Exposure to air pollution during pregnancy has been linked to the risk of childhood cancer, but the evidence remains inconclusive. In the present study, we used land use regression modeling to estimate prenatal exposures to traffic exhaust and evaluate the associations with cancer risk in very young children. Participants in the Air Pollution and Childhood Cancers Study who were 5 years of age or younger and diagnosed with cancer between 1988 and 2008 were had their records linked to California birth certificates, and controls were selected from birth certificates. Land use regression–based estimates of exposures to nitric oxide, nitrogen dioxide, and nitrogen oxides were assigned based on birthplace residence and temporally adjusted using routine monitoring station data to evaluate air pollution exposures during specific pregnancy periods. Logistic regression models were adjusted for maternal age, race/ethnicity, educational level, parity, insurance type, and Census-based socioeconomic status, as well as child’s sex and birth year. The odds of acute lymphoblastic leukemia increased by 9%, 23%, and 8% for each 25-ppb increase in average nitric oxide, nitrogen dioxide, and nitrogen oxide levels, respectively, over the entire pregnancy. Second- and third-trimester exposures increased the odds of bilateral retinoblastoma. No associations were found for annual average exposures without temporal components or for any other cancer type. These results lend support to a link between prenatal exposure to traffic exhaust and the risk of acute lymphoblastic leukemia and bilateral retinoblastoma.

Abbreviations: ALL, acute lymphoblastic leukemia; LUR, land use regression; OR, odds ratio; SES, socioeconomic status.
prenatal or birth place exposures, 2 of which were conducted in Europe (Denmark and France) (17, 18) and 2 of which were conducted in California using traffic count data for exposure assessment (19, 20).

In the present study, we used a land use regression (LUR) model for Los Angeles County, California, that we developed to estimate exposure to vehicle exhaust, the most important contributor to air pollution in that region. LUR models capture small-area variations in primary traffic pollutants, leading to improved individual-level exposure characterization (21, 22). We examined whether these prenatal exposures increased the risk of cancers in early childhood and whether specific time periods in pregnancy are more sensitive to the influence of such exposures.

MATERIALS AND METHODS

Data sources

The Air Pollution and Childhood Cancers Study is a case-control study of children born in California. We selected all cancer cases among children 0–5 years of age who were diagnosed in California from 1988 to 2008 from the California Cancer Registry (23), which included information on the date of birth, cases’ and parents’ names, cancer type, and diagnosis date. We used electronic birth certificates from the California Department of Public Health to select births to mothers residing in California between January 1, 1986, and December 31, 2007. The data on these certificates included the mother’s residential address at delivery, demographic information, and birth characteristics.

We used Link Plus software (Centers for Disease Control and Prevention, Atlanta, Georgia) to conduct probabilistic linkage of cancer registry data with birth certificates based on the child’s first and last name and date of birth (89% linkage rate). Unlinked cases had a larger percentage of non-Hispanic white and older participants than did linked cases, but sex and socioeconomic status (SES) distributions were similar. Controls were randomly selected from birth records among children without a cancer diagnosis at a 20:1 ratio and were frequency matched by birth year to account for potential unmeasured confounders that vary over time.

The mothers’ residential addresses were geocoded using the University of Southern California Geographic Information Systems Research Laboratory geocoding engine (webgis.usc.edu), and we restricted the dataset to addresses within Los Angeles County (n = 89,734). We excluded births with missing age data (144 cases, 3,283 controls) or extreme gestational age data most likely caused by clerical errors (≤140 days or ≥315 days; 72 cases, 1,562 controls). The remaining 4,015 cases and 80,658 controls were assigned exposure estimates based on the geocoded address locations and the dates of each pregnancy period (based on gestational age information). We did not have sufficient information to assign childhood air pollution exposures.

LUR model and seasonalization

Our LUR models for the Los Angeles Basin represent traffic-related air pollution (24) and were based on measurements of nitrogen dioxide and nitrogen oxides at 201 locations. Models were calibrated with a training dataset of 167 sites and explained 81%, 86%, and 85% of the variation in concentrations of nitric oxide, nitrogen dioxide, and nitrogen oxides, respectively (24). Cross-validation $R^2$ values were greater than 0.87 for all pollutants. The LUR model represents long-term spatial patterns and approximate annual average concentrations (21, 22). We included all 3 pollutants in our analyses to represent volatile primary traffic exhaust (nitric oxide), secondary pollutants (nitrogen dioxide), and the sum total of these as a stable marker of these pollutants (nitrogen oxides).

