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Perinatal Exposures to Ambient Fine Particulate Matter and Outdoor Artificial Light at Night and Risk of Pediatric Papillary Thyroid Cancer

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Background: Pediatric thyroid cancer incidence has been increasing globally, with environmental exposures being a hypothesized risk factor.

Objective: We evaluated the association between pediatric thyroid cancer risk and perinatal exposure to ambient fine particulate matter (PM) with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) and outdoor artificial light at night (O-ALAN). Both are considered environmental carcinogens with evidence of thyroid function disruption, reported associations with thyroid cancer in adults, and concerns of distributive inequity. O-ALAN may also serve as a proxy for other outdoor air pollutants or urbanization.

Methods: We conducted a case–control study of papillary thyroid cancer nested within a California birth cohort that included 736 cases diagnosed at 0–19 y of age and born in 1982–2011 and 36,800 controls frequency-matched on birth year. We assigned individual-level exposures for residence at birth for ambient $PM_{2.5}$ concentrations from a validated, ensemble-based prediction model and O-ALAN using the New World Atlas of Artificial Night Sky Brightness. We calculated odds ratios (OR) and 95% confidence intervals (CI) using logistic regression adjusting for potential confounders and stratified by age and race/ethnicity.

Results: We observed statistically significant associations between $PM_{2.5}$ exposure and papillary thyroid cancer risk overall (OR per 10-$\mu g/m^3$ increase in $PM_{2.5}$ = 1.07, 95% CI: 1.01, 1.14), among the 15–19 y age group (OR = 1.08; 95% CI: 1.00, 1.16), and among Hispanic children (OR = 1.13; 95% CI: 1.02, 1.24). For O-ALAN, we observed statistically significantly increased odds of papillary thyroid cancer in higher exposure tertiles in comparison with the reference tertile in the overall population (tertile 2: OR = 1.25, 95% CI: 1.04, 1.50; tertile 3: OR = 1.23, 95% CI: 1.02, 1.50) and when modeled as a continuous variable (OR = 1.07 per 1 mcd/m^2). In age-stratified analyses, significant associations were observed among the 15–19 y age group, but not the 0–14 y age group. No significant differences were found by race/ethnicity.

Discussion: This study provides new evidence suggesting associations between early-life exposure to $PM_{2.5}$ and O-ALAN and pediatric papillary thyroid cancer. Given that O-ALAN may also represent other air pollutants or broader urbanization patterns, further research and refinements to exposure metrics are needed to disentangle these factors. https://doi.org/10.1289/EHP14849

Introduction

Incidence rates of pediatric thyroid cancer (0–19 y of age) have been increasing globally.[1,2] In the United States, rates have increased 4% per year on average during the period 2000–2018.[3] This trend is consistent with rising thyroid cancer incidence in adults.[4] In comparison with adults, children with thyroid cancer tend to present at more advanced stages with larger tumor sizes, involvement of regional lymph nodes, and pulmonary metastasis.[5–7] Pediatric thyroid cancer survivors are at risk of developing treatment-related sequelae, such as temperature dysregulation, headaches, physical disabilities, and mental fatigue, as well as second primary malignancies.[8–11] The diagnosis, treatment, and surveillance associated with the disease pose challenges to important life milestones (e.g., education, employment, family formation)[11] and may lead to psychosocial outcomes, such as anxiety and depression.[12–14]

Although overdiagnosis due to advanced imaging technologies and increased diagnostic scrutiny explains a substantial part of the observed increase of thyroid cancer incidence in adults,[15–17] overdiagnosis is likely less of an issue for children, who are not aggressively targeted for screening.[18–20] In addition, increased incidence in children has been observed for larger tumors and is not limited to small, indolent tumors that are more likely to be identified from imaging.[21–23] In children, the etiology of thyroid cancer remains obscure. Ionizing radiation is the only established modifiable risk factor, based on studies of populations with high exposure.[24,25]

We focused on the perinatal time period because early life is considered a critical time period for childhood cancer development.[26] This stage has been found to be an important time period for the established risk factor of ionizing radiation.[27,28] Studies of environmental chemicals in relation to adult thyroid cancer have observed that early-life exposures may be more etiologically relevant than later time windows.[29,30] In addition, studies of perinatal characteristics have found that perinatal conditions such as birth weight and maternal thyroid disorders were associated with increased risk of subsequent pediatric thyroid cancer.[31–33] Taken together, this provides a strong basis for evaluating early life exposures to environmental exposures as potential risk factors for pediatric thyroid cancer.

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Outdoor air pollution is a mixture of chemicals with carcinogenic constituents and endocrine-disrupting properties. Outdoor air pollution and particulate matter (PM) specifically are classified as known human carcinogens (Group 1) by the International Agency for Research on Cancer, with the preponderance of evidence for adult lung cancer.[34] Exposure to fine PM, i.e., particles with aerodynamic equivalent diameters $\leq$2.5 μm ($PM_{2.5}$), has been linked to adverse birth outcomes (e.g., low birth weight) and neurodevelopmental outcomes with thyroid hormone disruption gaining attention as a potential mechanism or mediator of these effects.[35] In addition, evidence suggests associations between exposure to outdoor air pollution and childhood cancers such as leukemia and central nervous system tumors.[36,37] A few studies have evaluated the relationship between $PM_{2.5}$ exposure and thyroid cancer in adults. A US-based study of adults found that a 10 $\mu g/m^3$ increase in cumulative $PM_{2.5}$ concentrations over 1, 2, or 3 y prior to diagnosis was associated with increased likelihood of diagnosis with papillary thyroid cancer.[38,39] Ecological studies in Iran[40] and Brazil[41] observed correlations between ambient PM concentration and thyroid cancer incidence in adults. To our knowledge, no published studies have evaluated associations between air pollution and pediatric thyroid cancer.

