Title
Air Pollution, Neighbourhood Socioeconomic Factors, and Neural Tube Defects in the San Joaquin Valley of California

Journal
Paediatric and Perinatal Epidemiology, 29(6)

ISSN
0269-5022

Authors
Padula, Amy M
Yang, Wei
Carmichael, Suzan L
et al.

Publication Date
2015-11-01

DOI
10.1111/ppe.12244

Peer reviewed

HHS Public Access

Author manuscript

Paediatr Perinat Epidemiol. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Paediatr Perinat Epidemiol. 2015 November ; 29(6): 536–545. doi:10.1111/ppe.12244.

Air Pollution, Neighbourhood Socioeconomic Factors and Neural Tube Defects in the San Joaquin Valley of California

Amy M. Padula[a], **Wei Yang**[a], **Suzan L. Carmichael**[a], **Ira B. Tager**[b], **Frederick Lurmann**[c], **S. Katharine Hammond**[b], and **Gary M. Shaw**[a]

[a]Stanford University, Stanford, CA

[b]University of California, Berkeley, Berkeley, CA

[c]Sonoma Technology, Inc., Petaluma, CA

Abstract

Background—Environmental pollutants and neighbourhood socioeconomic factors have been associated with neural tube defects, but the potential impact of interaction between ambient air pollution and neighbourhood socioeconomic factors on the risks of neural tube defects is not well understood.

Methods—We used data from the California Center of the National Birth Defects Study and the Children's Health and Air Pollution Study to investigate whether associations between air pollutant exposure in early gestation and neural tube defects were modified by neighbourhood socioeconomic factors in the San Joaquin Valley of California, 1997–2006. Five pollutant exposures, three outcomes and 9 neighbourhood socioeconomic factors were included for a total of 135 investigated associations. Estimates were adjusted for maternal race-ethnicity, education and multivitamin use.

Results—We present below odds ratios that exclude 1 and a chi-square test of homogeneity p-value of <0.05. We observed increased odds of spina bifida comparing the highest to lowest quartile of particulate matter <10 micrometres (PM_{10}) among those living in a neighbourhood with: a) median household income of less than $30,000 per year (OR 5.1, 95% CI 1.7, 15.3); b) more than 20% living below the federal poverty level (OR 2.6, 95% CI 1.1, 6.0); and c) more than 30% with less than or equal to a high school education (OR 3.2, 95% CI 1.4, 7.4). The ORs were not statistically significant among those higher SES neighbourhoods.

Conclusions—Our results demonstrate effect modification by neighbourhood socioeconomic factors in the association of particulate matter and neural tube defects in California.

Keywords

Neural tube defects; Air Pollution; Socioeconomic status; Neighbourhood

Corresponding author: Amy M. Padula, Stanford University, 1265 Welch Road, Stanford, CA 94305-5415, Ph:650-724-1322/Fax: 650-724-5371, ampadula@stanford.edu.

Conflict of interest: none declared.

Neural tube defects (NTDs) result from incomplete closure of the neural tube within about 28 days following conception [1]. NTDs, comprised primarily of spine bifida and anencephaly, are among the most common groups of birth defects affecting more than 320,000 pregnancies worldwide per year [2] and about 3000 in the United States [3]. Record and McKeown's landmark paper [4] described variations in NTD prevalence by geographic location and time, socioeconomic status and other factors including social acceptance of pregnancy termination. The birth prevalence of NTDs worldwide has decreased over the past 30 years [5]. This decline has been attributed to advancements in detection with increasing availability and social acceptance of termination and the introduction of fortification of staple foods with folic acid in many countries including the U.S. NTDs remain an important public health problem and aetiologies since folic acid fortification are largely unknown, though risk factors include both genetic and environmental influences [6].

The few epidemiologic studies of ambient air pollution and NTDs have produced inconsistent results in Texas, Spain, and California [7–9]. Lupo et al.[7] found associations between census-tract level benzene and spina bifida (N=533 cases) in Texas with a more than two-fold increase comparing the highest to lowest quintile of exposure. No associations were observed between several pollutants (nitrogen oxide, nitrogen dioxide, particulate matter less than 2.5 and 10 microns and coarse fraction) and NTDs as a group (N=139) in Barcelona, Spain [8]. In the San Joaquin Valley of California with more precise exposure assessment, associations were observed between several pollutants and NTDs (N=215 cases) [9]. Spina bifida was associated with approximately 2-fold risks for carbon monoxide and nitrogen dioxide and anencephaly was associated approximately 3-fold risks for nitrogen oxide when highest to lowest quartiles were compared; however, no associations were found with particulate matter less than 10 or 2.5 microns[9].

