Environmental Research 146 (2016) 315–322

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Maternal residential proximity to major roadways at delivery and childhood central nervous system tumors

Heather E. Danysh [a,b], Kai Zhang [b], Laura E. Mitchell [b], Michael E. Scheurer [a], Philip J. Lupo [a,*]

[a] Department of Pediatrics, Hematology-Oncology Section, Texas Children's Cancer Center, Dan L. Duncan Cancer Center, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, United States
[b] Department of Epidemiology, Human Genetics and Environmental Sciences, University of Texas School of Public Health, 1200 Hermann Pressler Drive, Houston, TX 77030, United States

ARTICLE INFO

Article history:
Received 21 November 2015
Received in revised form
22 December 2015
Accepted 11 January 2016
Available online 20 January 2016

Keywords:
Air pollution
Ependymoma
Epidemiology
Primitive neuroectodermal tumor
Traffic

ABSTRACT

Background: Due to concerns over the impact of traffic-related air pollution on childhood cancers, we evaluated the association between residential proximity to major roadways and childhood central nervous system (CNS) tumors.

Methods: The Texas Cancer Registry provided information on children diagnosed with a CNS tumor at <5 years of age and born in Texas for the period 2003–2009 ($n=315$). Birth certificate controls were frequency matched to cases (5:1) on birth year ($n=1575$). We assigned exposures to traffic-related air pollution using residential proximity to major roadways based on the maternal residence at the time of delivery. Logistic regression was used to generate unadjusted and adjusted odds ratios and 95% confidence intervals (CI). We evaluated CNS tumors as a group and by histologic type.

Results: Maternal residential proximity to major roadways at delivery was positively associated with the odds of offspring having a CNS tumor. Specifically, for every kilometer closer to a major roadway, the odds of offspring having a CNS tumor increased by 30% (95% CI: 1.0, 1.7). Mothers living ≤ 500 meters (m) from a major roadway were 31% (95% CI: 1.0, 1.8) more likely to have offspring with any CNS tumor and 3.1-times (95% CI: 0.9, 10.4) more likely to have offspring with an ependymoma compared to mothers living >500 m from the nearest major roadway. Moreover, compared to mothers living in areas with low roadway density, those living in areas with high roadway density were 51% (95% CI: 1.1, 2.1) more likely to have offspring with any CNS tumor and 4.2-times (95% CI: 1.2, 14.9) more likely to have offspring with an ependymoma. There were no statistically significant associations observed between continuous distance to major roadways and ependymoma as well as between the proximity measures and the other evaluated CNS tumor phenotypic groups.

Conclusions: The results of this large population-based study indicate that mothers who live near major roadways or in areas with high roadway density may be more likely to have offspring with a CNS tumor, particularly an ependymoma.

1. Introduction

The environmental and health effects of urbanization remain a concern as more populations shift from rural to urban areas. In fact, as of 2014, 81% of the United States (U.S.) population lives in an urban area (Population Reference Bureau, 2014). Growing metropolitan areas require large roadways and dense roadway networks to accommodate the increasing number of motor vehicles, one of the leading sources of urban air pollution. Motor vehicle emissions are a complex mixture of compounds, including nitrogen oxides, carbon monoxide, particulate matter, and hydrocarbons (e.g., benzene), many of which are known to be hazardous to human health (Health Effects Institute, 2010). The highest

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; CNS, central nervous system; DNA, deoxyribonucleic acid; GIS, geographic information systems; ICCC-3, International Classification of Childhood Cancer, third edition; ICD-O-3, International Classification of Diseases for Oncology, third edition; IQR, interquartile range; IRR, incidence rate ratio; JPA, juvenile pilocytic astrocytoma; km, kilometers; m, meters; OR, odds ratio; PAH, polycyclic aromatic hydrocarbons; $PM_{2.5}$, fine particulate matter ≤ 2.5 micrometers in aerodynamic diameter; PNET, primitive neuroectodermal tumor; SES, socioeconomic status; TCR, Texas Cancer Registry; TX DSHS, Texas Department of State Health Services; U.S., United States

* Correspondence to: Baylor College of Medicine, Department of Pediatrics, Section of Hematology-Oncology, One Baylor Plaza, MS: BCM305, Houston, TX 77030, United States.
E-mail addresses: danysh@bcm.edu (H.E. Danysh), Kai.Zhang@uth.tmc.edu (K. Zhang), Laura.E.Mitchell@uth.tmc.edu (L.E. Mitchell), scheurer@bcm.edu (M.E. Scheurer), Philip.Lupo@bcm.edu (P.J. Lupo).

http://dx.doi.org/10.1016/j.envres.2016.01.012
0013-9351/

concentrations of these pollutants are in the near-road environment where approximately 30–45% of the urban population lives, suggesting important implications for air pollution-related health risks (Health Effects Institute, 2010; Karner et al., 2010).

There is a growing concern over the impact of traffic-related air pollution exposure on childhood cancers, including central nervous system (CNS) tumors (Ghosh et al., 2013; Heck et al., 2013; Raaschou-Nielsen and Reynolds, 2006). Among children in the U. S., central nervous system (CNS) tumors are the most common group of solid malignancies and the leading cause of cancer-related mortality (Ward et al., 2014). While survival has improved in recent decades due to advances in therapy, these children suffer from several treatment-related chronic health conditions including neurocognitive deficits, hearing loss, cardiovascular disease, and overall poor quality of life (Armstrong, 2010). The few established risk factors for childhood CNS tumors (e.g., exposure to ionizing radiation and genetic predisposition syndromes) account for $<5\%$ of all cases, leaving the causes of most cases to be unknown (Gurney et al., 1999; Johnson et al., 2014).

Environmental exposures, such as air pollution, are suspected to be involved in the etiology of CNS tumors in children. However, the few studies that have evaluated the association between traffic-related air pollution exposure and childhood CNS tumors have provided conflicting results. This is likely due to variations in exposure assessment and exposure timing, heterogeneity across the CNS tumor phenotypes (e.g., astrocytoma and medulloblastoma), and differences in study design (Danysh et al., 2015b; Ghosh et al., 2013; Heck et al., 2013; Reynolds et al., 2004; Savitz and Feingold, 1989).

