annual NOx (ppb)	1360	18.70 ± 19.02	31.30 ± 20.86	34.88 ± 22.69	33.94 ± 18.92	<0.0001

a. Overall exposure defined as the individual-level average of 1-year exposure estimated prior to each IQ assessment
b. Baseline referred to the first valid assessment of IQ (either Wave 1 or Wave 5 in this study).
c. Total number of subjects decrease slightly due to missing values.
d. P-value from the ANOVA test comparing means of continuous variables or Pearson χ^2 test comparing the distribution of VIQ across categorical variables across the quartile of outcome variable.
e. Higher score represented a more negative perception of neighborhood quality.

Table 2. Population Characteristics at Baseline in Relation to Full-Scale IQ

Population Characteristics	N[a]	Quartile of IQ				
		45-92 Median=83	93-103 Median=99	104-114 Median=109	115-149 Median=121	
	1360	(N=351)	(N=327)	(N=345)	(N=337)	p-value[b]
Age	1360	10.73 ± 3.01	10.55 ± 2.85	10.83 ± 3.27	10.91 ± 3.40	0.4707
Gender						0.5498
Male	690	176 (25.51%)	164 (23.77%)	168 (24.35%)	182 (26.38%)	
Female	670	175 (26.12%)	163 (24.33%)	177 (26.42%)	155 (23.13%)	
Ethnicity						<0.0001
Caucasian	378	28 (7.41%)	58 (15.34%)	106 (28.04%)	186 (49.21%)	
Hispanic	504	182 (36.11%)	156 (30.95%)	110 (21.83%)	56 (11.11%)	
Black	188	73 (38.83%)	49 (26.06%)	40 (21.28%)	26 (13.83%)	
Asian	58	11 (18.97%)	16 (27.59%)	20 (34.48%)	11 (18.97%)	
Other or Mixed	232	57 (24.57%)	48 (20.69%)	69 (29.74%)	58 (25.00 %)	
Household socioeconomic status	1360	36.65 ± 9.70	39.14 ± 11.31	44.43 ± 10.73	48.94 ± 10.36	<0.0001
Neighborhood socioeconomic status	1360	-0.54 ± 0.59	-0.16 ± 0.90	0.07 ± 0.91	0.39 ± 1.17	<0.0001
Neighborhood quality[c]	1344	30.01 ± 12.02	27.58 ± 10.67	27.4 ± 9.39	26.35 ± 8.96	<0.0001
Maternal smoking during pregnancy						<0.0001
No	1216	296 (24.34%)	295 (24.26%)	308 (25.33%)	317 (26.07%)	
Yes	84	34 (40.48%)	21 (25.00%)	21 (25.00%)	8 (9.52%)	
Parental WJ Score – Letter Word	1099	53.34 ± 8.23	54.21 ± 8.06	55.51 ± 7.68	57.33 ± 7.67	<0.0001
Parental WJ Score – Word Attack	1099	22.31 ± 6.30	22.75 ± 5.09	24.02 ± 4.57	25.43 ± 3.81	<0.0001
Parental Stress	1346	33.70 ± 8.57	32.60 ± 8.05	31.95 ± 8.72	30.07 ± 7.76	<0.0001
NDVI 1-year prior in 1000m area	1360	0.29 ± 0.06	0.31 ± 0.08	0.33 ± 0.08	0.35 ± 0.09	<0.0001
Traffic density in 300m area	1360	90.85 ± 146.9	88.42 ± 148.94	86.99 ± 142.76	69.87 ± 109.65	0.1801
Temperature 1-year prior (°C)	1360	17.41 ± 0.70	17.47 ± 0.72	17.46 ± 0.77	17.41 ± 0.72	0.6110
Relative humidity 1-year prior (%)	1360	62.62 ± 5.92	61.64 ± 6.27	61.23 ± 6.65	60.76 ± 6.37	0.0010
Total annual NOx (ppb)	1360	32.80 ± 21.83	31.25 ± 22.38	28.74 ± 21.58	26.01 ± 19.21	0.0002

a. Total number of subjects decrease slightly due to missing values.