Although numerous studies have examined the association of socioeconomic status with NTD risk, few have more specifically focused on neighbourhood social factors [10,11]. Among California births from 1989–1991, Wasserman found associations between both individual- and neighbourhood-level socioeconomic factors and NTDs [10]. The effects of the neighbourhood were stronger than those of the individual. In a similar study by Grewal et al., NTDs were associated with low maternal education among California births from 1999–2003 [11]. That association was further elevated when the mother lived also lived in a neighbourhood where a majority of residents had not graduated from high school.

Our goal in the current investigation was to examine associations of social and economic factors in combination with air pollution with risk for NTDs in a region of the US with known poor air quality and social disparity. This analysis employed data from the California Center of the National Birth Defects Prevention Study [12] and the Children's Health and Air Pollution Study. We to specifically investigate whether previously observed associations between ambient air pollutants and NTD (exclusive to spina bifida and anencephaly) risk are further modified by neighbourhood socioeconomic factors in the San Joaquin Valley of California [9].

Methods

Study population

The California Center of the National Birth Defects Prevention Study is a collaborative partnership between Stanford University and the California Birth Defects Monitoring Program in the Department of Public Health. Since 1997, the Center has been collecting data from women residing in eight counties (San Joaquin, Stanislaus, Merced, Madera, Fresno, Kings, Tulare, and Kern) in the San Joaquin Valley. The California Birth Defects Monitoring Program is a active surveillance program that is population-based (*i.e.*, not hospital-based)[13]. To identify infants or foetuses (cases) with birth defects, highly trained data collection staff visit all hospitals with obstetric or paediatric services, cytogenetic laboratories and all clinical genetics prenatal and postnatal outpatient services to review and abstract cases including those diagnosed prenatally with birth defects.

Cases in the current analysis included infants or foetuses with anencephaly or spina bifida, as confirmed by clinical, surgical, or autopsy reports. Cases resulting from known single gene or chromosomal abnormalities or with identifiable syndromes were ineligible, given their presumed distinct underlying aetiology. Each case was also classified as isolated if there was no additional major unrelated congenital anomaly or as non-isolated if there was at least one unrelated major anomaly according to guidelines for case classification for the National Birth Defects Prevention Study [14].

Eligible cases included live births, stillbirths, and pregnancy terminations and were selected from the Center's surveillance system based on strict eligibility criteria[14]. Controls included non-malformed live-born infants randomly selected from birth hospitals to represent the population from which the cases arise (approximately 150 per study year). Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, between six weeks and 24 months after the infant's estimated date of delivery. Estimated date of conception was derived by subtracting 266 days from expected date of delivery. Expected date of delivery was based on self-report; if unknown, it was estimated from information in the medical record (<2% of participants) [12].

Interviews were conducted with mothers of 67% of eligible cases and 69% of controls. The present analysis included 215 cases (77 anencephaly and 138 spina bifida) and 849 controls with an estimated delivery date between October 1, 1997 and December 31, 2006. Mothers reported a full residential history from one month before conception through delivery, including start and stop dates for each residence. Mothers with diabetes (Type 1 or 2) prior to gestation were excluded. Addresses were geocoded using the Centrus Software (Stamford, CT), which combines reference street networks from Tele Atlas ('s-Hertogenbosch, Netherlands) and United States Postal Service data. Geocodes were available for 95% of cases and 93% of controls.

Exposure assessment

As part of the Children's Health and Air Pollution Study, ambient air pollution measurements were assigned to each of the geocoded residences reported by study subjects corresponding to their first and second month of pregnancy. If there was more than one

address during the period, exposure assignments were calculated for number of days at each residence. Exposure assignments were made if the geocodes were within the San Joaquin Valley and were available for at least 75% of each month. Daily 24-hour averages of the following traffic-related pollutants were averaged over the first two months of pregnancy: nitrogen dioxide (NO_2), nitrogen oxide (NO), carbon monoxide (CO), particulate matter ≤ than 10 μm (PM_{10}), and PM ≤ than 2.5 μm ($PM_{2.5}$).

Ambient air quality data have been collected routinely at over 20 locations in the San Joaquin Valley since the 1970s and these data were acquired from U.S. Environmental Protection Agency's Air Quality System database (www.epa.gov/ttn/airs/airsaqs). The station-specific daily air quality data were spatially interpolated using inverse distance-squared weighting. Data from up to four air quality measurement stations were included in each interpolation. Owing to the regional nature of NO_2, PM_{10}, and $PM_{2.5}$ concentrations, a maximum interpolation radius of 50 km was used. NO and CO were interpolated using a smaller maximum interpolation radius of 25 km, since they are directly emitted pollutants with larger spatial gradients. When a residence was located within 5 km of one or more monitoring stations, the interpolation was based solely on the nearby values.