To our knowledge, no study has comprehensively assessed residential proximity to major roadways and the association with childhood CNS tumors and, in particular, the association with specific CNS tumor phenotypes. The aim of the current study is to evaluate the associations between maternal residential proximity to major roadways, including roadway density, and the odds of having offspring with an astrocytoma, ependymoma, medulloblastoma, and primitive neuroectodermal tumor (PNET) in a population-based sample of children in Texas.

2. Methods

2.1. Study population

We identified 436 children born during the period of 1 January 2003 and 31 December 2009 and diagnosed with a CNS tumor at <5 years of age from the Texas Cancer Registry (TCR), which is part of the Texas Department of State Health Services (TX DSHS). The TCR is a large population-based registry with gold certification from the North American Association of Central Cancer Registries during the study period. We included all CNS tumor cases as defined under group III of the *International Classification of Childhood Cancer, third edition* (ICCC-3) (Steliarova-Foucher et al., 2005). The major CNS tumor phenotypes included: (1) juvenile pilocytic astrocytoma (JPA) (*International Classification of Diseases for Oncology, third edition* [ICD-O-3] code 9421); (2) astrocytoma (ICCC-3 group IIIb, excluding JPA); (3) ependymoma (ICCC-3 group IIIa.1); 4) medulloblastoma (ICCC-3 group IIIc.1); and (5) PNET (ICCC-3 group IIIc.2). Cases included only those children with a CNS tumor as their first malignancy. In addition to tumor histology information, we obtained information on age at diagnosis for each CNS tumor case from the TCR. We obtained birth certificate information for each CNS tumor case from the TX DSHS Center for Health Statistics. CNS tumor cases that did not have a Texas birth certificate (i.e., were not born in Texas) were excluded.

We randomly selected population-based controls from the birth certificate files of children born to Texas residents during the period of 2003–2009 and who were not listed in the TCR. Controls were frequency-matched to CNS tumor cases on birth year at a ratio of five controls to one CNS tumor case. For cases and controls, we obtained information on child and maternal demographics as well as maternal residential information at delivery from each subject's birth certificate file. The Institutional Review Boards of the University of Texas Health Science Center at Houston, Baylor College of Medicine, and the TX DSHS approved the study protocol.

2.2. Exposure assessment

To measure maternal residential proximity to major roadways, we obtained the Texas roadway network StratMap for 2006, the midpoint of the study period (2003–2009), from the Texas National Resources Information System (Texas Natural Resources Information System, 2014). We assessed exposure to traffic-related air pollution utilizing three surrogate measures, each a measure of the proximity of the maternal residence to major roadways: (1) continuous distance of the residence to the nearest major roadway, (2) the presence of a major roadway within a 500-meter (m) radius of the residence, and (3) the density of major roadways within a 500-m radius of the residence. In a recent report, the Health Effects Institute concluded that the zone of 500 m from a major roadway is that which has the highest concentration of primary air pollutants from traffic emissions (Health Effects Institute, 2010), and, therefore, this was selected as the area of interest to assess exposure. A major roadway was defined as any road with an A1, A2, or A3 Feature Class Code as designated by the U.S. Census Bureau, which includes interstate, state, county, and toll highways (U.S. Census Bureau, 2007).

The Center for Health Statistics geocoded the maternal residential address at the time of delivery as recorded on each subject's birth certificate. The longitude and latitude data points from the geocoded addresses were used to assess residential proximity to major roadways. A geographic information systems (GIS) approach was used to assess exposure. Specifically, we used the spatial analysis capabilities of ArcGIS, version 10.0 (Environmental Systems Research Institute Inc., Redlands, CA).

The Euclidean distance (i.e., “as the crow flies”) defined the distance of the maternal residence to the nearest side of the nearest major roadway, and was modeled as a continuous variable (kilometers [km]). Buffer analysis was used to determine if a major roadway was within the 500-m radius from the maternal residence at the time of delivery. Exposure was then defined as a dichotomous variable if a major roadway fell within the 500-m residential radius (yes or no). Roadway density was calculated by summing all major roadway segments (km) that fell within the 500-m radius of the maternal residence, which was then modeled as a categorical variable. The “low roadway density” category included mothers living further than 500 m from the nearest major roadway. Mothers living within 500 m of a major roadway were designated living in an area with “medium roadway density” or “high roadway density.” The cut point of 1.53 km of major roadways within a 500-m residential radius defined medium *vs.* high roadway density and was based on the median split of the distribution of roadway density among the control subjects living within 500 m of a major roadway.

2.3. Covariates

We considered several potential confounders that are known or suspected to be associated with childhood CNS tumors and air pollution exposure. Child factors included sex and season of birth (summer, fall, winter, or spring) (Hertz-Picciotto et al., 2008; Matz et al., 2014). Maternal factors included race/ethnicity (non-Hispanic white, Hispanic, and other) as well as age (years) and

Table 1
Demographic characteristics of CNS tumor cases and birth certificate controls in Texas, 2003–2009.

