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The Effect of Transportation-Related Air Pollution on the HPA Axis and Adverse Birth Outcomes

Author
Wing, Samuel

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The Effect of Transportation-Related Air Pollution on the HPA Axis and Adverse Birth Outcomes

A dissertation submitted in partial satisfaction of the

requirements for the degree of Doctor of Philosophy

in Epidemiology

by

Samuel Eng Wing

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ABSTRACT OF THE DISSERTATION

The Effect of Transportation- and Aircraft-Related Air Pollution on the HPA Axis and Adverse Birth Outcomes

by

Samuel Eng Wing

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2019

Professor Beate R. Ritz, Chair

Exposure to air pollution causes dysfunction in human physiology, including in the endocrine system and reproductive process. Transportation-related air pollutants are products of combustion engines, which can come from mobile ground and air sources. Los Angeles County is home to the world's fourth busiest passenger airport and almost 22,000 miles of maintained roadway, of which approximately 500 miles are freeway. Communities located proximal to these sources experience a considerable health burden from these exposures, especially among sensitive populations like children and pregnant mothers.

The first study of this dissertation examines the role of traffic-related air pollution in dysregulation of the hypothalamus-adrenal-pituitary gland (HPA) axis. Subjects were

adolescents enrolled in the Los Angeles Family and Neighborhood Survey (LAFANS) between 2006 and 2008. We built a land use regression (LUR) model to estimate chronic nitrogen dioxide (NO_2) exposure, a marker of traffic-related air pollution. We then generated model-based estimates of the association between the cortisol, a measure of HPA axis functioning, and NO_2 exposure one year prior to cortisol sampling. Our results indicate that increased exposure to NO_2 was associated with a flattened diurnal slope of cortisol, an indicator of an abnormal cortisol response. We hypothesize that this may be a mechanism through which air pollution may affect respiratory function and asthma in adolescents.

The second and third studies of this dissertation use birth outcome data from birth certificates supplied by the California Department of Public Health and exposure data from novel ultrafine particle (UFP) dispersion model. The second study estimates the association between in utero exposure to aircraft-related UFPs from planes landing at Los Angeles International Airport and preterm birth (PTB). Women were included in this study if they delivered babies between 2008 and 2016 and lived within 15 km of the airport. Controlling other pollutants and demographic factors, we found that the risk of PTB was elevated among women more highly exposed to aircraft-related UFPs during their pregnancy. This association was strongest among foreign-born women, especially those of Hispanic and Asian descent.

The third study is a causal mediation analysis, that examines the role of pregnancy-induced hypertension (PIH), including preeclampsia, as a mediator in the previously described relationship between UFP and PTB. We used a weighted marginal structural models approach to estimate the natural direct and indirect effects of UFP on PTB risk, with PIH as a mediating factor. We found that approximately 13% of the UFP-PTB relationship was mediated through UFP exposure-caused hypertensive disorders. We hypothesize that UFP exposure may lead to an

inflammatory response which puts expectant mothers at greater risk for hypertensive disorders that can lead to iatrogenic preterm births.

In conclusion, our findings present evidence of the detrimental effects of exposure to air pollution both in utero and during adolescence. These environmental exposures are widespread in urban settings like Los Angeles and impact large populations. The burden of these health effects is often carried by low socioeconomic status communities co-exposed to other pollutants. This research exposes potential processes through which air pollution impacts human health, adding plausible biologic mechanisms that strengthen the understanding of how transportation-related emissions impact a city's most vulnerable groups.

The dissertation of Samuel Eng Wing is approved.

Ondine von Ehrenstein

Michael Leo Brennan Jerrett

Donatello Telesca

Beate R. Ritz, Committee Chair

University of California, Los Angeles

2019

DEDICATION

To my parents and wife, without whom none of this would have been possible.