Gaseous pollutants were measured using Federal Reference Method continuous monitors. Particulate matter data were primarily limited to those collected with Federal Reference Method samplers and Federal Equivalent Method monitors. The national air monitoring networks began measuring $PM_{2.5}$ in 1999, therefore births with dates of conception prior to 1999 were not part of the analyses of $PM_{2.5}$.

We created 3 categories of "cumulative" exposure based on the number of high exposures to which each participant was exposed. Those who were exposed to air pollutant levels in the lowest three quartiles for all exposures were in the zero category, those with 1–2 exposures in the highest quartile were in the middle category and those in the highest quartile for 3–5 pollutants were in the highest exposure category. Participants with data on at least 3 pollutants were included.

Statistical analysis

Analyses were conducted to examine the association between the pollutants. Each pollutant was examined by quartile as determined by the distribution in the controls. Quartiles were chosen so that the results could be more easily compared to previous studies and the controls were the best representation of the general population. We examined the following covariates as potential confounders: maternal race/ethnicity (non-Hispanic white, U.S.-born Hispanic, foreign-born Hispanic, or other); maternal education (less than high school, high school, more than high school); age (<25, 25–34, ≥35 years); plurality (singletons, multiples); parity (0, 1, >1); early pregnancy multi-vitamin use (one month prior to and/or first two months of pregnancy); active and/or passive smoking during pregnancy; year of estimated delivery category (1997–2000, 2001–2003, 2004–2006); and infant sex.

Multivariable logistic regression analyses were conducted to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CI) reflecting the association between ambient air pollutants and NTDs. NTDs were analysed as a group and separately as spina bifida and

anencephaly. The highest quartile of each pollutant was compared to the lowest quartile. When statistically significant associations were identified, the second and third quartiles were examined to evaluate exposure-response relationships. Multivariable analyses were performed adjusting for maternal race/ethnicity, education and early prenatal vitamin use. These covariates were selected *a priori* and based on causal assumptions derived from subject matter knowledge [15]. The remaining covariates (age, parity, active and/or passive smoking, year of birth, infant sex) were examined as potential confounders in bivariate analyses using chi square tests of association (results not shown). Adjustment for multiple comparisons was not made.

To examine the contributions of neighbourhood social factors, analyses were stratified near their median by the following variables from the 2000 U.S. census at the block group level: maternal education (proportion with less than high school education greater than 30%), income from public assistance (proportion greater than 10%), income below the federal poverty level (proportion greater than 20%), male and female unemployment (greater than 10%), median annual income (less than $30,000), median home value (less than $100,000), housing built before 1980 (proportion greater than 50%). A principal component analysis was run to reduce these 8 variables to a summary variable. The first component from the PCA had an eigenvalue >1 and was used to create an indicator of socioeconomic variables (component scores were categorized at greater than or less than zero, which coincided with the median). This summary variable was considered as an effect modifier in addition to the individual variables. Tests of homogeneity using the Wald chi square were calculated to evaluate effect modification. Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, 2014–2015). The study protocol was reviewed and approved by the institutional review boards of Stanford University and the California Department of Public Health.

Results

All of the cases and 849 of the 853 controls were assigned at least one exposure metric. Completeness for exposure assignments was 74% for CO, 84% for NO, 98% for NO_2, and 97% for PM_{10}. Among those born after January 1st 1999, 97% of the participants were assigned an estimate for $PM_{2.5}$ exposure.

Most study subjects were Hispanic, and almost half were greater than 25 years old at delivery or had at least a high school education (Table 1). Approximately two-thirds took a multivitamin early in pregnancy, and anencephaly cases were more likely to be exposed to active and passive smoke compared to controls. Controls were all live births by definition and 66% anencephaly cases and 12% of spina bifida cases were not live born.

Correlations among controls of CO with NO (r=0.81), NO_2 (r=0.73) and $PM_{2.5}$ (r=0.84) were high, which reflects the common exposure source of motor vehicles (Table 2). PM_{10} was less correlated with the other pollutants. Farming operations, re-suspended road dust, and fugitive windblown dust are the largest sources of PM_{10} emission in the study area (http://www.arb.ca.gov/ei/emissiondata.htm).

As expected, the neighbourhood factors were strongly correlated with each other (Table 3). Pollutants were not strongly associated with the neighbourhood factors. For instance, the correlations (as determined by Pearson coefficients) between PM_{10} and the neighbourhood factors ranged from 0.02 (older housing) to 0.17 (home value less than $100,000). Poverty and PM_{10} had a correlation of 0.12. Neighbourhood factors were not associated with NTDs after adjusting for the same covariates (data not shown).