Characteristic	Cases, *n* (%)					
	All CNS tumors[a]	Astrocytoma	JPA	Ependymoma	Medulloblastoma	Controls
	n=315	*n*=66 (21.0%)	*n*=43 (13.7%)	*n*=26 (8.3%)	*n*=29 (9.2%)	*n*=1575
Child						
Sex, *n* (%)						
Male	173 (54.9)	36 (54.5)	23 (53.5)	21 (80.8)	21 (72.4)	792 (50.3)
Female	142 (45.1)	30 (45.5)	20 (46.5)	5 (19.2)	8 (27.6)	783 (49.7)
Season of Birth, *n* (%)						
Summer (June–August)	92 (29.2)	17 (25.8)	15 (34.9)	10 (38.5)	8 (27.6)	412 (26.2)
Fall (September–November)	55 (17.5)	11 (16.7)	6 (14.0)	6 (23.1)	4 (13.8)	413 (26.2)
Winter (December–February)	89 (28.3)	18 (27.3)	15 (34.9)	5 (19.2)	11 (37.9)	350 (22.2)
Spring (March–May)	79 (25.1)	20 (30.3)	7 (16.2)	5 (19.2)	6 (20.7)	400 (25.4)
Age at diagnosis (years), *n* (%)						
< 2	164 (52.1)	29 (43.9)	18 (41.9)	16 (61.5)	14 (48.3)	
2 to < 5	151 (47.9)	37 (56.1)	25 (58.1)	10 (38.5)	15 (51.7)	
Maternal						
Race/ethnicity, *n* (%)						
Non-Hispanic white	128 (40.6)	31 (47.0)	24 (55.8)	9 (34.6)	8 (27.6)	623 (39.6)
Hispanic	151 (47.9)	28 (42.4)	18 (41.9)	14 (53.9)	14 (48.3)	758 (48.1)
Other	36 (11.4)	7 (10.6)	1 (2.3)	3 (11.5)	7 (24.2)	194 (12.3)
Age at Delivery (years), *n* (%)						
< 25	107 (34.0)	21 (37.9)	18 (41.8)	7 (26.9)	8 (27.6)	655 (41.6)
25 to < 30	94 (29.9)	18 (27.3)	14 (32.6)	9 (34.6)	12 (41.4)	410 (26.0)
30 to < 35	65 (20.6)	11 (16.7)	6 (14.0)	4 (15.4)	4 (13.8)	327 (20.8)
≥ 35	49 (15.6)	16 (24.2)	5 (11.6)	6 (23.1)	5 (17.2)	183 (11.6)
Education, *n* (%)						
< High School	74 (23.5)	13 (19.7)	11 (25.6)	7 (26.9)	10 (34.5)	482 (30.6)
Completed High School	95 (30.2)	17 (25.8)	12 (27.9)	11 (42.3)	10 (34.5)	427 (27.1)
> High School	144 (45.7)	35 (53.0)	20 (46.5)	8 (30.8)	9 (31.0)	657 (41.7)
Neighborhood at Birth						
Area-level Poverty, *n* (%)						
< 15% of households	199 (63.2)	49 (74.2)	25 (58.1)	20 (76.9)	12 (41.4)	888 (56.4)
≥ 15% of households	116 (36.8)	17 (25.8)	18 (41.9)	6 (23.1)	17 (58.6)	687 (43.6)
Urban Status, *n* (%)						
Rural	22 (7.0)	NR	NR	NR	NR	72 (4.6)
Urban	293 (93.0)	NR	NR	NR	NR	1,503 (95.4)
Maternal Proximity to Major Roads						
Continuous distance (km), mean (SD)	0.36 (0.43)	0.39 (0.53)	0.35 (0.37)	0.34 (0.39)	0.29 (0.25)	0.42 (0.63)
Within 500 m, *n* (%)						
> 500 m	69 (21.9)	14 (21.2)	10 (23.3)	3 (11.5)	6 (20.7)	393 (25.0)
≤ 500 m	246 (78.1)	52 (78.8)	33 (76.7)	23 (88.5)	23 (79.3)	1173 (75.0)
Roadway Density[b], *n* (%)						
Low	69 (21.9)	14 (21.2)	10 (23.3)	3 (11.5)	6 (20.7)	393 (25.0)
Medium	105 (33.3)	29 (43.9)	11 (25.6)	8 (30.8)	10 (34.5)	591 (37.5)
High	141 (44.8)	23 (34.9)	22 (51.2)	15 (57.7)	13 (44.8)	591 (37.5)

Abbreviations: CNS, central nervous system tumors; JPA, juvenile pilocytic astrocytoma; km, kilometer; m, meter; NR, not reported due to small cell sizes and protection of confidentiality; SD, standard deviation.

[a] Primitive neuroectodermal tumor (PNET; *n*=10 [3.2%]) distributions not shown due to small cell sizes and protection of confidentiality.

[b] Low, residence > 500 m from nearest major roadway; Medium, > 0 and < 1.53 km of major roadways within 500-m residential radius; High, ≥ 1.53 km of major roadways within 500-m residential radius.

education level (less than high school, completed high school, and more than high school) at the time of delivery (Gray et al., 2014; Johnson et al., 2014). Information on child and maternal factors was obtained from the child's birth certificate. Additionally, we considered socioeconomic status (SES) as a potential confounder (Linder et al., 2008). We used area-level poverty as a proxy for SES as information on individual-level SES (e.g., household income) is not available from birth certificates in Texas. Specifically, we

Table 2
Associations between Continuous Distance (kilometers) of Maternal Residence to Nearest Major Roadway and CNS Tumors in Offspring.

CNS tumor phenotype	Cases, mean (SD)	Controls, mean (SD)	Unadjusted OR [95% CI]	Adjusted OR [95% CI]
All CNS tumors	0.36 (0.43)	0.42 (0.63)	1.23 [0.97, 1.57]	1.30 [1.01, 1.67][a]
Astrocytoma (non-JPA)	0.39 (0.53)	0.42 (0.63)	1.11 [0.71, 1.73]	1.27 [0.79, 2.07][a]
JPA	0.35 (0.37)	0.42 (0.63)	1.29 [0.68, 2.45]	1.29 [0.66, 2.51][b]
Ependymoma	0.34 (0.39)	0.42 (0.63)	1.37 [0.57, 3.30]	1.67 [0.64, 4.39][a]
Medulloblastoma	0.29 (0.25)	0.42 (0.63)	1.87 [0.66, 5.33]	1.61 [0.59, 4.43][a]
PNET	0.23 (0.22)	0.42 (0.63)	3.82 [0.33, 44.39]	3.92 [0.34, 45.72][b]

Abbreviations: CI, confidence interval; CNS, central nervous system tumors; JPA, juvenile pilocytic astrocytoma; OR, odds ratio; PNET, primitive neuroectodermal tumor; SD, standard deviation.

[a] Adjusted for area-level poverty and birth year.
[b] Adjusted for birth year.

obtained information from the 2000 U.S. Census on the proportion of households with an income lower than the poverty level in a census tract. A census tract is a small statistical subdivision of a county designed to represent a relatively homogenous group of approximately 4000 individuals (U.S. Census Bureau, 2015). Low census tract-level poverty was defined as living in a census tract where $<15\%$ of households had an income below the poverty level, whereas high census tract-level poverty was defined as living in a census tract where $\geq 15\%$ of households had an income below the poverty level.