Artificial light at night (ALAN) has been associated with multiple cancers, including breast, colorectal, endometrial, and prostate.[42–44] Although mechanisms likely vary by cancer type, disruption of circadian processes may lead to dysfunction of cell proliferation, cell death, DNA repair, and metabolic alterations.[45] Exposure to ALAN has specifically been hypothesized as a childhood carcinogen due to dysregulation of physiological processes in pregnant women or neonates.[46] The phenomenon of ALAN can be divided into indoor and outdoor nighttime illumination. Outdoor ALAN (O-ALAN), or light pollution, specifically has been linked to different cancer types, although findings are mixed.[47–49] In addition, comparisons of satellite-based O-ALAN and indoor or personal exposure to ALAN have not yielded strong correlations,[50,51] likely due to variations in individual-level factors such as housing type, window treatments, and personal behaviors, which raises concerns about the utility of O-ALAN as a proxy for personal ALAN exposure because of the potential for exposure misclassification. Because O-ALAN has been associated with cancer and other health outcomes, O-ALAN may be capturing other environmental or demographic features of urbanized areas, such as traffic-related air pollution, population density, or economic activity.[50,52–54] To our knowledge, there has been only one study of exposure to ALAN and thyroid cancer, and it focused on O-ALAN exposure in older adults in six US states.[55] This study reported a 55% increase in risk in thyroid cancer in the most highly exposed group.

In addition to their carcinogenic and endocrine-disrupting potential, $PM_{2.5}$ and O-ALAN also present issues of environmental justice. Multiple studies demonstrate that people of color are exposed to higher levels of air pollution than non-Hispanic White individuals in the United States.[56–59] This higher exposure is attributable to a pervasive and persistent consequence of redlining, inequitable siting of emission sources (e.g., highways and industrial facilities), and other structural and policy factors.[60,61] In addition, recent studies have reported that communities with more social disadvantage or a greater proportion of racial and ethnic minoritized groups experience higher levels of ALAN in comparison with those with less disadvantage or non-Hispanic White individuals.[62,63] The disproportionate exposures are important to consider because our previous work observed a greater incidence in the pediatric thyroid cancer among Hispanic children,[31] and evidence of downstream health disparities suggests that non-White and Hispanic patients are diagnosed at later stages.[64]

To advance understanding of the potential etiological role of environmental exposures in relation to risk of pediatric papillary thyroid cancer, we evaluated associations with two environmental exposures with evidence of disruption to the thyroid endocrine system and exposure disparities—outdoor $PM_{2.5}$ and O-ALAN—in a large, nested case–control study in California.

Methods

Study Population and Design

This evaluation was conducted within the California Linkage Study of Early Onset Cancers, which joined California birth records maintained by the Center for Health Statistics and Informatics, California Department of Public Health (for birth years 1982–2011), to statewide cancer diagnosis data from the California Cancer Registry (for the years 1988–2015). Cases were children whose maternal residential address at birth was in California and who were diagnosed with their first, primary papillary thyroid cancer in the state of California by the age of 19 y. Papillary thyroid cancer was defined as a diagnosis with *International Classification of Diseases for Oncology, third edition* codes of 8050, 8052, 8130, 8260, 8340–8344, 8450, or 8452. We excluded cases with missing data on birth order ($n = 2$), maternal country of birth ($n = 1$), presence of a congenital abnormality or unknown congenital abnormality ($n = 6$), or $PM_{2.5}$ at their birth residence ($n = 21$). For each eligible case, 50 control subjects were randomly selected from children born in California during the same year and not diagnosed with any cancer through age 19 y, yielding 736 cases and 36,800 controls. The study protocol was approved by the institutional review boards at the California Health and Human Services Agency; University of California, Berkeley; and Yale University. The study was based on a linkage of existing data and did not involve tracking of or contact with subjects, and no informed consent was required.

Assessment of Perinatal Exposure to $PM_{2.5}$

We obtained daily $PM_{2.5}$ concentrations (in $\mu g/m^3$) at a spatial resolution of 1-km^2 grids from a validated, ensemble-based prediction model used extensively in prior studies.[65] This approach combines three machine learning algorithms: a random forest regression, a gradient boosting machine, and an artificial neural network. These models used dozens of predictor variables from satellite data, land-use information, meteorological data, and chemical transport predictions to produce highly accurate estimates yielding strong agreement with $PM_{2.5}$ measurements ($R^2 = 0.86$–0.89).[65,66] Daily $PM_{2.5}$ concentration measurements were only available from 2000 to 2016, after the launch of US Environmental Protection Agency (US EPA) monitoring networks. To maximize the availability of the full cohort, we applied two historical prediction models to estimate $PM_{2.5}$ exposures for individuals born during the period 1982–1999. First, we extrapolated the monthly averaged $PM_{2.5}$ concentrations at each 1-km^2 grid using a spatiotemporal regression model with year as a continuous variable and calendar month as a categorical variable. Second, we obtained historical average monthly $PM_{2.5}$ estimates at a 1-km^2 resolution for the years 1989–2016 from a validated, publicly available model incorporating chemical transport modeling, satellite remote sensing, and ground-based measurements.[67,68] Data provided to the authors by request (https://drive.google.com/drive/folders/10Rr5SJAInjSm57mEcfl7J86D4KB-4wbw). Because this model was available starting from January 1989, we restricted this second analysis to the 540 cases and 27,000 frequency-matched controls who were born in February 1989 or later.[67]