b. P-value from the ANOVA test comparing means of continuous variables or Pearson χ^2 test comparing the distribution of VIQ across categorical variables across the quartile of outcome variable.

c. Higher score represented a more negative perception of neighborhood quality.

or VIQ (Vocabulary; Similarities). We found the negative $PM_{2.5}$-PIQ association primarily reflected the adverse effect on Matrix Reasoning. Interestingly, although the negative PM2.5-VIQ associations were not statistically significant (S1 Fig), we found evidence for adverse effects on VIQ Similarities present for both 1-y (p = .04) and 2-year (p = .02) $PM_{2.5}$ exposures (S1 Fig). Annual NO_x exposure also predicted lower IQ scores in the crude analyses (S4 Table), but their associations were largely abolished in the adjusted analyses (S4 Table).

Table 3. Associations between $PM_{2.5}$ and IQ Measures

Models	N[a]	Full-Scale IQ β (95% CI)[b]	VIQ β (95% CI)[b]	PIQ β (95% CI)[b]
Crude Analysis	1360	-2.46 (-3.48, -1.44)*	-1.66 (-2.76, -0.56)*	-2.14 (-3.16, -1.12)*
Adjusted Model I[c]	1093	-1.93 (-4.75, 0.89)	-1.37 (-4.39, 1.65)	-2.91 (-5.83, 0.01)
Adjusted Model II[d]	1085	-2.00 (-4.84, 0.84)	-1.42 (-4.48, 1.64)	-3.08 (-6.04, -0.12)*
Sensitivity Analyses				
Sensitivity Model I[e]	1085	-1.84 (-4.86, 1.18)	-1.14 (-4.37, 2.09)	-3.50 (-6.62, -0.38)*
Sensitivity Model II[f]	1085	-2.08 (-4.96, 0.80)	-1.76 (-4.84, 1.32)	-3.01 (-5.99, -0.03)*
Sensitivity Model III[g]	1042	-2.05 (-4.87, 0.77)	-1.13 (-4.17, 1.91)	-3.66 (-6.62, -0.70)*

* $P < .05$

a. Total number of participants differed because of missing values.

b. Estimate reflected the change in each IQ score and the resulting 95% confidence interval per each inter-quartile range (IQR) increase in $PM_{2.5}$.

c. Adjusted for age, gender, ethnicity, family SES and parents' cognitive abilities.

d. Adjusted Model I + neighborhood SES, self-reported neighborhood quality, traffic density (300m) and neighborhood greenness (1000m, 1-year preceding).

e. Adjusted Model II + temperature and relative humidity 1-year prior to test.

f. Adjusted Model II + total annual NO_x.

g. Adjusted Model II + parental stress and maternal smoking during pregnancy.

Moderation Roles of Socio-Demographic Characteristics

Results of our moderation analyses showed that the adverse $PM_{2.5}$ effects on PIQ were not uniform across socio-demographic characteristics (upper panel, Fig 1). Sex and family SES both significantly modified the association between $PM_{2.5}$ and PIQ score (interaction p < .01 for both moderators), with exposure conferring 150% stronger influence in males (β = -4.68, 95% CI

= [-7.90, -1.47]) than in females (β = -1.87, 95% CI = [-4.89, 1.16]); and 89% stronger in low SES families (β = -3.83, 95% CI = [-6.98, -0.69]) than in high SES families (β = -2.03, 95% CI = [-6.12, 2.36]). Although the adverse $PM_{2.5}$-PIQ effect (β = -3.27; 95% CI = [-6.44, -0.10]) at age 9-11 was 74% greater than the corresponding estimate (β = -1.88; 95% CI = [-6.12, 2.36]) during emerging adulthood, this observed difference by age did not reach statistical significance (interaction p = .49),

The moderation analyses of VIQ did not reveal remarkable findings, except for a statistically significant interaction (p = .03) between gender and $PM_{2.5}$ (lower panel, Fig 1). Our results suggested that the $PM_{2.5}$-VIQ effect might be qualitatively different between males (β = -2.16; 95% CI = [-5.5, 1.18]) and females (β = 0.78, 95% CI = [-2.37, 3.93]), albeit an overlap between these two CIs (please refer to Knezevik (31) for an explanation of why a significant difference could have overlapping CIs).