2.4. Statistical analysis

We calculated frequency distributions of child and maternal demographic factors as well as area-level factors, including poverty and urban status, for case subjects, by each CNS tumor phenotype, and control subjects. Information on census tract-level urban status was obtained from the 2000 U.S. Census. We used logistic regression to assess the association between maternal residential proximity to major roadways at birth and each childhood CNS tumor phenotype. In addition to estimating unadjusted odds ratios (OR) and 95% confidence intervals (CI) using univariable logistic regression, we also generated adjusted ORs (aOR) and 95% CIs using multivariable logistic regression. A variable was included as a confounder in a multivariable model if its inclusion resulted in at least a 10% change in the effect estimate between the maternal residential proximity measure and the CNS tumor phenotype. Any covariate remaining in the multivariable model for a specific residential proximity measure and any of the CNS tumor phenotypes was also included in the multivariable model used to assess the residential proximity measure and all CNS tumors as a group. Birth year was included in all multivariable models as this was the matching factor for cases and controls. To test for a trend in the association between roadway density and CNS tumors, we repeated the analyses where the categorized roadway density variable was included in the regression models as a continuous variable; trends were considered statistically significant if the P for trend was <0.05. All statistical analyses were conducted using Stata, version 13.1 (StataCorp LP, College Station, TX).

3. Results

3.1. Sample characteristics

We identified 436 children born during the period of 2003–2009 and residing in Texas at the time of their CNS tumor diagnosis. Of these, the TCR successfully linked 357 (81.9%) to their Texas birth certificate. The remaining 79 (18.1%) CNS tumor cases were likely born outside of Texas and were excluded from this assessment. Of those with a Texas birth certificate, an additional 42 (11.8%) cases were excluded due to missing maternal residential information. A similar proportion of potential control subjects were also missing maternal residential information (1118 of 10,211 [11.0%]). Excluded cases with invalid addresses were similar to cases retained in the analysis on child and maternal characteristics as well as area-level characteristics (data not shown).

Of the 315 (72.2%) CNS tumor cases included in this assessment, the largest phenotypic group was non-JPA astrocytoma ($n=66$ [21.0%]) followed by JPA ($n=43$ [13.7%]), medulloblastoma ($n=29$ [9.2%]), ependymoma ($n=26$ [8.3%]), and PNET ($n=10$ [3.2%]) (Table 1). Half of these (52.1%) were diagnosed before two years of age. Compared to control subjects, case subjects were more likely to be born in the winter (28.3% of cases *vs.* 22.2% of controls) and less likely to be born in the fall (17.5% of cases *vs.* 26.2% of controls). At delivery, case mothers were more likely to be 35 years of age or older (66.0% of case mothers *vs.* 58.4% of control mothers), have at least a high school diploma (75.9% of case mothers *vs.* 68.8% of control mothers), and live in an area with low poverty (63.2% of case mothers *vs.* 56.4% of control mothers).

3.2. Continuous distance to nearest major roadway

For every one km closer a mother lived to a major roadway at delivery, the odds of her offspring having a CNS tumor increased by 30% (95% CI: 1.01, 1.67) (Table 2). Positive associations were observed between closer residential proximity to a major roadway and each of the CNS tumor phenotypes, with the strongest associations observed with ependymoma (aOR [95% CI]: 1.67 [0.64, 4.39]) and PNET (aOR [95% CI]: 3.92 [0.34, 45.72]).

3.3. Within 500 m of major roadway

Mothers living within 500 m of a major roadway at delivery were more likely to have offspring with a CNS tumor (aOR [95% CI]: 1.31 [0.97, 1.76]) compared to those living further than 500 m from the nearest major roadway (Table 3). The strongest associations were observed with ependymoma (aOR [95% CI]: 3.08 [0.91, 10.42]) and PNET (aOR [95% CI]: 3.04 [0.38, 24.07]).

3.4. Roadway density

Mothers living in areas with medium roadway density (>0 km and <1.53 km of major roadways within the 500-m residential radius) and high roadway density (≥ 1.53 km of major roadways within the 500-m residential radius) were more likely to have offspring that developed any CNS tumor (aOR [95% CI]: 1.11 [0.80, 1.56] and 1.51 [1.09, 2.09], respectively; P for trend $=0.033$) compared to mothers living in areas with low roadway density (Table 4). The strongest associations were observed between medium

Table 3
Associations between Maternal Residential Proximity within 500 m of a Major Roadway and CNS Tumors in Offspring.

Proximity to major roadway	Cases, *n* (%)	Controls, *n* (%)	Unadjusted OR [95% CI]	Adjusted OR [95% CI]
All CNS tumors				
> 500 m (reference)	69 (21.9)	393 (25.0)	1.00	1.00
≤ 500 m	246 (78.1)	1173 (75.0)	1.19 [0.89, 1.58]	1.31 [0.97, 1.76][a]
Astrocytoma (non-JPA)				
> 500 m (reference)	14 (21.2)	393 (25.0)	1.00	1.00
≤ 500 m	52 (78.8)	1173 (75.0)	1.23 [0.68, 2.26]	1.62 [0.86, 3.04][b]
JPA				
> 500 m (reference)	10 (23.3)	393 (25.0)	1.00	1.00
≤ 500 m	33 (76.7)	1173 (75.0)	1.10 [0.54, 2.25]	1.23 [0.60, 2.54][c]
Ependymoma				
> 500 m (reference)	3 (11.5)	393 (25.0)	1.00	1.00
≤ 500 m	23 (88.5)	1173 (75.0)	2.55 [0.76, 8.54]	3.08 [0.91, 10.42][d]
Medulloblastoma				
> 500 m (reference)	6 (20.7)	393 (25.0)	1.00	1.00
≤ 500 m	23 (79.3)	1173 (75.0)	1.27 [0.52, 3.15]	1.03 [0.40, 2.59][e]
PNET				
> 500 m (reference)	1 (10.0)	393 (25.0)	1.00	1.00
≤ 500 m	9 (90.0)	1173 (75.0)	2.99 [0.38, 23.69]	3.04 [0.38, 24.07][f]

Abbreviations: CI, confidence interval; CNS, central nervous system tumors; JPA, juvenile pilocytic astrocytoma; m, meters; OR, odds ratio; PNET, primitive neuroectodermal tumor.

[a] Adjusted for maternal race/ethnicity, education, area-level poverty, and birth year.
[b] Adjusted for maternal education, area-level poverty, and birth year.
[c] Adjusted for maternal race/ethnicity and birth year.
[d] Adjusted for area-level poverty and birth year.
[e] Adjusted for maternal race/ethnicity, area-level poverty, and birth year.
[f] Adjusted for birth year.

Table 4
Associations between Maternal Residential Roadway Density and CNS Tumors in Offspring.