We assigned LUR annual average estimates (“unseasonalized estimates”) based on the model values at the geocoded residential addresses. In addition, we created “seasonalized” LUR measures by weighting the unseasonalized estimates using data from 45 Los Angeles County air monitoring stations operated by the California Air Resources Board that measure hourly levels of nitric oxide, nitrogen dioxide, and nitrogen oxides. We chose the closest station within 20 miles of the home address that had available data for the dates of the pregnancy period being evaluated. (Not all monitors were active for the entire study period.) The seasonalization methods have been detailed elsewhere (25). Briefly, we multiplied the LUR estimates with the ratio of the month of pregnancy average divided by the 2006 air monitoring station average to generate pregnancy-month specific LUR values, which we then averaged over each trimester and the entire pregnancy. Seasonalized LUR values are missing for births for which no station within 20 miles had sufficient data (<50% of possible measurements in each month) for the pregnancy period being evaluated or for seasonalization (for nitric oxide, 931 cases, 18,254 controls); these records were excluded from the seasonalized LUR analyses. The subpopulation for which we created seasonalized LUR estimates had a lower SES profile, which was consistent with expectations because most of the monitoring stations are located in more polluted areas (26), which tend to have populations with overall lower SES profiles in Los Angeles County (27).

Statistical analysis

Analyses were conducted using SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina). We explored collinearity across pollutants and pregnancy periods using Pearson’s correlation coefficients. Cancer diagnoses were classified using the International Classification of Diseases for Oncology, Version 3, and the analysis was restricted to the following outcomes that had 70 or more cases (Web Table 1, available at http://aje.oxfordjournals.org/): ALL, acute myeloid leukemia, non-Hodgkin lymphoma, central nervous system tumors (including ependymomas and choroid plexus tumors, astrocytoma, intracranial and intraspinal embryonal tumors, other gliomas, and primitive neuroectodermal tumor), neuroblastoma and ganglioneuroblastoma, unilateral and bilateral retinoblastomas, Wilms tumor, hepatoblastoma, rhabdomyosarcoma, and germ cell tumors (including malignant extracranial and extragonadal germ cell tumors and teratomas).

Unconditional logistic regression was used to estimate the odds of each cancer outcome per 25-ppb increase in pregnancy-period exposures. The 25-ppb unit increase was chosen because...
it closely approximates the median interquartile range across all pollutant-period combinations in our dataset, allowing for direct comparisons of associations across pregnancy periods for each pollutant. We adjusted for several potential confounders: maternal age, race/ethnicity, educational level, parity, prenatal care insurance type, and SES score quintile (the composite score is based on Census block group data on educational level, income, and occupation) (28, 29) and child’s sex and birth year (matching variable). We additionally adjusted for prenatal care, mother’s birthplace, father’s race, father’s educational level, child’s birth weight, and birth season, but these did not change the main effect estimates by more than 5% for ALL and therefore were not included in final models. Although some of the additional variables may have changed the point estimates by more than 5% for other cancer outcomes, the differences were not large enough to change our interpretation of the results because of the wide and overlapping confidence intervals.

RESULTS

Characteristics of the study population

In the 4,015 cases in our study, the most common tumors were ALL (n = 1,346), neuroblastoma (n = 347), Wilms tumor (n = 308), astrocytoma (n = 262), retinoblastoma (n = 165 unilateral, n = 87 bilateral), intracranial and intraspinal embryonal tumors (n = 231), and acute myeloid leukemia (n = 216). More than 50% of mothers in the study were of Hispanic ethnicity and approximately 25% were non-Hispanic white (Table 1). Approximately 15% of children were born to mothers over 35 years of age, and more than 30% lived in Census tracts with less than 25% of mothers in the study were of Hispanic ethnicity and approximately 25% were non-Hispanic white (Table 1). Approximately 15% of children were born to mothers over 35 years of age, and more than 30% lived in Census tracts with the lowest SES score. There was a small male predominance in cases compared with controls (55.5% male cases vs. 50.8% male controls).