Table 4 displays results from multivariable logistic regression models of PM_{10} and spina bifida specifically and NTDs as a group, stratified by the three (of the 9 total) neighbourhood social factors for which we found significant differences (determined by a chi square test of homogeneity with $p<0.05$ and an odds ratio with the 95% confidence interval excluding one). We observed increased odds of spina bifida comparing the highest to lowest quartile of PM_{10} among those living in a neighbourhood with a median household income of less than $30,000 per year (OR 5.1, 95% CI 1.7, 15.3). The associations were consistent across the 2nd and 3rd quartiles. In neighbourhoods with more than 20% living below the federal poverty level the odds of spina bifida were higher when exposed to high levels of PM_{10} (OR 2.6, 95% CI 1.1, 6.0). Associations between PM_{10} and spina bifida were higher in neighbourhoods where the proportion of those with less than or equal to a high school education was more than 30% (OR 3.2, 95% CI 1.4, 7.4). Among neighbourhoods with higher socioeconomic status, the odds ratios were in the opposite direction, though most were not statistically significant. The patterns were similar though attenuated when analysing both spina bifida and anencephaly as a combined group of NTDs. The variance explained by the first component of the PCA was 4.89. The loadings from the 8 variables ranged from 0.37 (year of housing built) to 0.81 (income below the poverty level).

The full results for each pollutant and each neighbourhood factor are presented in the appendix (Tables A1–A5). The observed associations between the other studied pollutants (CO, NO, and NO_2) and NTDs were not modified by neighbourhood socioeconomic factors.

The results of the “cumulative” air pollutant exposure categories are presented in Table 5 stratified by each of the neighbourhood socioeconomic factors. In the combined NTDs analysis, associations were stronger when women were exposed to high levels of multiple pollutants. These associations were not statistically modified by neighbourhood socioeconomic factors. An exposure-response was evident across the categories of cumulative exposure.

Discussion

Associations between PM_{10} and spina bifida were modified by neighbourhood socioeconomic factors including poverty, income and education. When stratified by neighbourhood socioeconomic factors, increased risks of NTDs among those with higher PM_{10} exposure were observed only among those living in low socioeconomic neighbourhoods. This association was observed when estimates were controlled for the pertinent covariates: maternal race/ethnicity, education and vitamin use. In a previous analysis of this study population, associations between NTDs were observed with increased exposure to NO, NO_2 and CO during the first two months of pregnancy [9]. In this study,

there was no effect modification by neighbourhood socioeconomic factors in the associations between NO, NO_2 and CO and NTDs, but associations between PM_{10} and NTDs were revealed among those living in low socioeconomic neighbourhoods. The association of NTDs with exposure to high levels of multiple pollutants (i.e., the cumulative pollutant score) was not modified by neighbourhood socioeconomic factors.

This is the first study to our knowledge to examine associations of air pollution and NTDs overall and spina bifida specifically in the context of neighbourhood socioeconomic factors. Previous studies have investigated associations of NTDs with air pollution [7–9] and neighbourhood socioeconomic factors [10,11], but not the interaction of the two environmental "stressors." This study is also in an area of the state with relatively higher levels of pollution and lower socioeconomic status. Sources of PM_{10} typically include agricultural operations, industrial processes, combustion of wood or fossil fuels, windblown dust and wildfires, but do not explain why they would be more harmful in conjunction with lower socioeconomic neighbourhoods compared to other pollutants.

There are some potential limitations to this study. There is measurement error in the exposure assignment based on distance-weighted averages of the nearest monitors. Furthermore, it is unknown how much time the mother spent at her home during the first two months of pregnancy. For example, this could lead to potential exposure misclassification if a mother worked at a location associated with different exposure levels. The ambient air pollution levels also do not account for indoor sources of similar air pollutants that may have been present. This misclassification of exposure would bias results in an unknown direction. Data obtained from retrospective studies are always subject to recall error. However, recall error did not affect the exposure assignment because it was based on residential history and objective measures of air pollutant concentrations. It is unknown whether women who did versus did not participate in the study were systematically different with respect to air pollution exposure. In addition, some women had to be excluded from various aspects of the analysis because of missing data on exposure levels; whether this incurred some bias in our results is unknown. The lack of statistically significant associations between $PM_{2.5}$ and NTDs may be attributable to exclusion of data from 1997–1998 when the $PM_{2.5}$ monitoring network was not yet established throughout California and levels were higher. An alternative approach would have been to apply multilevel models with individual and neighbourhood-level variables considered separately. Although we chose to stratify by neighbourhood factors in this analysis to examine how the effects of air pollution may differ in neighbourhoods of different socioeconomic status, multilevel models could be considered in future analyses to examine the effects of neighbourhood on neural tube defects.