Our primary exposure metric examined $PM_{2.5}$ concentrations averaged over a 3-month perinatal window that included the birth month, the prior month, and the subsequent month. We selected this exposure window based on prior studies of air pollution and other childhood cancers and thyroid hormone disruption end points, although the critical exposure window for pediatric thyroid cancer is unknown.[69–71] We evaluated $PM_{2.5}$ concentrations continuously (per 10 $\mu g/m^3$) and as tertiles based on the distribution among controls. We selected a change of 10 $\mu g/m^3$ as an interpretable number similar to but less than the interquartile range of 17.6 $\mu g/m^3$ among controls (Table 1).

Assessment of Perinatal Exposure to O-ALAN

We geocoded maternal residence at birth for all study subjects using the ArcGIS Business Analyst Extension (version 10.6), and US Census Bureau 2010 TIGER shapefiles. For O-ALAN, we used the 2015 World Atlas of Artificial Night Sky Brightness, a computational technique for mapping light pollution.[72] In brief, this database uses remote sensing of upward radiance from the Visible Infrared Imaging Radiometer Suite Day-Night Band on the Suomi National Polar-orbiting Partnership satellite in conjunction with thousands of handheld measurements to calculate zenith brightness (the artificial sky brightness at a point directly overhead). The World Atlas provides global measures of brightness in millicandela per square meter (mcd/m^2) at a spatial resolution of 750-m grids. The World Atlas has numerous strengths in terms of dynamic range, spatial resolution, and calibration. World Atlas values were found to be more highly correlated with ground-level measurements of light exposure than other methods such as those based on the US Air Force Defense Meteorological Satellite Program—Operational Linescan System.[73] Because of data availability constraints and challenges in merging data across years with substantial changes in spatial resolution, we assigned each individual an exposure using values from May through December 2014. We applied this 6-month average retrospectively to the birth residence of study participants. Although this approach introduces some uncertainty, O-ALAN in the United States including California has remained relatively stable,[73–75] and satellite estimates based on multiple approaches (World Atlas, US Defense Meteorological Satellite Operational Linescan System, and Visible Infrared Imaging Radiometer Suite Day/Night Band) and measured in different years (1996–2017) in California are highly correlated (0.69–0.98).[76] We examined the exposure continuously (per 1 mcd/m^2) and as tertiles based on the distributions among controls.

Individual-Level and Area-Level Covariates

We abstracted several potential covariates from birth records that had evidence of associations with pediatric thyroid cancer, other childhood cancers, adult thyroid cancer, or a plausible influence on thyroid hormone levels.[26,31,77–80] Variables included: year of birth in categories to yield similar numbers of births per category (1982–1989, 1990–1994, 1995–2011), sex (male, female), race and ethnicity (Hispanic, non-Hispanic White, Asian, and other races), birth weight (modeled continuously as 500 g increments), gestational age (22–36, 37–41, 42–44 wk; unknown), maternal age (<20, 20–24, 25–29, 30–34, ≥35 y), maternal education (≤8, 9–11, 12, 13–15, ≥16 y; unknown years), mother's birth place (US, foreign), paternal age (<25, 25–29, 30–34, 35–39, ≥40 y), birth order (first, second, third and above), and history of Cesarean delivery (never, ever, unknown). The Other race categories included 17 non-Hispanic Black cases and 3 cases of other or unknown race or ethnicity, which were aggregated due to small numbers. We also considered adjustment or stratification by urban–rural designations using the 2000 Rural Urban Commuting Area (RUCA) Codes for all California census tracts. Assigning urban as levels 1–6 (metropolitan and micropolitan areas) and rural as 7–10 (small town and rural) yielded only 6 rural cases; therefore, we were unable to examine this further.

Statistical Analyses

We evaluated the association between perinatal exposure to outdoor $PM_{2.5}$ and O-ALAN and risk of pediatric thyroid cancer by calculating odds ratios (OR) and 95% confidence intervals (CI) using logistic regression. Our sample size enabled us to adjust for all covariates described above, including the matching variable (year of birth) and all sex, race, birth weight, gestational age, birth order, maternal age, mother's birthplace, maternal education, history of Cesarean delivery, and paternal age. Missing values were coded as unknown to allow all participants to be included in statistical models. We modeled the full study population and conducted subgroup analyses stratified by race and ethnicity [Hispanic, non-Hispanic White (groups with sufficient sample sizes)] and age at diagnosis (0–14, 15–19 y). We stratified by age groups to account for potential differences in etiology and susceptibility across the life course, which is of particular importance for hormonally related cancers due to endocrine changes across development. We stratified by race to assess potential health disparities driven by environmental, social, and structural factors that may influence exposure–response relationships. Understanding whether there are differences by age or race can also inform researchers and clinicians regarding screening practices or policy measures. Our primary models considered $PM_{2.5}$ and O-ALAN separately because the two exposures were moderately correlated (Spearman $r = 0.57$) and are thought to act via different mechanisms. All tests were two-sided with an α of 0.05; analyses were conducted in SAS 9.4 (SAS Institute, Inc.).