Exposure metrics and correlations

Unseasonalized LUR estimates of the levels of nitric oxide, nitrogen dioxide, and nitrogen oxides (i.e., annual average estimates) were strongly correlated with each other (r ≈ 0.77–0.92) and moderately to strongly correlated with seasonized LUR estimates for the entire pregnancy (r ≈ 0.64–0.75) (Web Table 2). Within each pregnancy period, seasonized LUR estimates were moderately to strongly correlated (r ≈ 0.64–0.95). Entire-pregnancy averages were strongly correlated with estimates in each trimester for nitrogen dioxide and with second-trimester averages for nitric oxide and nitrogen oxides. Correlations across pregnancy trimesters were weak to moderate (positive), with weak negative correlations between first- and third-trimester averages. The seasonized exposure metrics had larger variances than did the unseasonalized metrics because of the contribution of the seasonal component of exposure (Web Figure 1).

Seasonalized LUR results

Odds of ALL were associated with higher air pollution exposures for each pregnancy period, but associations were strongest for the entire-pregnancy averages (Table 2). Odds increased by 9% per 25-ppb increase in nitric oxide (odds ratio (OR) = 1.09, 95% confidence interval: 1.01, 1.18).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% of Cases (n = 4,015)</th>
<th>% of Controls (n = 80,658)</th>
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<tr>
<td>Mother’s age when child was born, years</td>
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<td></td>
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<td>10.3</td>
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<td>21.2</td>
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<td>25–29</td>
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<tr>
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<tr>
<td>Female</td>
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</tr>
</tbody>
</table>

Abbreviation: SES, socioeconomic status.

a Private insurance, insurance through a health maintenance organization, or Blue Cross-Blue Shield.
b Medicare, Medi-Cal, other government program, other nongovernment program, self-payment, medically indignant, no charge, or no prenatal care.

The odds of developing bilateral retinoblastoma increased with entire-pregnancy, second-trimester, and third-trimester increases in seasonized LUR-estimated air pollution levels.
but first-trimester associations were null. For every 25-ppb increase in third-trimester pollutant concentrations, the odds of developing bilateral retinoblastoma increased by 15% (95% confidence interval: 1.01, 1.31) and 13% (95% confidence interval: 0.99, 1.29) for nitric oxide and nitrogen dioxide, respectively. We did not find any associations with unilateral retinoblastoma or with the other cancers in our study (except for a negative association with extracranial tumors), although confidence intervals were wide and included the null in most models (Web Table 3).

In sensitivity analysis that were restricted to subjects who lived 5 miles or less from an ambient monitoring station, associations between seasonalyzed estimates and ALL remained similar or increased slightly. Because nitrogen oxide emissions decreased approximately 35% in Los Angeles County over the study period (30), we stratified models for ALL by birth year period (1986–1994 or 1995–2007) and found similar associations for both periods (for average entire-pregnancy nitric oxide in birth years 1995–2007, OR = 1.07, 95% confidence interval = 0.96, 1.10; in birth years 1986–1994, OR = 1.12, 95% confidence interval = 1.00, 1.27), with confidence intervals mostly overlapping. There were too few cases of bilateral retinoblastoma to evaluate these outcomes in sensitivity analysis.

### Unseasonalized LUR results

Unseasonalized LUR-estimated exposures to nitric oxide, nitrogen dioxide, and nitrogen oxides were not associated with increased risk for any of the cancers evaluated. To evaluate whether the demographic differences impacted the unseasonalized LUR results, we further restricted the dataset to records with unseasonalized LUR values for entire-pregnancy averages for all 3 pollutants (n = 65,162). Associations with most cancers remained null (e.g., for ALL and nitric oxide, OR = 1.01, 95% confidence interval: 0.86, 1.18) except for positive associations with ependymoma and negative associations with extracranial tumors, although confidence intervals were very wide.

### DISCUSSION

The present study is one of only a few to report on the associations between prenatal exposures to traffic-related air pollution and early childhood cancers. We found that higher exposures may increase the odds of ALL and bilateral retinoblastoma in the offspring. To our knowledge, this study is the first air pollution study in which retinoblastoma risk has been evaluated. The first and second trimesters may be more sensitive time periods for ALL, whereas later pregnancy periods are important for bilateral retinoblastoma; however, entire-pregnancy average exposures were also important. This is consistent with what is known about retinal development in utero, which occurs mainly in the second and third trimesters (31, 32).