Fig 1. Plot of regression coefficients and 95% confidence intervals for the association between $PM_{2.5}$ 1-year prior to test and the IQ scores, moderation by age, sex, and family socioeconomic status (RFAB Cohort 2000-2014). The gray reference band in each IQ subscale represented the 95% CI of the final-adjusted main effect of $PM_{2.5}$ on that IQ score. Significant moderation was highlighted in yellow.

Discussion

To our knowledge, this is the first longitudinal study examining the effects of ambient air pollutants on IQ spanning two different developmental stages: pre-/early-adolescence (aged 9-11) and emerging adulthood (aged 18-20). We found strong evidence for a decreased PIQ score with higher exposure to ambient $PM_{2.5}$ estimated at residential locations, even after adjusting for socio-demographic factors, spatial characteristics of residential neighborhoods, and parents' cognitive abilities. The corresponding associations with VIQ were less evident. The adverse

243 $PM_{2.5}$-PIQ effect was much greater in low SES families and in males, indicative of
244 socioeconomic disparities and sexual dimorphism in the developmental neurotoxicity of $PM_{2.5}$
245 exposure.

246 The observation of stronger adverse $PM_{2.5}$ effects on IQ among RFAB participants
247 growing up in low SES families offers a useful view-scope to unify the findings reported in the
248 extant literature (11 studies from 7 birth cohorts with individual-level exposure data) on PM-IQ
249 associations (A4 in S1 File). For those 4 studies conducted outside the US (19, 20, 23, 25),
250 differences in PM characterization and primary exposure source may explain the discrepancies in
251 reported associations. Of the 7 US-based studies, 6 reported a statistically significant association
252 between early-life exposure to PM and low performance of IQ testing in children. These
253 included 4 studies based in the Columbia Center for Children's Environmental Health Birth
254 Cohort, which included children of minority (Black or Dominican-American) women primarily
255 with low SES (74% families with annual family income <$20,000) and residing in a community
256 where traffic and residential heating were major exposure sources (18, 21, 24, 26). The other 3
257 studies, despite all having been based in the greater Boston area and employing the same
258 approaches to estimating residential exposure at birth locations, yielded very different results. In
259 the Project Viva (22), neither black carbon nor $PM_{2.5}$ exposure predicted lower IQ in children
260 (with an average age of 8) of relatively well-off (73% with annual family income >$70,000) and
261 well-educated parents (68% maternal/ 63% paternal education ≥college). For the other two
262 studies including mothers primarily of minorities and/or with limited educational attainment (69-
263 82% with maternal education≤ high school), $PM_{2.5}$ was associated with low full-scale IQ in boys
264 of school age (6.5 ± 0.98 years) (27), whereas black carbon exposure predicted low Matrices
265 score on the Kaufman Brief Intelligence Test at 8-11 years of age (17). All these study findings

point to the importance of population social context (32) for designing epidemiological studies and interpreting data on developmental neurotoxicity of ambient air pollutants.