We conducted a series of sensitivity analyses to test the robustness of our findings. We constructed a model that included both $PM_{2.5}$ and O-ALAN jointly to evaluate their independent contributions. We constructed models without birth weight, gestational age, and history of Cesarean delivery because these gestational outcomes could serve as potential mediators, rendering adjustment inappropriate. In sensitivity analyses specific to the perinatal $PM_{2.5}$ exposures, we tested alternative exposure windows, including birth month only, pregnancy, and first year of life; we also repeated analyses using natural log-transformed $PM_{2.5}$ concentrations. In addition, because the multidecade feature of our cohort necessitated extrapolation to time periods prior to the availability of a comprehensive $PM_{2.5}$ monitoring network, we ran analyses stratified by whether the exposure estimates were derived from contemporaneous monitors (born in the year 2000 or later) or extrapolated to a period prior to widespread monitors (born pre-2000).

Results

Study Population Characteristics

In comparison with controls, cases were more likely to be female and Hispanic or Asian; a smaller proportion of cases were classified as other races (Table 1). Cases were more likely to have a lower birth order; have mothers with higher education, older age, and born outside the United States; and have older fathers (all $p < 0.05$). In terms of environmental exposures, cases tended to have higher exposure to ALAN as evidenced by their overrepresentation in the second (35.7%) and third exposure tertiles (35.3% vs. 33.3% in controls, $p = 0.04$). The distribution of $PM_{2.5}$

Table 1. Fine particulate matter ($PM_{2.5}$) and outdoor artificial light at night perinatal exposure distributions and individual-level characteristics for pediatric papillary thyroid cancer cases and controls in a California nested case–control study.

	Cases ($n = 736$)	Controls ($n = 36{,}800$)	
	n (%)	*n* (%)	*p*-Value[a]
Average ambient $PM_{2.5}$ concentration during 3-month birth window ($\mu g/m^3$)			
Tertile 1 ($\leq$16.2)	219 (29.8)	12,255 (33.3)	0.09
Tertile 2 (>16.2 to $\leq$27.7)	250 (34)	12,292 (33.4)	—
Tertile 3 (>27.7)	267 (36.3)	12,253 (33.3)	—
Mean $\pm$ SD ($\mu g/m^3$)	25.02 $\pm$ 12.94	24.10 $\pm$ 12.68	0.05[b]
Median [IQR ($\mu g/m^3$)]	22.61 (14.81, 31.99)	21.56 (14.03, 31.64)	—
Outdoor artificial light at night (mcd/m^2)			
Tertile 1 ($\leq$2.597)	213 (28.9)	12,289 (33.4)	0.04
Tertile 2 (>2.597 to $\leq$5.13)	263 (35.7)	12,272 (33.3)	—
Tertile 3 (>5.13)	260 (35.3)	12,239 (33.3)	—
Mean $\pm$ SD (mcd/m^2)	4.51 $\pm$ 2.73	4.32 $\pm$ 2.78	—
Median (IQR) (mcd/m^2)	3.91 (2.45, 6.55)	3.68 (2.15, 6.27)	—
Sex			
Female	605 (82.2)	18,210 (49.5)	<0.01
Male	131 (17.8)	18,590 (50.5)	—
Race and ethnicity			
Hispanic	368 (50)	17,045 (46.3)	<0.01
Non-Hispanic White	259 (35.2)	12,712 (34.5)	—
Asian	89 (12.1)	3,638 (9.9)	—
Other races[c]	20 (2.7)	3,405 (9.3)	—
Birth weight (g)			
250–2,499	37 (5)	2,187 (5.9)	0.65
2,500–2,999	118 (16)	5,553 (15.1)	—
3,000–3,499	267 (36.3)	13,915 (37.8)	—
3,500–3,999	233 (31.7)	11,074 (30.1)	—
$\geq$4,000	81 (11)	4,071 (11.1)	—
Gestational age (wk)			
37–41	70 (9.5)	3,544 (9.6)	0.79
22–36	563 (76.5)	27,777 (75.5)	—
42–44	60 (8.2)	3,248 (8.8)	—
Unknown	43 (5.8)	2,231 (6.1)	—
Birth order			
1st	307 (41.7)	14,612 (39.7)	<0.01
2nd	254 (34.5)	11,400 (31)	—
3rd and higher	175 (23.8)	10,788 (29.3)	—
Birth year			
1982–1989	234 (31.8)	11,700 (31.8)	1.00
1990–1994	248 (33.7)	12,400 (33.7)	—
1995–2011	254 (34.5)	12,700 (34.5)	—
Maternal age (y)			
<20	54 (7.3)	4,174 (11.3)	<0.01
20–24	178 (24.2)	9,347 (25.4)	—
25–29	228 (31)	10,642 (28.9)	—
30–34	186 (25.3)	8,261 (22.4)	—
$\geq$35	90 (12.2)	4,376 (11.9)	—
Maternal education			
$\leq$11 y	142 (19.3)	9,013 (24.5)	<0.01
12 y	143 (19.4)	7,867 (21.4)	—
13–15 y	131 (17.8)	5,234 (14.2)	—
$\geq$16 y	121 (16.4)	4,781 (13)	—
Unknown	199 (27)	9,905 (26.9)	—
Mother's place of birth			
United States	391 (53.1)	21,554 (58.6)	<0.01
Foreign	345 (46.9)	15,246 (41.4)	—
Previous Cesarean delivery			
Never	672 (91.3)	33,461 (90.9)	0.74
Ever	64 (8.7)	3,327 (9)	—
Unknown	0 (0)	12 (0.03)	—
Paternal age (y)			
<25	143 (19.4)	8,303 (22.6)	0.05
25–29	193 (26.2)	9,531 (25.9)	—
30–34	180 (24.5)	8,880 (24.1)	—
35–39	126 (17.1)	5,153 (14)	—
$\geq$40	67 (9.1)	2,875 (7.8)	—
Unknown	27 (3.7)	2,058 (5.6)	—