			Unadjusted		Adjusted	
Roadway density[*]	Cases, *n* (%)	Controls, *n* (%)	OR [95% CI]	P for trend	OR [95% CI]	P for trend
All CNS tumors						
Low (reference)	69 (21.9)	393 (25.0)	1.00		1.00	
Medium	105 (33.3)	591 (37.5)	1.01 [0.73, 1.41]		1.11 [0.80, 1.56][a]	
High	141 (44.8)	591 (37.5)	1.36 [0.99, 1.86]	0.033	1.51 [1.09, 2.09][a]	0.008
Astrocytoma (non-JPA)						
Low (reference)	14 (21.2)	393 (25.0)	1.00		1.00	
Medium	29 (43.9)	591 (37.5)	1.38 [0.72, 2.64]		1.75 [0.89, 3.44][b]	
High	23 (34.9)	591 (37.5)	1.09 [0.56, 2.15]	0.913	1.48 [0.73, 2.99][b]	0.352
JPA						
Low (reference)	10 (23.3)	393 (25.0)	1.00		1.00	
Medium	11 (25.6)	591 (37.5)	0.73 [0.31, 1.74]		0.80 [0.34, 1.92][c]	
High	22 (51.2)	591 (37.5)	1.47 [0.69, 3.12]	0.206	1.70 [0.79, 3.66][c]	0.112
Ependymoma						
Low (reference)	3 (11.5)	393 (25.0)	1.00		1.00	
Medium	8 (30.8)	591 (37.5)	1.77 [0.47, 6.73]		2.07 [0.54, 7.91][d]	
High	15 (57.7)	591 (37.5)	3.32 [0.96, 11.56]	0.034	4.23 [1.20, 14.88][d]	0.013
Medulloblastoma						
Low (reference)	6 (20.7)	393 (25.0)	1.00		1.00	
Medium	10 (34.5)	591 (37.5)	1.11 [0.40, 3.07]		0.92 [0.32, 2.59][e]	
High	13 (44.8)	591 (37.5)	1.44 [0.54, 3.82]	0.430	1.13 [0.41, 3.07][e]	0.740
PNET						
Low (reference)	1 (10.0)	393 (25.0)	1.00		1.00	
Medium	2 (20.0)	591 (37.5)	1.33 [0.12, 14.72]		1.43 [0.13, 15.84][c]	
High	7 (70.0)	591 (37.5)	4.65 [0.57, 37.98]	0.070	5.37 [0.65, 44.18][c]	0.053

Abbreviations: CI, confidence interval; CNS, central nervous system tumors; JPA, juvenile pilocytic astrocytoma; OR, odds ratio; PNET, primitive neuroectodermal tumor.

[*] Low, residence > 500 meters (m) from nearest major roadway; Medium, > 0 and < 1.53 kilometers (km) of major roadways within 500-m residential radius; High, ≥ 1.53 km of major roadways within 500-m residential radius
[a] Adjusted for maternal race/ethnicity, education, area-level poverty, and birth year.
[b] Adjusted for maternal education, area-level poverty, and birth year.
[c] Adjusted for maternal race/ethnicity and birth year.
[d] Adjusted for area-level poverty and birth year.
[e] Adjusted for maternal race/ethnicity, area-level poverty, and birth year.

and high roadway density and ependymoma (aOR [95% CI]: 2.07 [0.54, 7.91] and 4.23 [1.20, 14.88], respectively; *P* for trend = 0.013) and PNET (aOR [95% CI]: 1.43 [0.13, 15.84] and 5.37 [0.65, 44.18], respectively; *P* for trend = 0.053).

4. Discussion

Overall, mothers living near major roads (≤ 500 m) with the highest levels of roadway density were more likely to have

offspring with a CNS tumor, especially an ependymoma, compared to mothers living in areas with low roadway density (i.e., not living in close proximity to a major roadway [> 500 m]). In fact, mothers living in high roadway density areas were more than 4-times more likely to have offspring that developed an ependymoma compared to mothers living in low roadway density areas. Furthermore, there was a dose-response relationship between increasing roadway density and the odds of ependymoma. It should be noted that these results are based on a small sample of ependymoma cases ($n=26$), which may explain the lack of an observed statistically significant association when evaluating maternal residential proximity as a continuous variable. There appeared to be strong and consistent associations between maternal residential proximity to major roadways and PNET in offspring. However, there were few PNET cases in our sample ($n=10$) resulting in wide 95% CIs. Overall, associations between the residential proximity measures and each of the CNS tumor phenotypes were consistently positive with few effect estimates close to 1.0. This suggests that close maternal residential proximity to major roadways at the time of delivery may increase the odds of having offspring with a CNS tumor.

Our findings are consistent with previous reports of traffic-related air pollution exposure and childhood CNS tumors. Savitz and Feingold (1989) conducted a study in Denver, Colorado, and reported that children < 5 years old and living in high traffic density areas at the time of diagnosis were 5-times more likely to have a CNS tumor compared to children living in low traffic density areas (OR [95% CI]: 5.2 [1.4, 19.6]) (Savitz and Feingold, 1989). Likewise, Reynolds et al. (2004) used a sample derived from the California Cancer Registry (1988–1997) and reported that mothers living in high traffic density areas (90th percentile) at delivery were 22% more likely (95% CI: 0.87, 1.70) to have offspring with any CNS tumor (diagnosed at < 5 years of age) compared to mothers living in low traffic density areas (25th percentile). However, no substantial association was observed between roadway density and CNS tumors (OR [95% CI]: 1.03 [0.75, 1.43]) (Reynolds et al., 2004). Differences in the magnitude of effect between the Savitz and Feingold (1989) and Reynolds et al. (2004) studies may be due to differences in the timing of exposure (at diagnosis *vs.* at birth, respectively) and possible heterogeneity within their CNS tumor case groups as both studies only evaluated CNS tumors together as a group and did not independently evaluate the various CNS tumor phenotypes (Reynolds et al., 2004; Savitz and Feingold, 1989).