Our finding of socioeconomic disparities in the adverse $PM_{2.5}$-PIQ effect has important implications for future research on the environmental neurosciences in neurodevelopmental toxicity of particulate air pollutants. First, $PM_{2.5}$ exposure and socioeconomic adversities may have converged on common pathways with resulting exacerbated neurotoxicity, although the exact models for their respective mechanistic actions remain unclear. Possible brain regions and structures with shared vulnerability may include hippocampus (33, 34), prefrontal cortex (35, 36), and cerebral white matter (24, 37). Second, high-SES families may provide their children with more exposure to advantageous experiences (e.g., early-life educational resources), which could partly off-set the brain damage from $PM_{2.5}$ exposure. Third, although our analyses accounted for parental cognitive abilities, low-SES families may not be able to engage in activities with parental nurturance critical for cognitive development. Fourth, growing up in low SES families indicates the possibility of concurrent exposures to other psychosocial and environmental stressors (e.g., violence exposure, early onset of alcohol use) adversely affecting IQ development. Better understanding of the causes of socioeconomic disparities in PM neurotoxicity will not only shed light on the mechanistic pathways, but also help identify more susceptible populations who can benefit the greatest from environmental regulation, social policies (e.g., reducing family poverty; early education program), or family interventions (e.g., parental caring behaviors).

Although PIQ and VIQ were moderately correlated, the adverse $PM_{2.5}$-IQ effect was statistically significant for PIQ only (primarily affecting the Matrix Reasoning component). This divergence may reflect a more detrimental impact of PM on fluid cognitive abilities. Fluid intelligence (Gf) refers to the capabilities to reason and solve novel problems, in contrast to

crystallized intelligence (Gc), another factor of intelligence concerning acquired knowledge, skills and experiences (38, 39). This classical distinction laid the theoretical foundation for the development of PIQ and VIQ. It is interesting to note that our *ad hoc* analyses (S1 Fig) also showed that increased $PM_{2.5}$ (1- and 2-year average) exposure was associated with decreased scores in the VIQ subtest Similarity, a measure intended for Gc but actually tapping into Gf (likely more than the PIQ subtest Block Design, a spatial visualization task) as it relies upon the ability to abstract common patterns beyond the knowledge of words and their meanings (40). Because Gf is more reliant on and sensitive to lesions to frontal lobe than Gc (41-45), the differential $PM_{2.5}$ effect on fluid intelligence implies possible damage to frontal brain networks, which was supported by the emerging data from neurotoxicological and neuroimaging studies. For instance, persistent glial activation in frontal cortex was demonstrated in mouse models with early-life exposure to concentrated ambient ultrafine particles (46). *In utero* exposure to a low concentration of diesel exhaust also altered the neurochemical monoamine metabolism in prefrontal cortex (47). In a birth cohort study based in Rotterdam, the Netherlands, early-life exposure to $PM_{2.5}$ was associated with cortical thinning in the frontal lobe at age 9 (48).

Two recent studies have reported adverse PM effects on IQ (27) and working memory (49) assessed in school age were stronger in boys than girls, although none of the exposure interaction with sex was statistically significant. Our study showed that the adverse $PM_{2.5}$ effects on both PIQ and VIQ scores assessed during early adolescence and emerging adulthood were stronger in males than females (interaction p-value < .05; Fig 1), despite female RFAB participants being more likely to reside in locations with higher $PM_{2.5}$ (3^{rd} and 4^{th} quartiles in Table 1). Multiple biological differences may help explain the observed differences between males and females in observed adverse $PM_{2.5}$-IQ effects in the current study. Neurotoxicologists

have documented sexually dimorphic neurobehavioral responses to various environmental chemicals (e.g., dioxin, bisphenol-A), a phenomenon often inferred as an indicator for exposure-induced endocrine-disrupting effects on the brain, largely through interference with the actions of gonadal hormones (50). Animal studies support the neuroendocrine disruption with inhaled exposure to particles (51, 52), but the mechanisms underlying sexual dimorphism in neurotoxicity may also involve neurobiological pathways with exposure interacting with sex-linked genes (53). Although earlier studies did not show clear evidence for sex differences in general intelligence (54), new findings support the presence of cognitive sex differences depending on task characteristics and contextual experience (55). However, studies relating pubertal sex hormones to cognitive abilities in adolescents have yielded mixed results (56, 57). Nonetheless, our findings give strong rationale for future studies to investigate whether sexual dimorphism is also present in other neurodevelopmental and behavioral effects of ambient air pollutants. Better understanding of the neurobiological processes underlying the sexual dimorphism in the $PM_{2.5}$-IQ effect may inform better sex-sensitive intervention strategies to reduce harmful environmental exposures to optimize the brain-behavioral health for both men and women.