Strengths of the present study include the rigorous, population-based design and careful case ascertainment. The study also included detailed information on potential covariates specifically during the critical period of the first 8 weeks of pregnancy including maternal residence, multi-vitamin use and smoking. These study characteristics limited potential selection bias and residual confounding. This study covered a wide geographic area with among the highest levels of air pollution exposure in the United States. During the study period, all 8 counties in the study area were in nonattainment for particulate matter <10 μm

for each year in the study period according to the National Ambient Air Quality Standards set by the U.S. Environmental Protection Agency (http://www.epa.gov/oaqps001/greenbk/index.html). Our study benefited from detailed air pollution metrics with precise spatial and temporal considerations.

In conclusion, we found associations between PM_{10} and NTDs overall, specifically for spina bifida, were modified by several neighbourhood socioeconomic factors. That is, there is a double jeopardy of being exposed to both high levels of PM_{10} and living in a neighbourhood with lower socioeconomic status. We do not know what the underlying biologic meaning may be based on this complex observation. A multifactorial pathway is likely to explain the development of NTDs. These factors can have a cumulative and detrimental effect on health and help explain the health disparities found in adverse birth outcomes including neural tube defects. Given the continuing occurrence of NTDs despite folic acid fortification in the United States food system, additional pathways for prevention should be explored. Further studies are needed to understand the interaction of environmental and socioeconomic factors in the aetiology of NTDs to achieve health equality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institute for Environmental Health Science (K99ES021470, P01ES022849, P20 ES018173), the United States Environmental Protection Agency (R834596) and the Centers for Disease Control and Prevention, Center of Excellence Award U50/CCU913241.

The authors thank the California Department of Public Health Maternal Child and Adolescent Health Division. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the California Department of Public Health.

References

1. Botto LD, Moore CA, Khoury MJ, Erickson JD. Neural-tube defects. The New England journal of medicine. Nov 11; 1999 341(20):1509–1519. [PubMed: 10559453]
2. Christianson, A.; Howson, CP.; Modell, B. March of Dimes Global Report on Birth Defects. White Plains, New York: March of Dimes Birth Defects Foundation; 2006.
3. CDC. Spina Bifida and Anencephaly Beofre and After Folic Acid Mandate -- United States 1995–1996 and 1999–2000. MMWR. 2004; 53(17):362–365. [PubMed: 15129193]
4. Record RG, Mc KT. Congenital malformations of the central nervous system; maternal reproductive history and familial incidence. British journal of social medicine. Jan; 1950 4(1):26–50. [PubMed: 15426747]
5. Kondo A, Kamihira O, Ozawa H. Neural tube defects: prevalence, etiology and prevention. International journal of urology : official journal of the Japanese Urological Association. Jan; 2009 16(1):49–57. [PubMed: 19120526]
6. Wallingford JB, Niswander LA, Shaw GM, Finnell RH. The continuing challenge of understanding, preventing, and treating neural tube defects. Science. Mar 1.2013 339(6123):1222002. [PubMed: 23449594]
7. Lupo PJ, Symanski E, Waller DK, et al. Maternal exposure to ambient levels of benzene and neural tube defects among offspring: Texas, 1999–2004. Environ Health Perspect. Mar; 2011 119(3):397–402. [PubMed: 20923742]

8. Schembari A, Nieuwenhuijsen MJ, Salvador J, et al. Traffic-related air pollution and congenital anomalies in Barcelona. Environ Health Perspect. Mar; 2014 122(3):317–323. [PubMed: 24380957]
9. Padula AM, Tager IB, Carmichael SL, Hammond SK, Lurmann F, Shaw GM. The association of ambient air pollution and traffic exposures with selected congenital anomalies in the San Joaquin Valley of California. Am J Epidemiol. May 15; 2013 177(10):1074–1085. [PubMed: 23538941]
10. Wasserman CR, Shaw GM, Selvin S, Gould JB, Syme SL. Socioeconomic status, neighborhood social conditions, and neural tube defects. American journal of public health. Nov; 1998 88(11): 1674–1680. [PubMed: 9807535]
11. Grewal J, Carmichael SL, Song J, Shaw GM. Neural tube defects: an analysis of neighbourhood- and individual-level socio-economic characteristics. Paediatr Perinat Epidemiol. Mar; 2009 23(2): 116–124. [PubMed: 19159398]
12. Yoon PW, Rasmussen SA, Lynberg MC, et al. The National Birth Defects Prevention Study. Public Health Rep. 2001; 116(Suppl 1):32–40. [PubMed: 11889273]
13. Croen LA, Shaw GM, Jensvold NG, Harris JA. Birth defects monitoring in California: a resource for epidemiological research. Paediatr Perinat Epidemiol. Oct; 1991 5(4):423–427. [PubMed: 1754501]
14. Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol. Mar; 2003 67(3):193–201. [PubMed: 12797461]
15. Hernan MA, Hernandez-Diaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am J Epidemiol. Jan 15; 2002 155(2):176–184. [PubMed: 11790682]

Table 1

Demographic characteristics (%) of subjects born between 1997 and 2006 in 8 counties in the San Joaquin Valley of California (N=1064).