Previous assessments of traffic-related air pollution and ependymoma in children have provided mixed results. Heck et al. (2013) used a sample derived from the California Cancer Registry (1998–2007) and observed a positive association between a one interquartile range (IQR) increase in modeled concentrations of fine particulate matter (≤ 2.5 μm in aerodynamic diameter, $PM_{2.5}$), a pollutant highly associated with motor vehicle emissions in urban areas, and ependymoma risk in children ≤ 5 years old (OR [95% CI]: 1.26 [0.96, 1.20]). This same study also reported a weak positive association between a one IQR increase in traffic density within a 500-m radius from the maternal residence at delivery and ependymoma risk (OR [95% CI]: 1.07 [0.72, 2.21]) (Heck et al., 2013). Conversely, Danysh *et al.* (2015b) conducted an ecologic assessment evaluating CNS tumor incidence in Texas, and did not observe a positive association between census tract-level estimates of traffic-related hazardous air pollutants (HAPs; i.e., 1,3-butadiene, benzene, and diesel particulate matter) and census tract-level ependymoma incidence (all incidence rate ratios [IRR] ≈ 1.0 or < 1.0) (Danysh et al., 2015b). However, this previous assessment relied on area-based estimates of HAPs at the residence of diagnosis to assess exposure, and therefore exposure misclassification may have biased the effect estimates toward the null.

PNET is a highly malignant embryonal tumor that can quickly disseminate throughout the CNS; however, due to the rare nature of PNET, very little is known about the etiology of these tumors (Pollack et al., 2002). Although our findings on maternal residential proximity to major roadways and PNET are based on a relatively small set of cases ($n=10$), the effect estimates suggest potential strong positive associations. In addition, our findings are consistent with those previously reported by Danysh *et al.* (2015b) that areas with high levels of estimated traffic-related HAP concentrations also had increased PNET incidence ($IRR_{1,3\text{-butadiene}}$ [95% CI]: 2.40 [0.83, 6.93]; $IRR_{benzene}$ [95% CI]: 2.09 [0.78, 5.55]) compared to areas with the lowest HAP concentrations (Danysh et al., 2015b). Taken together, our findings with those of Danysh *et al.* (2015b) suggest that air pollution from traffic may be important for PNET etiology and warrant future studies to further explore this potential mechanism.

In the current assessment, we observed positive associations between maternal residential proximity to major roadways, including high roadway density, and astrocytoma (both JPA and non-JPA) in offspring, although these associations were not as strong as those observed with ependymoma and PNET. These findings are also consistent with the assessment by Danysh *et al.* indicating an increased incidence of non-JPA astrocytoma in areas with increased concentrations of traffic-related HAPs (Danysh et al., 2015b).

We relied on the maternal residence at the time of delivery (i.e., the time of the child's birth) to assess exposure. The important period of exposure for childhood CNS tumors is unknown. However, CNS tumor incidence is highest in children < 5 years old. Consequently, exposures occurring *in utero*, near the time of birth, or in early life may be the most relevant for this group of tumors (Selevan et al., 2000). Notably, ependymoma and PNET are diagnosed most commonly in younger children (median diagnosis age of 3 and 4 years, respectively) (Gurney et al., 1999; Ostrom et al., 2015), and were the two phenotypes with the strongest associations with residential proximity to major roadways at the time of birth. Alternatively, we observed weaker associations for astrocytoma and medulloblastoma, which tend to occur in older children (median diagnosis age of 7 and 6 years, respectively) (Gurney et al., 1999; Ostrom et al., 2015).

Although the etiologic mechanisms for childhood CNS tumors are mostly unknown, there is evidence suggesting that gaseous pollutants and particulate matter generated from vehicles may play a role in tumorigenesis in children. Maternal exposure to high levels of polycyclic aromatic hydrocarbons (PAHs), carcinogenic pollutants formed during incomplete combustion and found in motor vehicle exhaust, is associated with mutagenic PAH-DNA adduct formation in the fetus, which could subsequently predispose the fetus to cancer development (Herbstman et al., 2012; Perera et al., 2005). Furthermore, both animal and human studies have shown that exposure to particulate matter generated from vehicle emissions produces DNA oxidative damage in the brain, which may promote carcinogenesis in the CNS (Lucchini et al., 2012; Moller et al., 2010). Given the carcinogenic properties of traffic-related air pollutants as well as their apparent associations with other CNS disorders (Genc et al., 2012; Volk et al., 2013), it is biologically plausible that exposure to high levels of traffic-related air pollution may be a risk factor for childhood CNS tumors.

While we considered several confounding variables in our assessment (i.e., child's sex and season of birth as well as maternal race/ethnicity, age, education level, and area-level poverty), a few potential confounders were not accounted for due to the unavailability of data. First, while it has been shown that children living near major roadways are more likely to have asthma (Porebski et al., 2014), several studies have shown that children with asthma are less likely to be diagnosed with a CNS tumor (Harding et al., 2008; Roncarolo and Infante-Rivard, 2012); therefore, it is

possible that asthma may have biased our estimates toward the null, underestimating the effect of residential proximity to major roadways and childhood CNS tumors. In addition, maternal smoking was not accounted for in this assessment; however, the existing evidence for a potential link between maternal smoking and childhood CNS tumors is inconsistent (Baldwin and Preston-Martin, 2004; Johnson et al., 2014). Lastly, there are other established risk factors (e.g., exposure to ionizing radiation, cancer genetic predisposition syndromes) and potential risk factors (e.g., exposure to pesticides, maternal dietary *N*-nitroso compounds) for childhood CNS tumors that were not considered as confounders in this assessment (Baldwin and Preston-Martin, 2004; Johnson et al., 2014); however, there is no clear evidence that these variables are associated with air pollution exposure or with living near major roadways.