Our moderation analyses revealed no statistical interaction of exposure effect by age group, despite the fact that the adverse $PM_{2.5}$-PIQ effect was 74% stronger in pre-/early-adolescence than in emerging adulthood. Behavior genetic research has reported that environmental contribution to IQ variation decreases across age (12, 58). As neural structure and network approach maturation by the end of adolescence (4, 10), IQ of young adults may be less subject to environmental influences. Previous studies have shown that the use of neurotoxic agents, such as alcohol and other drugs, posed more threats to memory and memory-related brain

function in adolescents than adults (59). However, given a relatively small sample (n=510) assessed during emerging adulthood, our results must be viewed with caution, as they did not necessarily mean that the neurotoxic threats of ambient air pollutants disappeared once into adulthood. Hippocampal damage with cognitive impairments was previously documented in mice with long-term inhaled exposure to concentrated $PM_{2.5}$ starting in youth (33). Future studies with larger samples could help clarify this important uncertainty in the adverse $PM_{2.5}$–IQ effect during the transition into young adults.

The strengths of our study included its base in Southern California with wide exposure contrast, sampled from a population with rich diversity in race/ethnicity, sex and family SES, and the inclusion of repeated IQ assessment for longitudinal analyses. This unique sample and prospective longitudinal design provided adequate power to investigate heterogeneity in the PM-IQ associations across age, sex, and SES. Nonetheless, there are several limitations that should be considered. First, we caution the interpretation of selective $PM_{2.5}$-PIQ effect. Because our assessment of IQ was based on the WASI (an abbreviated Wechsler intelligence scale, rather than the full scale), some significant domains (e.g., working memory; processing speed) presumably sensitive to $PM_{2.5}$ neurotoxicity were not captured in our analyses. Second, although we were able to conduct longitudinal analyses, the inference of our results was based on the statistical assumption of data missing at random given the unbalanced data structure with repeated measures. Third, we were not able to study prenatal exposure effects, because extensive monitoring of $PM_{2.5}$ data were not available until after 1999, while the birth years of the cohort ranged from 1990-1995. The relative contribution to adverse $PM_{2.5}$-IQ effects by exposure in early life versus adolescence needs to be investigated further. Fourth, our analyses only included the estimate of $PM_{2.5}$ mass, and we did not study the specific neurotoxicity of $PM_{2.5}$ constituents

(e.g., metals; organic chemicals). Fifth, while $PM_{2.5}$ estimates based on spatiotemporal interpolation of monitored concentrations were statistically cross-validated, there are expected non-differential measurement errors in such estimates, which would likely have attenuated the observed associations.

In this first longitudinal study with repeated cognitive assessment, we found lower PIQ scores in youth living in locations with higher exposure to ambient $PM_{2.5}$, with stronger adverse effects observed in low SES families and in males. Better understanding of the socioeconomic disparities and sexual dimorphism in neurotoxic effects of $PM_{2.5}$ on intellectual development may help elucidate the underlying mechanisms and shed light for targeted and effective interventions.