Note: —, no data; IQR, interquartile range; $PM_{2.5}$, particulate matter with aerodynamic diameter $\leq$2.5 μm; SD, standard deviation.
[a]*p*-Values are derived from Chi-square tests between cases and controls unless otherwise noted.
[b]*p*-Value derived from *t*-test of means between cases and controls.
[c]The other races category includes 17 non-Hispanic Black cases and 3 cases who reported other races or for whom race or ethnicity were unknown. The 20 cases were aggregated due to small numbers. Controls who were non-Hispanic Black or had other or unknown race or ethnicity data were also grouped.

exposure was also elevated among cases in comparison with controls (mean: 25.02 $\mu g/m^3$ vs. 24.10 $\mu g/m^3$ in controls, $p = 0.05$). The average ambient $PM_{2.5}$ concentrations exceeded the current US EPA annual standard of 12 $\mu g/m^3$.

Outdoor $PM_{2.5}$ and Pediatric Thyroid Cancer

We observed a statistically significant association between continuous $PM_{2.5}$ exposure and pediatric thyroid cancer (OR per 10-$\mu g/m^3$ increase: 1.07, 95% CI: 1.01, 1.14) and at the third tertile (OR = 1.27; 95% CI: 1.04, 1.54) (Figure 1). When stratified, significant associations were also observed for those diagnosed at 15–19 y of age (OR per 10 $\mu g/m^3$ $PM_{2.5}$: 1.08, 95% CI: 1.00, 1.16) and for Hispanic individuals (OR for 10 $\mu g/m^3$: 1.13, 95% CI: 1.02, 1.24) (Figure 1); differences between age and race/ethnicity groups were not statistically significant ($p_{interaction}$ for age = 0.79; $p_{interaction}$ for race/ethnicity = 0.40). Unadjusted and adjusted models yielded very similar results (Tables S1–S2).

In sensitivity analyses, results were very similar when considering alternative exposure time windows (Table S3). The $PM_{2.5}$ estimates derived from the two modeling approaches yielded