Our findings should be considered in light of certain limitations. First, we relied on residential proximity to major roadways as a surrogate measure for exposure to traffic-related air pollution, which may have resulted in some exposure misclassification. Exposure measurement based on personal monitoring is the gold standard when assessing exposure to air pollutants, however, these methods are typically expensive and not feasible when assessing rare diseases such as childhood CNS tumors (Health Effects Institute, 2010). Although proximity measures have limitations (e.g., do not account for traffic volume, vehicle classification, meteorological conditions and time-activity patterns) (Health Effects Institute, 2010; Zhang and Batterman, 2009), several validation studies suggest that they are a reasonable surrogate for personal monitoring of exposure to air pollutants (Gilbert et al., 2003; van Roosbroeck et al., 2006). Therefore, epidemiologic studies have relied extensively on proximity to traffic and major roadways to assess traffic-related air pollution exposure on health outcomes (Boothe and Shendell, 2008). Another potential limitation is that we did not have residential information for the time of conception, throughout pregnancy, or after the child's birth; therefore, we could not directly assess exposure other than at the time of birth. However, previous evidence suggests that air pollution exposure assessed at the time of birth may be a reasonable proxy for exposures occurring over the course of pregnancy (Lupo et al., 2010), during the first year of life (Heck et al., 2013), and at the time of diagnosis for those diagnosed at <5 years of age (Danysh et al., 2015a). Therefore, we restricted our sample to include children diagnosed at <5 years of age in this assessment, limiting the window of potential exposure time beyond birth. Lastly, although nearly all incident cases with CNS tumors who were both born and diagnosed in Texas during the period of 2003–2009 ($n=315$) were included in this assessment, the sample sizes were substantially reduced when assessing the individual CNS tumor phenotypes ($n=10$–66), and this was especially true for ependymoma ($n=26$) and PNET ($n=10$). As a result, it is possible that there was insufficient power to detect meager effect sizes within each of the CNS tumor phenotypes. In addition, exploring associations in these phenotypes may have resulted in biased estimates of effects due to relatively small sample sizes. Larger assessments are needed to validate our findings and to further explore the rarer CNS tumor phenotypes.

Our study has several important strengths. We used a population-based sample of CNS tumor cases drawn from across the state of Texas. Additionally, to our knowledge, this is the largest assessment of residential proximity to major roadways and the childhood CNS tumor phenotypic groups. This assessment included several measures of residential proximity to major roadways, across which we observed consistent associations among the CNS tumor phenotypes. Further, reliance on proximity measures to assess traffic-related air pollution exposure may, to a certain extent, account for the complex mixture of vehicle emissions and emissions by-products, in contrast to using a single-pollutant approach to exposure assessment. Finally, Texas provides an ideal setting for this study, as it is a state characterized by variable levels of traffic-related air pollution and large metropolitan areas with dense networks of major roadways.

5. Conclusions

In this population-based assessment, our findings indicate that mothers living near major roadways (≤ 500 m) with high roadway density at the time of delivery were more likely to have offspring with a CNS tumor, especially an ependymoma, at <5 years of age compared to mothers living in areas with low roadway density (i.e., not living in close proximity to a major roadway [>500 m]). There appeared to be strong associations with PNET, however, these findings require validation with a larger sample. Our findings may have important public health implications as larger segments of the U.S. population are living in or near major metropolitan areas with dense networks of major roadways. More studies are needed to confirm our findings and further explore the relationship between exposure to traffic-related air pollutants and the CNS tumor phenotypes in children.

Conflict of interest

The authors have no conflicts of interest to disclose.

Funding

This work was supported in part by the Kurt Groten Family Research Scholars Award (P. Lupo).

Human subjects research

The study protocol was reviewed and approved by the Institutional Review Boards of the University of Texas Health Science Center at Houston, Baylor College of Medicine, and the Texas Department of State Health Services prior to beginning the study. Data received from the Texas Department of State Health Services were de-identified, and therefore, obtaining informed consent from individual subjects was not required.

Acknowledgments

The authors acknowledge the contributions of the Texas Department of State Health Services for providing cancer data from the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, and birth certificate data from the Center for Health Statistics. This work was supported in part by the Kurt Groten Family Research Scholars Award (P. Lupo).

References

Armstrong, G.T., 2010. Long-term survivors of childhood central nervous system malignancies: the experience of the Childhood Cancer Survivor Study. Eur. J. Paediatr. Neurol. 14, 298–303.

Baldwin, R.T., Preston-Martin, S., 2004. Epidemiology of brain tumors in childhood – a review. Toxicol. Appl. Pharmacol. 199, 118–131.

Boothe, V.L., Shendell, D.G., 2008. Potential health effects associated with residential proximity to freeways and primary roads: review of scientific literature, 1999–2006. J. Environ. Health. 70 (33–41), 55–56.

Danysh, H.E., Mitchell, L.E., Zhang, K., Scheurer, M.E., Lupo, P.J., 2015a. Differences in environmental exposure assignment due to residential mobility among children with a central nervous system tumor: Texas, 1995–2009. J. Expo. Sci. Environ. Epidemiol. http://dx.doi.org/10.1038/jes.2015.63.

Danysh, H.E., Mitchell, L.E., Zhang, K., Scheurer, M.E., Lupo, P.J., 2015b. Traffic-Related Air Pollution and the Incidence of Childhood Central Nervous System Tumors: Texas, 2001–2009. Pediatr. Blood Cancer 62, 1572–1578.

Genc, S., Zadeoglulari, Z., Fuss, S.H., Genc, K., 2012. The adverse effects of air pollution on the nervous system. J. Toxicol. 2012, 782462.

Ghosh, J.K., Heck, J.E., Cockburn, M., Su, J., Jerrett, M., Ritz, B., 2013. Prenatal exposure to traffic-related air pollution and risk of early childhood cancers. Am. J. Epidemiol. 178, 1233–1239.

Gilbert, N.L., Woodhouse, S., Stieb, D.M., Brook, J.R., 2003. Ambient nitrogen dioxide and distance from a major highway. Sci. Total Environ. 312, 43–46.

Gray, S.C., Edwards, S.E., Schultz, B.D., Miranda, M.L., 2014. Assessing the impact of race, social factors and air pollution on birth outcomes: a population-based study. Environ. Health. 13, 4.

Gurney, J., Smith, M., Bunin, G., 1999. CNS and Miscellaneous Intracranial and Intraspinal Neoplasms. Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995. National Cancer Institute SEER Program, pp. 51–64.

Harding, N.J., Birch, J.M., Hepworth, S.J., McKinney, P.A., 2008. Atopic dysfunction and risk of central nervous system tumours in children. Eur. J. Cancer 44, 92–99.

Health Effects Institute, Traffic-related air pollution: a critical review of the literature on emissions, exposure and health effects, 2010 Special Report #17. Health Effects Institute, Boston, 2010.

Heck, J.E., Wu, J., Lombardi, C., Qiu, J., Meyers, T.J., Wilhelm, M., Cockburn, M., Ritz, B., 2013. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. Environ. Health Perspect. 121, 1385–1391.