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References

1. Lynn R, Vanhanen T. IQ and global inequality: Washington Summit Publishers; 2006.
2. Grosse SD, Matte TD, Schwartz J, Jackson RJ. Economic gains resulting from the reduction in children's exposure to lead in the United States. Environmental Health Perspectives. 2002;110(6):563.
3. Strenze T. Intelligence and socioeconomic success: A meta-analytic review of longitudinal research. Intelligence. 2007;35(5):401-26.
4. Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. Neuroscience & Biobehavioral Reviews. 2006;30(6):718-29.
5. Ramsden S, Richardson FM, Josse G, Thomas MS, Ellis C, Shakeshaft C, et al. Verbal and non-verbal intelligence changes in the teenage brain. Nature. 2011;479(7371):113-6.
6. WHO. Adolescent Development2011 2016 August. Available from: http://www.who.int/maternal_child_adolescent/topics/adolescence/dev/en/.
7. Dahl RE. Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address. Annals of the New York Academy of Sciences. 2004;1021(1):1-22.
8. Giorgio A, Watkins K, Chadwick M, James S, Winmill L, Douaud G, et al. Longitudinal changes in grey and white matter during adolescence. Neuroimage. 2010;49(1):94-103.
9. Tamnes CK, Østby Y, Fjell AM, Westlye LT, Due-Tønnessen P, Walhovd KB. Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. Cerebral cortex. 2010;20(3):534-48.
10. Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(21):8174-9.
11. Turkheimer E, Haley A, Waldron M, D'Onofrio B, Gottesman II. Socioeconomic status modifies heritability of IQ in young children. Psychological science. 2003;14(6):623-8.
12. Bergen SE, Gardner CO, Kendler KS. Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: a meta-analysis. Twin Research and Human Genetics. 2007;10(03):423-33.
13. McLoyd VC. Socioeconomic disadvantage and child development. American psychologist. 1998;53(2):185.
14. Van Ijzendoorn MH, Juffer F, Poelhuis CWK. Adoption and cognitive development: a meta-analytic comparison of adopted and nonadopted children's IQ and school performance. Psychological bulletin. 2005;131(2):301.
15. Christian K, Bachnan H, Morrison F. Schooling and cognitive development. Environmental effects on cognitive abilities. 2001:287-335.
16. Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen J-C, et al. The outdoor air pollution and brain health workshop. Neurotoxicology. 2012;33(5):972-84.
17. Suglia SF, Gryparis A, Wright R, Schwartz J, Wright R. Association of black carbon with cognition among children in a prospective birth cohort study. American journal of epidemiology. 2008;167(3):280-6.
18. Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, Camann D, et al. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. Pediatrics. 2009;124(2):e195-e202.
19. Edwards SC, Jedrychowski W, Butscher M, Camann D, Kieltyka A, Mroz E, et al. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland. Environmental health perspectives. 2010;118(9):1326.
20. Perera F, Li T, Lin C, Tang D. Effects of prenatal polycyclic aromatic hydrocarbon exposure and environmental tobacco smoke on child IQ in a Chinese cohort. Environmental research. 2012;114:40-6.