	Controls (n=849)	Neural Tube Defects[a] (n=215)	Spina Bifida (n=138)	Anencephaly (n=77)
Maternal education (years)				
<12	32	35	33	38
12	27	34	34	35
>12	40	31	33	27
Missing	<1	0	0	0
Maternal race/ethnicity				
White	31	26	24	30
Foreign-born Hispanic	29	38	38	36
U.S.- born Hispanic	26	27	30	22
Other	14	9	8	10
Missing	<1	<1	0	1
Multi-vitamin use[b]				
Yes	65	65	62	70
No	33	31	35	25
Missing	2	4	3	5
Smoking[c]				
None	74	74	71	79
Active only	8	8	9	8
Passive only	10	15	18	9
Active and passive	6	3	2	4
Missing	<1	0	0	0
Maternal age (years)				
<20	18	14	12	18
20–24	29	26	30	18
25–29	25	33	35	31
30–34	18	18	16	21
≥35	10	9	7	12
Infant sex				
Male	52	47	49	45
Female	48	48	49	47
Missing	0	4	2	8
Plurality				
Singletons	99	96	97	95
Multiples	1	4	3	5
Parity				
0	38	28	31	23
1	30	34	30	40
2+	32	38	39	36

	Controls (n=849)	Neural Tube Defects[a] (n=215)	Spina Bifida (n=138)	Anencephaly (n=77)
Year of expected delivery date				
1997–2000	37	36	36	35
2001–2003	32	35	37	32
2004–2006	31	29	27	32

[a] 1 case with anencephaly and spina bifida is counted only as anencephaly case.

[b] Any folate-containing multi-vitamin use during one month before through two months after conception.

[c] Any smoking during one month before through two months after conception.

Table 2

Pearson correlation coefficients[a] of exposures[b] among controls born between 1997 and 2006 in 8 counties in the San Joaquin Valley of California (N=849).

	CO	NO	NO_2	PM_{10}	$PM_{2.5}$
Carbon monoxide (CO)	1				
Nitrogen oxide (NO)	0.81	1			
Nitrogen dioxide (NO_2)	0.73	0.74	1		
Particulate matter <10 μm (PM_{10})	0.40	0.22	0.51	1	
Particulate matter <2.5 μm ($PM_{2.5}$)	0.84	0.75	0.62	0.54	1

[a] $p<0.0001$

[b] Pollutant levels are based on 24-hour average measurements.

Paediatr Perinat Epidemiol. Author manuscript; available in PMC 2016 November 01.

Paediatr Perinat Epidemiol. Author manuscript; available in PMC 2016 November 01.

Table 3

Pearson correlation coefficients[a] of neighbourhood factors among controls born between 1997 and 2006 in 8 counties in the San Joaquin Valley of California (N=849).

	Poverty	Income	Education	Male unemployment	Female unemployment	Public assistance	Home value	Age of housing	PCA [b]
Poverty	1								
Low income	0.76	1							
Low education	0.56	0.48	1						
Male unemployment	0.52	0.44	0.53	1					
Female unemployment	0.53	0.50	0.57	0.51	1				
Public assistance	0.59	0.55	0.47	0.43	0.47	1			
Low home value	0.57	0.52	0.52	0.50	0.47	0.47	1		
Older housing	0.42	0.44	0.31	0.36	0.37	0.33	0.44	1	
PCA	0.79	0.70	0.68	0.62	0.67	0.63	0.63	0.45	1

[a] $p<0.001$

[b] Principal component analysis

Table 4

Adjusted[a] odds ratios (AOR) and 95% confidence intervals (CI) of neural tube defects and spina bifida comparing each quartile of exposure to PM_{10}[b] to the lowest (1st) quartile, stratified by neighbourhood socioeconomic factors, among births between 1997 and 2006 in 8 counties in the San Joaquin Valley of California.