Retinoblastoma results from the mutation of both alleles of the retinoblastoma protein tumor-suppressor gene and occurs most commonly in children under 6 years of age (33, 34). Typically, hereditary retinoblastoma occurs when the embryo has a mutation in one retinoblastoma protein allele and the second allele is lost somatically. All bilateral retinoblastomas can be inherited, although most children with heritable retinoblastomas carry a retinoblastoma protein mutation that is not found in the parents (33), indicating that the mutation occurred during germ cell or embryonic development. Only a small proportion of unilateral retinoblastomas are heritable. The mean age at diagnosis of bilateral retinoblastoma is younger than it is for unilateral retinoblastoma (13 months vs. 25 months in the United States (33), which supports the hypothesis that the damage to the second allele which causes bilateral retinoblastoma likely occurs in utero, whereas environmental factors in infancy or early childhood could be risk factors for unilateral disease (35). We recently reported paternal age as a risk factor for bilateral retinoblastoma (23), but further adjustment for father’s age did not change our air pollution effect estimates.

ALL is the most common childhood cancer in wealthier nations, and there is substantial evidence supporting a prenatal origin of the disease (14). Studies have found preleukemic cells in neonatal blood spots for patients later diagnosed in childhood (14). These genetic changes in utero can be followed by a postnatal event that leads to malignant cancer (36). Higher birth weight and advanced maternal age have been found to increase ALL risk (14), and we also observed this association in our data. Our models already controlled for confounding by maternal age, and additional adjustment for

![Table 2. Adjusted Odds Ratios and 95% Confidence Intervals for Unseasonalized and Seasonalized Pollutants per 25-ppb Increase in Pollutant Concentrations, Air Pollution and Childhood Cancers Study (Birth Years 1986–2007; Diagnosis Years 1988–2008)](https://academic.oup.com/aje/article-abstract/178/8/1233/83907)
birth weight did not change the main results. Because rates of ALL are higher among Hispanics (37) and infant cases can differ from cases of early childhood ALL (38, 39), we stratified the analysis by mother’s and father’s Hispanic race and the child’s age at diagnosis (<1 year vs. 1–5 years of age) but found no differences in effect estimates. Our results support the hypothesis of a prenatal origin of ALL, and evidence has shown that air pollution can cause genetic alterations in the fetus (40).

We observed an increased risk of cancer with pregnancy period–specific estimates only and no associations with annual average exposure estimates, which suggests that exposures during specific vulnerable prenatal periods are important and that ignoring seasonal aspects of exposures in addition to the spatial patterns may produce null associations. The seasonalized LUR measures had larger interquartile range values than did the unseasonalized measures (Web Table 2), reflecting increased exposure contrasts when incorporating temporal adjustment factors. Although selection bias is possible, because of demographic differences between participants with versus without seasonalized exposure data, the similarities in results when using unseasonalized LUR estimates for the entire dataset (4,015 cases, 80,658 controls) versus the restricted dataset (3,063 cases, 62,099 controls) do not suggest such a bias.

Our findings stand in contrast to the 2 previous studies in California that also examined air pollution exposures at the birth residence (19, 20) but found no associations with ALL or other childhood cancers. These previous studies used annual average measures of traffic density (vehicle miles traveled), road density, and traffic counts to estimate air pollution exposures, and one study additionally considered background benzene emissions (20). Such proxy traffic-related air pollution exposure measures do not account for differences in vehicle mix on the roads, topographic differences, seasonal contributions, or other factors that determine exposure levels (41). In a Danish study, Raaschou-Nielsen et al. (18) found no associations with prenatal air pollution exposures when using traffic density measures but did find positive associations for lymphomas with exposure to modeled benzene and nitrogen dioxide, which indicates that exposure misclassification may have contributed to the null result in the previous California studies. Our LUR model accounted for traffic volumes, truck routes and road networks, land use, vegetation greenness and soil brightness, and truck route slope gradients (24), providing an improved exposure measure compared with simple proximity-based measures (41).

An innovation of the present study is the use of LUR-based air pollution exposure estimates in a study of childhood cancer. Although the LUR model was based on air pollution monitors deployed in 2006–2007, studies conducted in Vancouver, Canada (42), Rome, Italy (43), and the Netherlands (26) have demonstrated the temporal stability of the spatial surface and predictive capability of the LUR model across time, even though the performance is somewhat decreased in backcasting because of decreases in air pollution that result in smaller spatial contrasts. Our temporal adjustment method using the monitoring station data from the dates of the pregnancy period account for temporal and seasonal changes in pollutant levels. Additionally, the sensitivity analysis stratified by birth year did not indicate that associations for earlier birth years were different from those for later years.