21. Lovasi GS, Eldred-Skemp N, Quinn JW, Chang H-w, Rauh VA, Rundle A, et al. Neighborhood social context and individual polycyclic aromatic hydrocarbon exposures associated with child cognitive test scores. Journal of child and family studies. 2014;23(5):785-99.
22. Harris MH, Gold DR, Rifas-Shiman SL, Melly SJ, Zanobetti A, Coull BA, et al. Prenatal and childhood traffic-related pollution exposure and childhood cognition in the project viva cohort (Massachusetts, USA). Environmental health perspectives. 2015;123(10):1072.
23. Jedrychowski WA, Perera FP, Camann D, Spengler J, Butscher M, Mroz E, et al. Prenatal exposure to polycyclic aromatic hydrocarbons and cognitive dysfunction in children. Environmental Science and Pollution Research. 2015;22(5):3631-9.
24. Peterson BS, Rauh VA, Bansal R, Hao X, Toth Z, Nati G, et al. Effects of prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) on the development of brain white matter, cognition, and behavior in later childhood. JAMA psychiatry. 2015;72(6):531-40.
25. Porta D, Narduzzi S, Badaloni C, Bucci S, Cesaroni G, Colelli V, et al. Air pollution and cognitive development at age seven in a prospective Italian birth cohort. Epidemiology (Cambridge, Mass). 2015.
26. Vishnevetsky J, Tang D, Chang H-W, Roen EL, Wang Y, Rauh V, et al. Combined effects of prenatal polycyclic aromatic hydrocarbons and material hardship on child IQ. Neurotoxicology and teratology. 2015;49:74-80.
27. Chiu Y-HM, Hsu H-HL, Coull BA, Bellinger DC, Kloog I, Schwartz J, et al. Prenatal particulate air pollution and neurodevelopment in urban children: Examining sensitive windows and sex-specific associations. Environment international. 2016;87:56-65.
28. Calderón-Garcidueñas L, Engle R, Mora-Tiscareño A, Styner M, Gómez-Garza G, Zhu H, et al. Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. Brain and cognition. 2011;77(3):345-55.
29. Baker LA, Tuvblad C, Wang P, Gomez K, Bezdjian S, Niv S, et al. The Southern California Twin Register at the University of Southern California: III. Twin Research and Human Genetics. 2013;16(01):336-43.
30. Wechsler D. Wechsler abbreviated scale of intelligence. San Antonio, TX: Harcourt Assessment; 1999.
31. Knezevic A. Overlapping Confidence Intervals and Statistical Significance 2008 [Available from: https://www.cscu.cornell.edu/news/statnews/stnews73.pdf.
32. Bellinger DC, Matthews-Bellinger JA, Kordas K. A developmental perspective on early-life exposure to neurotoxicants. Environment international. 2016;94:103-12.
33. Fonken L, Xu X, Weil ZM, Chen G, Sun Q, Rajagopalan S, et al. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. Molecular psychiatry. 2011;16(10):987-95.
34. Noble KG, Houston SM, Brito NH, Bartsch H, Kan E, Kuperman JM, et al. Family income, parental education and brain structure in children and adolescents. Nature neuroscience. 2015;18(5):773-8.
35. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends in neurosciences. 2009;32(9):506-16.
36. Johnson SB, Riis JL, Noble KG. State of the art review: poverty and the developing brain. Pediatrics. 2016;137(4):peds. 2015-3075.
37. Noble KG, Korgaonkar MS, Grieve SM, Brickman AM. Higher education is an age□independent predictor of white matter integrity and cognitive control in late adolescence. Developmental science. 2013;16(5):653-64.
38. Cattell RB. Theory of fluid and crystallized intelligence: A critical experiment. Journal of educational psychology. 1963;54(1):1.
39. Cattell RB. Abilities: Their structure, growth, and action. Oxford, England: Houghton Mifflin; 1971.