Neighbourhood Factor[c]	PM_{10} quartile	Controls N	Neural tube defects		Spina bifida	
			Cases N	AOR (95% CI)	Cases N	AOR (95% CI)
High poverty	4th	117	40	1.92 (1.01, 3.67)	27	2.58 (1.11, 5.98)
	3rd	89	25	1.56 (0.78, 3.13)	20	2.51 (1.05, 6.02)
	2nd	95	17	0.94 (0.45, 1.99)	12	1.31 (0.51, 3.37)
	1st	91	16	1.00 (Reference)	8	1.00 (Reference)
Low poverty	4th	83	19	0.77 (0.41, 1.46)	13	0.78 (0.37, 1.65)
	3rd	113	19	0.57 (0.30, 1.07)	12	0.52 (0.24, 1.10)
	2nd	109	31	0.98 (0.56, 1.73)	16	0.74 (0.37, 1.49)
	1st	107	34	1.00 (Reference)	23	1.00 (Reference)
Low income	4th	104	33	2.37 (1.15, 4.90)	24	5.07 (1.68, 15.26)
	3rd	83	24	2.14 (1.00, 4.57)	19	5.02 (1.68, 15.46)
	2nd	94	17	1.30 (0.58, 2.89)	14	3.15 (0.99, 9.99)
	1st	88	12	1.00 (Reference)	4	1.00 (Reference)
High income	4th	96	26	0.81 (0.45, 1.43)	16	0.71 (0.36, 1.40)
	3rd	119	20	0.51 (0.28, 0.94)	13	0.46 (0.22, 0.94)
	2nd	110	31	0.86 (0.49, 1.49)	14	0.54 (0.27, 1.09)
	1st	110	38	1.00 (Reference)	27	1.00 (Reference)
Low education	4th	113	42	1.88 (1.03, 3.43)	29	3.20 (1.39, 7.36)
	3rd	96	25	1.28 (0.66, 2.46)	18	2.28 (0.94, 5.53)
	2nd	105	19	0.86 (0.43, 1.72)	15	1.70 (0.69, 4.20)
	1st	97	20	1.00 (Reference)	8	1.00 (Reference)
High education	4th	87	17	0.67 (0.35, 1.31)	11	0.57 (0.26, 1.25)
	3rd	106	19	0.64 (0.34, 1.22)	14	0.60 (0.29, 1.24)

Neighbourhood Factor[c]	PM_{10} quartile	Controls N	Neural tube defects		Spina bifida	
			Cases N	AOR (95% CI)	Cases N	AOR (95% CI)
	2nd	99	29	1.05 (0.58, 1.88)	13	0.60 (0.29, 1.26)
	1st	101	30	1.00 (Reference)	23	1.00 (Reference)

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

Wald chi-square test of homogeneity p<0.05 for all comparisons.

The results for anencephaly are presented in the web material

[a] Analyses are adjusted for maternal race/ethnicity, education and vitamin use (for the month prior to and/or the first two months of pregnancy)

[b] PM_{10} levels are based on 24-hour average measurements, which are then averaged over 1st and 2nd months of pregnancy and analysed in quartiles (determined from controls). Quartile ranges: 1st =7.90–25.24; 2nd =25.25–33.43; 3rd =33.44–44.08; 4th=44.09–95.32 μg/m^3

[c] Variables from the 2000 U.S. Census at the block group level stratified near the median

Table 5

Adjusted[a] odds ratios (AOR) and 95% confidence intervals (CI) of neural tube defects and spina bifida comparing each pollutant score to zero[b], stratified by neighbourhood socioeconomic factors, between 1997 and 2006 in 8 counties in the San Joaquin Valley of California.

Neighbourhood Factor[c]	Pollutant score	Controls N	Cases N	Neural tube defects AOR (95% CI)	Cases N	Spina bifida AOR (95% CI)
High poverty	3–5	79	25	1.78 (0.99, 3.22)	16	1.54 (0.77, 3.09)
	1–2	118	38	1.82 (1.07, 3.09)	26	1.70 (0.92, 3.14)
	Zero	180	32	1.00 (Reference)	23	1.00 (Reference)
Low poverty	3–5	83	29	1.78 (1.04, 3.05)	17	1.65 (0.85, 3.18)
	1–2	101	28	1.34 (0.79, 2.28)	17	1.27 (0.66, 2.42)
	Zero	223	45	1.00 (Reference)	29	1.00 (Reference)
Low income	3–5	72	24	1.86 (1.02, 3.40)	16	1.67 (0.83, 3.36)
	1–2	105	28	1.43 (0.81, 2.53)	20	1.41 (0.73, 2.69)
	Zero	177	32	1.00 (Reference)	23	1.00 (Reference)
High income	3–5	90	30	1.70 (1.00, 2.88)	17	1.51 (0.79, 2.90)
	1–2	114	38	1.66 (1.01, 2.71)	23	1.55 (0.86, 2.82)
	Zero	226	45	1.00 (Reference)	29	1.00 (Reference)
Low education	3–5	84	30	1.91 (1.10, 3.31)	18	1.75 (0.89, 3.44)
	1–2	120	37	1.64 (0.98, 2.76)	27	1.85 (1.01, 3.38)
	Zero	194	36	1.00 (Reference)	23	1.00 (Reference)
High education	3–5	78	24	1.65 (0.93, 2.93)	15	1.47 (0.74, 2.92)
	1–2	99	29	1.48 (0.86, 2.53)	16	1.16 (0.60, 2.25)
	Zero	209	41	1.00 (Reference)	29	1.00 (Reference)
High male unemployment	3–5	78	29	1.83 (1.06, 3.15)	19	1.73 (0.91, 3.28)
	1–2	116	41	1.73 (1.06, 2.81)	28	1.72 (0.97, 3.05)
	Zero	214	43	1.00 (Reference)	29	1.00 (Reference)
Low male unemployment	3–5	84	25	1.69 (0.94, 3.02)	14	1.41 (0.69, 2.90)
	1–2	103	25	1.33 (0.75, 2.36)	15	1.18 (0.59, 2.37)
	Zero	189	34	1.00 (Reference)	23	1.00 (Reference)
High female unemployment	3–5	94	32	1.82 (1.08, 3.06)	21	1.67 (0.91, 3.08)