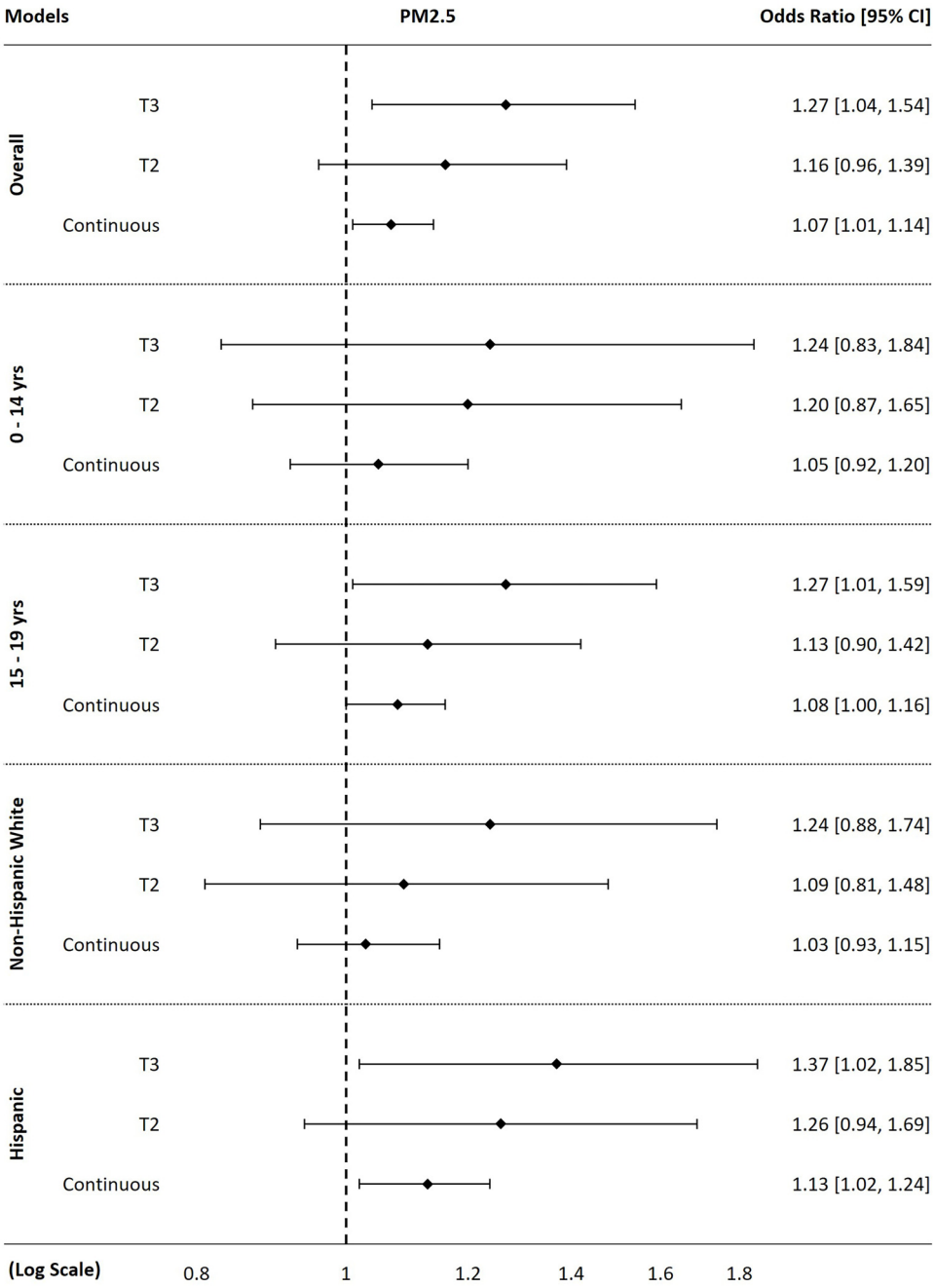

Figure 1. Odds ratios and 95% confidence intervals for pediatric papillary thyroid cancer in relation to perinatal exposure to ambient $PM_{2.5}$ concentrations as tertiles of exposure or with $PM_{2.5}$ modeled as a continuous variable (per 10 $\mu g/m^3$), overall and by age group, and race/ethnicity within a nested case–control study in California ($n = 736$ cases, 36,800 controls). Models for the overall population and age groups were adjusted for sex, race, birth weight, gestational age, birth order, birth year, maternal age, mother's birthplace, maternal education, history of C-section, and paternal age. Models for different racial and ethnic groups adjusted for the same covariates except race and ethnicity.

similar summary statistics [mean ± standard deviation (SD) among controls: $16.3 \pm 7.0\,\mu g/m^3$ in primary vs. $16.1 \pm 6.1\,\mu g/m^3$ in alternative model] and were moderately correlated when considering years for which both were available (2000–2015) ($r = 0.57$; $p < 0.0001$). The observed relationship when using the alternative $PM_{2.5}$ dataset derived using different models and for a different set of years, yielded very similar relationships (Table S4). In addition, similar results were observed when using log-transformed $PM_{2.5}$ concentrations (Table S3) and in models with both O-ALAN and $PM_{2.5}$ included concurrently (Table S5). Models with potential mediator variables removed were also nearly identical to the fully adjusted models (Table S6). Finally, models restricted to those born in 2000 and later, when air pollution monitoring networks were widespread, yielded similar results (Table S7).

ALAN and Pediatric Thyroid Cancer

In the overall population, we observed statistically significant increased odds of thyroid cancer for children in the second (OR = 1.25; 95% CI: 1.04, 1.50) and third exposure tertiles (OR = 1.23; 95% CI: 1.02, 1.50) in comparison with the first (reference)