40. Kaufman AS, Lichtenberger EO. Assessing adolescent and adult intelligence: John Wiley & Sons; 2005.
41. Nisbett RE, Aronson J, Blair C, Dickens W, Flynn J, Halpern DF, et al. Intelligence: new findings and theoretical developments. American psychologist. 2012;67(2):130.
42. Duncan J, Burgess P, Emslie H. Fluid intelligence after frontal lobe lesions. Neuropsychologia. 1995;33(3):261-8.
43. Roca M, Parr A, Thompson R, Woolgar A, Torralva T, Antoun N, et al. Executive function and fluid intelligence after frontal lobe lesions. Brain. 2009;118(2):234-47.
44. Woolgar A, Parr A, Cusack R, Thompson R, Nimmo-Smith I, Torralva T, et al. Fluid intelligence loss linked to restricted regions of damage within frontal and parietal cortex. Proceedings of the National Academy of Sciences. 2010;107(33):14899-902.
45. Barbey AK, Colom R, Paul EJ, Grafman J. Architecture of fluid intelligence and working memory revealed by lesion mapping. Brain Structure and Function. 2014;219(2):485-94.
46. Allen JL, Liu X, Weston D, Prince L, Oberdörster G, Finkelstein JN, et al. Developmental exposure to concentrated ambient ultrafine particulate matter air pollution in mice results in persistent and sex-dependent behavioral neurotoxicity and glial activation. Toxicological Sciences. 2014;140(1):160-78.
47. Suzuki T, Oshio S, Iwata M, Saburi H, Odagiri T, Udagawa T, et al. In utero exposure to a low concentration of diesel exhaust affects spontaneous locomotor activity and monoaminergic system in male mice. Particle and fibre toxicology. 2010;7(1):1.
48. Guxens M, Lubczynska MJ, Muetzel R, Dalmau A, Jaddoe VW, Verhulst FC, et al. Air pollution exposure during pregnancy and brain morphology in young children: a population-based prospective birth cohort study. Abstracts of the 2016l Epidemiology (ISEE). Research Triangle Park, NC: Environmental Health Perspectives; 2016.
49. Sunyer J, Esnaola M, Alvarez-Pedrerol M, Forns J, Rivas I, López-Vicente M, et al. Association between traffic-related air pollution in schools and cognitive development in primary school children: a prospective cohort study. PLoS Med. 2015;12(3):e1001792.
50. Weiss B. Sexually dimorphic nonreproductive behaviors as indicators of endocrine disruption. Environmental health perspectives. 2002;110(Suppl 3):387.
51. Tsukue N, Yoshida S, Sugawara I, Takeda K. Effect of diesel exhaust on development of fetal reproductive function in ICR female mice. Journal of health science. 2004;50(2):174-80.
52. Sirivelu MP, MohanKumar SM, Wagner JG, Harkema JR, MohanKumar PS. Activation of the stress axis and neurochemical alterations in specific brain areas by concentrated ambient particle exposure with concomitant allergic airway disease. Environmental health perspectives. 2006:870-4.
53. Davies W, Wilkinson LS. It is not all hormones: alternative explanations for sexual differentiation of the brain. Brain research. 2006;1126(1):36-45.
54. Halpern DF, LaMay ML. The Smarter Sex: A Critical Review of Sex Differences in Intelligence. Educational Psychology Review. 2000;12(2):229-46.
55. Miller DI, Halpern DF. The new science of cognitive sex differences. Trends in cognitive sciences. 2014;18(1):37-45.
56. Herlitz A, Reuterskiold L, Loven J, Thilers PP, Rehnman J. Cognitive sex differences are not magnified as a function of age, sex hormones, or puberty development during early adolescence. Dev Neuropsychol. 2013;38(3):167-79.
57. Vuoksimaa E, Kaprio J, Eriksson CJ, Rose RJ. Pubertal testosterone predicts mental rotation performance of young adult males. Psychoneuroendocrinology. 2012;37(11):1791-800.
58. Hoekstra RA, Bartels M, Boomsma DI. Longitudinal genetic study of verbal and nonverbal IQ from early childhood to young adulthood. Learning and Individual Differences. 2007;17(2):97-114.

59. White AM, Swartzwelder HS. Age-related effects of alcohol on memory and memory-related brain function in adolescents and adults. Recent developments in alcoholism: Springer; 2005. p. 161-76.

Supporting Information

S1 Table. Descriptive statistics of major demographic characteristics, $PM_{2.5}$ 1-year preceding and IQ scores of three sub-cohorts

S2 Table. Population Characteristics at Baseline in Relation to Levels of Verbal IQ

S3 Table. Population Characteristics at Baseline in Relation to Levels of Performance IQ

S4 Table. Associations between total annual NOx and subscales of IQ

S1 Fig. Plot of regression coefficients and 95% confidence intervals for the associations between $PM_{2.5}$ (1-, 2- and 3-year preceding test) and subscales of IQ from the final-adjusted model

S1 File. Appendix. A1. Map of Residential Locations during pre-/early- adolescence and emerging adulthood; A2. Temporal-spatial Modeling of $PM_{2.5}$ Exposure; A3. Relevant Covariates; A4. Summary Table of Air Pollution and IQ Studies