The seasonalization method we utilized uses monitoring data from the dates of the pregnancy period to adjust the unseasonalized LUR estimates, thereby incorporating a temporal component. This method assumes that ambient monitors up to 20 miles from a home can adequately characterize the local changes in air pollutant levels. Validation of this method would require a denser network of air pollution monitors providing continuous measurements, which are currently not available. However, previous studies have demonstrated that pollutant levels fluctuate in phases across stations, despite differences in concentrations based on geographic location (24). Approximately 66% of study subjects with valid seasonalized LUR estimates lived 5 miles or less from the monitoring station used for temporal adjustments, and sensitivity analyses produced consistent results when restricted to subjects living closer to monitoring stations.

A limitation is the assumption that birth certificate addresses adequately reflect pregnancy exposures. Approximately 20% of women from Los Angeles County change residence during pregnancy (44); however, they typically stay within the same neighborhood, resulting in only small changes in air pollution exposures (45, 46). Thus, the birth certificate address is a reasonable proxy for pregnancy residential location for air pollution exposure assessment, although we cannot rule out misclassification due to residential mobility. Another limitation is the lack of data on childhood air pollution exposures, which several studies have found to be important for some cancers (17, 18, 47–53), although 3 California studies reported no associations (19, 54, 55). In a recent French study, Amigou et al. (47) suggested that exposures in earlier time periods in a child’s life are likely to be more important than exposures later in life based on diagnosis/recruitment addresses. Most of these studies included children up to 14 years of age, and we intentionally limited our study to children 0–5 years of age to focus on exposures in the prenatal period. Many California families with young children change residences, meaning that exposure estimates based on birth certificate addresses are unlikely to be highly correlated with air pollution exposures in childhood. A study of pediatric leukemia patients in northern California indicated that among children diagnosed between 0–4 years of age, 32% moved within the first year of life and 55% moved between birth and diagnosis (56). Because of this high degree of residential mobility, air pollution exposure estimates in childhood are likely to differ from birthplace estimates. On the basis of this information, we conclude that our exposure estimates reflect prenatal exposures rather than exposures in early childhood, although we cannot rule out a possible contribution of childhood exposures in cancer initiation. Importantly, the peak incidence of these cancers in childhood occurs between 2–5 years of age for ALL (57) and before 1 year of age for retinoblastoma (58), which supports the hypothesis that prenatal initiation of such cancers is likely. Additionally, it is possible that some controls moved out of California after birth and were diagnosed with cancer out of state; however, given the rarity of these diseases in this age group, the potential for bias is extremely small.

Although we have adjusted for a variety of potential confounders, we acknowledge the possibility of residual confounding by other factors that we did not measure, for example, smoking, electromagnetic fields, and parental occupational exposure.
exposures. Many of these factors are associated with neighborhoods with lower overall SES, so adjusting for Census tract-based SES most likely helped control for the influence of these factors. We did not have information about other potential sources of air pollution exposures, such as commuting or personal measurements of exposure, which are not feasible in a large population-based study. Also, the LUR model was designed to reflect traffic exhaust exposures using nitric oxide, nitrogen dioxide, and nitrogen oxides as markers and does not estimate specific air toxins that may act as causal agents. Finally, although false positive findings due to multiple testing and confounding are possible, the plausibility of our findings is supported by biological evidence of the in utero initiation of these cancers (14, 35), as well as evidence that carcinogenic components of air pollution cause genetic changes in cord blood (16).

To our knowledge, the present study is the first childhood cancer study to use LUR methods to characterize air pollution exposures, providing an improved exposure model that addressed both spatial and temporal/seasonal variability. Our exposure modeling methods allowed us to examine specific pregnancy periods and demonstrated the importance of temporal components of air pollution exposure, which have not been considered in previous childhood cancer studies. By using a birth certificate–linkage design in a study of prenatal environmental exposures, we captured a large number of childhood cancer cases and eliminated issues of participation bias by using secondary data sources.

Our research contributes to a growing body of evidence linking prenatal air pollution exposures with early childhood cancers. Future studies should consider using exposure assessment tools that better reflect exhaust exposures, including temporal components of exposure, and evaluate both prenatal and childhood time periods.

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