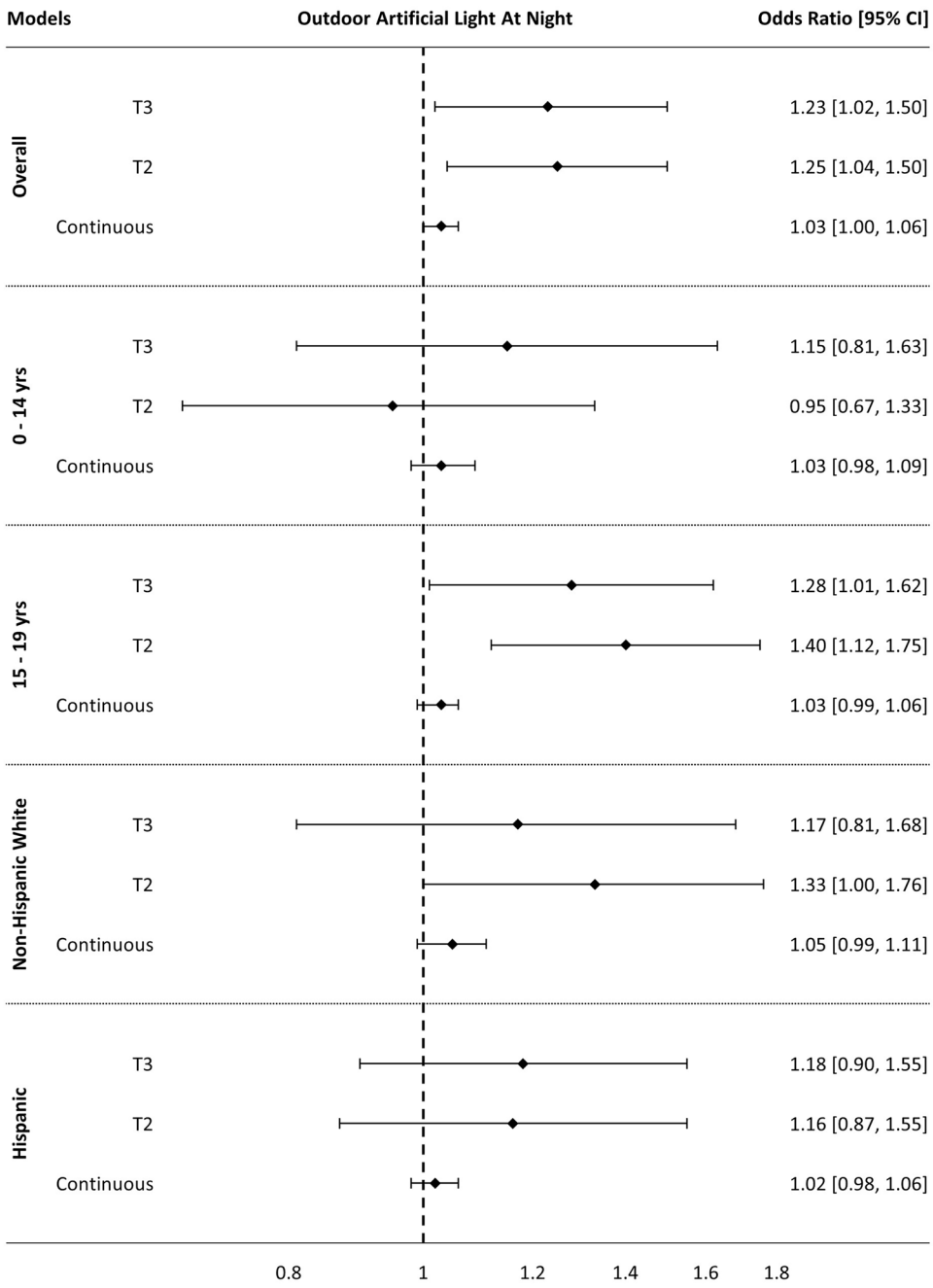

Figure 2. Odds ratios and 95% confidence intervals for pediatric papillary thyroid cancer in relation to perinatal exposure to outdoor artificial light at night (second and third tertiles compared with first tertile, or with light modeled as a continuous variable, per 1 mcd/m^2), overall and by age group, and race/ethnicity within a nested case–control study in California ($n = 736$ cases, 36,800 controls). Models for the overall population and different age groups were adjusted for sex, race, birth weight, gestational age, birth order, birth year, maternal age, mother's birthplace, maternal education, history of Cesarean-section, and paternal age. Models for different racial and ethnic groups adjusted for the same covariates except race and ethnicity.

tertile (Figure 2); effect estimates in the second and third tertiles were generally similar and nonmonotonic. The OR for the continuous exposure metric was OR = 1.03; 95% CI: 1.00, 1.06 per 1 mcd/m^2. The relationship appeared more pronounced among those who were 15–19 y of age at diagnosis (2nd tertile: OR = 1.28; 95% CI: 1.01, 1.62), in comparison with those 0–14 y of age (third tertile: OR = 1.15; 95% CI: 0.81, 1.63) (Figure 2), but the difference was not statistically significant ($p_{interaction} = 0.15$). Associations were observed among non-Hispanic White children at the second tertile (OR = 1.33; 95% CI: 1.00, 1.76) but not the third (OR = 1.17; 95% CI: 0.81, 1.68); no statistically significant associations were seen among Hispanic children ($p_{interaction} = 0.40$). Results for O-ALAN were somewhat attenuated when included in the model with $PM_{2.5}$ (Table S3).

Discussion

This large population-based study within a diverse population is among the first to examine associations between environmental exposures and risk of pediatric thyroid cancer, observing elevated ORs for both $PM_{2.5}$ and O-ALAN exposure and papillary thyroid cancer. Our finding of an association with $PM_{2.5}$ was consistent with the limited existing ecological analyses and a case–control study in adults the United States (2013–2016) including 1,990 patients with papillary thyroid cancer and 3,980 controls that assigned exposure data based on patients' residential zip codes at diagnosis using a validated deep learning neural network model that incorporated meteorological, satellite, and US EPA Air Quality System data.[40,81]

Our results for ambient $PM_{2.5}$ exposure were generally consistent with the literature on air pollution and risk of other pediatric cancers. A recent meta-analysis of 29 studies of exposure to air pollution and risk of childhood leukemia observed an association, but particularly at the highest levels of exposure.[37] For $PM_{2.5}$ specifically, Zhong et al. observed elevated risk of childhood acute lymphoblastic leukemia associated with exposure to $PM_{2.5}$ in non-Hispanic White children.[69] Our findings were consistent with two thyroid cancer studies in adult populations that observed increased likelihood of papillary thyroid cancer with greater exposure to ambient $PM_{2.5}$.[38,39] Although the potential mechanism requires further study, the small particle size allows penetration deep within the lung and systemic absorption and distribution within the body; the large surface area enables adsorption of numerous toxic chemical constituents.[82] Recent evidence suggests potential for thyroid hormone disruption in infants with prenatal exposures to $PM_{2.5}$.[70,71,83,84] Experimental studies in animals have found that exposure to $PM_{2.5}$ is capable of activating the hypothalamic–pituitary–thyroid (HPT) axis, altering thyroid hormone receptor levels, influencing thyroid hormone production and transport, and inducing oxidative stress and inflammatory responses.[85] Our use of two different validated, geographically based air pollution models provided flexible and widespread coverage in terms of space and retrospective estimates[86]; however, it is possible that the ambient estimates do not correlate with individual-level air pollution exposures, which are influenced by individual mobility and behaviors.