Neighbourhood Factor[C]	Pollutant score	Controls N	Cases N	Neural tube defects AOR (95% CI)	Cases N	Spina bifida AOR (95% CI)
	1–2	133	44	1.72 (1.07, 2.76)	32	1.77 (1.03, 3.04)
	Zero	233	44	1.00 (Reference)	31	1.00 (Reference)
Low female unemployment	3–5	68	22	1.68 (0.91, 3.11)	12	1.43 (0.66, 3.10)
	1–2	86	22	1.31 (0.72, 2.40)	11	1.02 (0.47, 2.22)
	Zero	170	33	1.00 (Reference)	21	1.00 (Reference)
High public assistance	3–5	58	17	1.43 (0.73, 2.81)	9	1.05 (0.45, 2.44)
	1–2	87	33	1.82 (1.03, 3.21)	22	1.70 (0.88, 3.28)
	Zero	148	30	1.00 (Reference)	21	1.00 (Reference)
Low public assistance	3–5	104	37	1.96 (1.20, 3.22)	24	1.94 (1.08, 3.49)
	1–2	132	33	1.34 (0.82, 2.21)	21	1.30 (0.71, 2.35)
	Zero	255	47	1.00 (Reference)	31	1.00 (Reference)
Low median home value	3–5	104	32	1.42 (0.85, 2.37)	18	1.03 (0.55, 1.93)
	1–2	141	43	1.40 (0.87, 2.24)	30	1.27 (0.74, 2.18)
	Zero	207	45	1.00 (Reference)	34	1.00 (Reference)
High median home value	3–5	58	22	2.44 (1.31, 4.56)	15	3.01 (1.41, 6.41)
	1–2	78	23	1.78 (0.97, 3.24)	13	1.81 (0.84, 3.88)
	Zero	196	32	1.00 (Reference)	18	1.00 (Reference)
Majority older housing	3–5	122	42	1.74 (1.10, 2.76)	26	1.58 (0.91, 2.74)
	1–2	157	47	1.44 (0.93, 2.24)	32	1.44 (0.86, 2.42)
	Zero	271	55	1.00 (Reference)	37	1.00 (Reference)
Majority newer housing	3–5	40	12	1.76 (0.79, 3.91)	7	1.54 (0.58, 4.07)
	1–2	62	19	1.83 (0.92, 3.65)	11	1.57 (0.68, 3.64)
	Zero	132	22	1.00 (Reference)	15	1.00 (Reference)
High PCA	3–5	85	26	1.49 (0.85, 2.62)	17	1.38 (0.71, 2.68)
	1–2	114	38	1.59 (0.96, 2.65)	26	1.55 (0.86, 2.80)
	Zero	191	39	1.00 (Reference)	27	1.00 (Reference)
Low PCA	3–5	77	28	2.09 (1.19, 3.66)	16	1.84 (0.92, 3.66)
	1–2	105	28	1.48 (0.86, 2.56)	17	1.37 (0.70, 2.65)
	Zero	212	38	1.00 (Reference)	25	1.00 (Reference)

The results for anencephaly are presented in the web material

[a] Analyses are adjusted for maternal race/ethnicity, education and vitamin use (for the month prior to and/or the first two months of pregnancy)

[b] Zero = below highest quartile for all five pollutants (CO, NO, NO_2, PM_{10}, and $PM_{2.5}$), 1–2 pollutant exposures above the highest quartile, and 3–5 pollutant exposures above the highest quartile. Participants with data on at least 3 pollutants were included.

[c] Variables from the 2000 U.S. Census at the block group level stratified near the median