Herbstman, J.B., Tang, D., Zhu, D., Qu, L., Sjodin, A., Li, Z., Camann, D., Perera, F.P., 2012. Prenatal exposure to polycyclic aromatic hydrocarbons, benzo[a]pyrene-DNA adducts, and genomic DNA methylation in cord blood. Environ. Health Perspect. 120, 733–738.

Hertz-Picciotto, I., Jusko, T.A., Willman, E.J., Baker, R.J., Keller, J.A., Teplin, S.W., Charles, M.J., 2008. A cohort study of in utero polychlorinated biphenyl (PCB) exposures in relation to secondary sex ratio. Environ. Health 7, 37.

Johnson, K.J., Cullen, J., Barnholtz-Sloan, J.S., Ostrom, Q.T., Langer, C.E., Turner, M.C., McKean-Cowdin, R., Fisher, J.L., Lupo, P.J., Partap, S., Schwartzbaum, J.A., Scheurer, M.E., 2014. Childhood Brain Tumor Epidemiology: A Brain Tumor Epidemiology Consortium Review. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.

Karner, A.A., Eisinger, D.S., Niemeier, D.A., 2010. Near-roadway air quality: synthesizing the findings from real-world data. Environ. Sci. Technol. 44, 5334–5344.

Linder, S.H., Marko, D., Sexton, K., 2008. Cumulative cancer risk from air pollution in Houston: disparities in risk burden and social disadvantage. Environ. Sci. Technol. 42, 4312–4322.

Lucchini, R.G., Dorman, D.C., Elder, A., Veronesi, B., 2012. Neurological impacts from inhalation of pollutants and the nose-brain connection. Neurotoxicology 33, 838–841.

Lupo, P.J., Symanski, E., Chan, W., Mitchell, L.E., Waller, D.K., Canfield, M.A., Langlois, P.H., 2010. Differences in exposure assignment between conception and delivery: the impact of maternal mobility. Paediatr. Perinat. Epidemiol. 24, 200–208.

Matz, C.J., Stieb, D.M., Davis, K., Egyed, M., Rose, A., Chou, B., Brion, O., 2014. Effects of age, season, gender and urban-rural status on time-activity: CanadianHuman Activity Pattern Survey 2 (CHAPS 2). Int. J. Environ. Res. Public Health 11, 2108–2124.

Moller, P., Jacobsen, N.R., Folkmann, J.K., Danielsen, P.H., Mikkelsen, L., Hemmingsen, J.G., Vesterdal, L.K., Forchhammer, L., Wallin, H., Loft, S., 2010. Role of oxidative damage in toxicity of particulates. Free Radic. Res. 44, 1–46.

Ostrom, Q.T., de Blank, P.M., Kruchko, C., Petersen, C.M., Liao, P., Finlay, J.L., Stearns, D.S., Wolff, J.E., Wolinsky, Y., Letterio, J.J., Barnholtz-Sloan, J.S., 2015. Alex Lemonade Stand Foundation Infant and Childhood Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007–2011. Neuro Oncol. 16 (Suppl. 10), x1–x36.

Perera, F., Tang, D., Whyatt, R., Lederman, S.A., Jedrychowski, W., 2005. DNA damage from polycyclic aromatic hydrocarbons measured by benzo[a]pyrene-DNA adducts in mothers and newborns from Northern Manhattan, the World Trade Center Area, Poland, and China. Cancer Epidemiol. Biomarkers Prev. 14, 709–714.

Pollack, I.F., Biegel, J., Yates, A., Hamilton, R., Finkelstein, S., 2002. Risk assignment in childhood brain tumors: the emerging role of molecular and biologic classification. Curr. Oncol. Rep. 4, 114–122.

Population Reference Bureau, 2014. 2014 World Population Data Sheet. (accessed 12.03.15), from ⟨http://www.prb.org/pdf14/2014-world-population-data-sheet_eng.pdf⟩.

Porebski, G., Wozniak, M., Czarnobilska, E., 2014. Residential proximity to major roadways is associated with increased prevalence of allergic respiratory symptoms in children. Ann. Agric. Environ. Med. 21, 760–766.

Raaschou-Nielsen, O., Reynolds, P., 2006. Air pollution and childhood cancer: a review of the epidemiological literature. Int. J. Cancer 118, 2920–2929.

Reynolds, P., Von Behren, J., Gunier, R.B., Goldberg, D.E., Hertz, A., 2004. Residential exposure to traffic in California and childhood cancer. Epidemiology 15, 6–12.

Roncarolo, F., Infante-Rivard, C., 2012. Asthma and risk of brain cancer in children. Cancer Causes Control 23, 617–623.

Savitz, D.A., Feingold, L., 1989. Association of childhood cancer with residential traffic density. Scand. J. Work. Environ. Health 15, 360–363.

Selevan, S.G., Kimmel, C.A., Mendola, P., 2000. Identifying critical windows of exposure for children health. Environ. Health Perspect. 108 (Suppl. 3), 451–455.

Steliarova-Foucher, E., Stiller, C., Lacour, B., Kaatsch, P., 2005. International Classification of Childhood Cancer, third edition. Cancer. 103, 1457–1467.

Texas Natural Resources Information System 2014. Maps & Data: Transportation StratMap, version 2 (2006). (accessed 01.12.14), from ⟨http://tnris.org/data-download/#/statewide⟩.

U.S. Census Bureau, 2015. Geographic Terms and Concepts – Census Tract. (accessed 15.10.14), from ⟨https://www.census.gov/geo/reference/gtc/gtc_ct.html⟩.

U.S. Census Bureau, TIGER/Line Files: Technical Documentation. U.S. Census Bureau, 2007, pp. pg. 89–91.

van Roosbroeck, S., Wichmann, J., Janssen, N.A., Hoek, G., van Wijnen, J.H., Lebret, E., Brunekreef, B., 2006. Long-term personal exposure to traffic-related air pollution among school children, a validation study. Sci. Total Environ. 368, 565–573.

Volk, H.E., Lurmann, F., Penfold, B., Hertz-Picciotto, I., McConnell, R., 2013. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry 70, 71–77.

Ward, E., DeSantis, C., Robbins, A., Kohler, B., Jemal, A., 2014. Childhood and adolescent cancer statistics, 2014. CA Cancer J. Clin. 64, 83–103.

Zhang, K., Batterman, S.A., 2009. Time allocation shifts and pollutant exposure due to traffic congestion: an analysis using the national human activity pattern survey. Sci. Total Environ. 407, 5493–5500.