Our finding of an association between exposure to O-ALAN and higher odds of thyroid cancer, particularly in older children, is consistent with the limited information in the literature. The single thyroid cancer study that we identified, which focused on older adults in six US states, reported excess risk of cancer at the highest quintile of exposure, particularly for papillary thyroid cancer in women.[55] As for pediatric cancers other than thyroid cancer, few studies have been conducted. Zhong et al. observed significantly increased risk of childhood leukemia associated with exposure to O-ALAN, particularly in Hispanic children.[69] The mechanistic underpinnings for an association between exposure to O-ALAN and thyroid cancer lies in the connection between the light-sensitive circadian system and its influence on the HPT axis.[87,88] The HPT axis maintains normal, circulating levels of thyroid hormones, which are critical for metabolism, temperature regulation, cognitive development, and other functions.[89] Thyroid hormones exhibit temporal fluctuations throughout the day or season and have been shown to respond to changes in light exposures.[88] Altered light-dark cycles can create temporal misalignment of genetic and metabolic processes.[90] Exposure to ALAN has been demonstrated to influence the pineal gland to temporarily suppress melatonin secretion, which can disrupt circadian patterns and sleep.[91] Sleep disruption influences thyroid-related hormone levels, particularly thyroid stimulating hormone.[88]

The outdoor light at night serves as a proxy of exposure to "light pollution"[72,92–94] and may capture light intrusion into children's bedrooms during sleep time and increased light exposure during nighttime activities.[46] Outdoor light at night could also indicate maternal exposure to light pollution during pregnancy. However, this metric does not account for indoor light sources, behaviors and activities, housing characteristics (blinds, curtains, window coverings), and outdoor features (vegetation, buildings, shielding), introducing error if used solely as a surrogate of personal exposure to light at night.[44,50] One study comparing personal measurements of indoor light at night exposure with remote sensing over a 1-wk period among 256 children in the Netherlands did not observe correlations.[50] Although future studies could employ improved surrogates or wearable and portable devices for individual-level measurements of ALAN exposures, these methods cannot be deployed in retrospective, registry-based studies that do not involve participant contact. This finding underscores a broader trade-off between registry-based studies that avoid selection bias and allow evaluation of a large population but do not provide for detailed, individual-level collection of measurements. O-ALAN may also reflect other socioeconomic or environmental exposures in urban areas, such as other air pollutants[50] or local economic development.[52] Although we were unable to examine urban-rural differences in the relationship between O-ALAN and pediatric thyroid cancer due to the limited number of rural cases, future studies with larger rural populations could help disentangle the effects of O-ALAN from other urban characteristics (e.g., greenspace).

Strengths of this study include a population-based design, a large, diverse study population, and the availability of data on individual-level covariates. The record-linkage design eliminates the need for participant contact and therefore all eligible subjects were included, leading to low probability of selection bias. The study design leveraged the appropriate temporal relationship by examining factors present at birth with the subsequent incidence of thyroid cancer and enabled a focus on the perinatal exposure window, a potentially relevant window of vulnerability. Information was ascertained from birth records, and use of multiple geospatial methods were objective approaches with no reliance on recall or subjective reports.

Several limitations also warrant consideration. Because participants were not contacted, we lacked information on postnatal behaviors and other factors such as physical activity and nutrition and exposure to indoor light, including blue light. Our study focused on exposures during the perinatal period, which is considered a critical exposure window, but other time periods may be important. Residential mobility during pregnancy or childhood could introduce exposure misclassification. Moving during pregnancy and childhood is fairly common and differs by age, parity, socioeconomic status, marital status, and race and ethnicity.[95–98] However, studies have also suggested that, although it is an important consideration, the impact on exposure–response relationships

in air pollution studies may be minor.[96] In addition, maximizing the use of our cohort required extrapolation to time periods beyond when measurement data were available, which could introduce measurement error.[99] We addressed this by using multiple $PM_{2.5}$ historical models and conducting multiple sensitivity analyses, including those restricted to years after the availability of monitoring; effect estimates were consistent. Similarly, we assigned O-ALAN exposure from a single 6-month period to participants over a 30-y span, which introduces uncertainty. Unfortunately, limited data from earlier time periods were available, and substantial improvements in spatial resolution of satellite-based remote sensing over time make comparisons across time periods difficult. We addressed this by using high-resolution data retrospectively.[100] The 6-month retrospective average we applied has been used in other similar studies and is supported by observations of steady increases in light at night in the United States and not large shifts in exposure status.[69] However, replication in future studies with more refined exposure metrics would help clarify these relationships. For example, extending our registry-based study to include more recent years would allow for the use of higher-resolution, time-varying satellite data. In addition, studies with direct participant contact could supplement satellite-based measures with questionnaires or indoor measurements to improve the exposure assessment.

In conclusion, our novel findings provide evidence supporting a relationship between perinatal exposure to higher ambient concentrations of fine PM and greater intensity of outdoor light at night and papillary thyroid cancer risk in children. Replication of these findings and refinements to the exposure metrics would be informative. This study highlights the need for additional research on environmental risk factors for pediatric thyroid cancer.

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