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LIST OF ABBREVIATIONS

Adverse birth outcomes (ABO)
California Department of Public Health (CDPH)
Community noise equivalent level (CNEL)
Confidence interval (CI)
Decibel (dB)
Deciliter (DL)
Hypothalamic-Pituitary-Adrenal axis (HPA)
Interquartile range (IQR)
Los Angeles (LA)
Los Angeles Family and Neighborhood Survey (LAFANS)
Los Angeles International Airport (LAX)
Land Use Regression (LUR)
Microgram (µg)
Nitrogen dioxide (NO_2)
Nitrogen oxide (NO)
Odds ratio (OR)

Parts per billion (PPB)
Oxides of nitrogen (NO_x)
Oxides of sulfur (SO_x)
Polycyclic aromatic hydrocarbon (PAH)
Pregnancy-induced hypertension (PIH)
Particulate matter (PM)
Particulate matter, aerodynamic diameter of less than 2.5 micrometers ($PM_{2.5}$)
Particulate matter, aerodynamic diameter of less than 10 micrometers (PM_{10})
Preterm birth (PTB)
Santa Monica Airport (SMO)
Socioeconomic status (SES)
Standard deviation (SD)
Ultrafine particle (UFP)
Volatile organic compound (VOC)

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VITA

EDUCATION

2010	B.A., Sociology
	Northwestern University
	Evanston, Illinois
2013	M.P.H, Epidemiology
	University of Illinois at Chicago
	Chicago, Illinois

PUBLICATIONS

Wing SE, Bandoli G, Telesca D, Su JG, Ritz B. Chronic exposure to inhaled, traffic-related nitrogen dioxide and a blunted cortisol response in adolescents. Environ Res. 2018; 163:201-207. doi:https://doi.org/10.1016/j.envres.2018.01.011.

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PRESENTATIONS

Society for Epidemiologic Research, 2017
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Chapter 1 – Introduction & Background

1.1 Introduction

The purpose of this dissertation is to study the role of ambient air pollution on children's and reproductive health. To achieve this, the first study uses data from the Los Angeles Family and Neighborhood Survey (LAFANS) and a Land Use Regression (LUR) model to examine the association between exposure to traffic-related nitrogen dioxide (NO_2) and changes in the neuroendocrine system among children under 18 years old. The second study assesses the role of in utero aircraft-related ultrafine particle (UFP) exposures and the risk of preterm birth among women living near the Los Angeles International Airport (LAX). The third study expands on the second, decomposing this relationship through mediation analysis, in order to describe components of the plausible biologic mechanisms at work between UFP exposures and preterm birth. These last two studies utilize a novel UFP dispersion model and comprehensive birth certificate data from the California Department of Public Health (CDPH).

1.2 The HPA Axis

The hypothalamus-pituitary-adrenal (HPA) axis is a major neuroendocrine system comprised of the hypothalamus, pituitary gland, and adrenal glands. These three organs interact with one another via hormone signaling to initiate and regulate a wide variety of bodily functions. However, dysregulation of the HPA axis can upset the homeostatic processes in which it is involved. HPA axis dysfunction has been identified in the etiology of mental illnesses, like depression and mood disorders,[1,2] cardiovascular disease,[3,4] and autoimmune diseases.[5]

The HPA axis signaling process begins with stimulation of the hypothalamus. This incitement may be due to an external stimulus, like exposure to a psychosocial stressor, an allergen, or an environmental toxicant. Following exposure to a stressor, the HPA axis is activated when neuronal activity stimulates the release of corticotropin-releasing hormone (CRH) from the hypothalamus. This results in the release of adrenocorticotropic hormone (ACTH) from the pituitary gland, which ultimately signals synthesis and release of the glucocorticoid cortisol from the adrenal glands. Once circulating in the immune system, cortisol binds to glucocorticoid receptors, which help regulate interleukins-4, -5, and -13 from T cells as well as histamine and eosinophil release from mast cells. In the context of the immune system, the release of cortisol by the HPA axis is a critical part of the downregulation of immune activity.[6]

After repeated activation, the HPA axis may become dysregulated. Chronic HPA axis stimulation, possibly due to psychosocial stress or environmental exposures, and the persistent release of cortisol can result in a state of glucocorticoid resistance. Usually, cortisol activates glucocorticoid receptors which has an inhibatory effect. However, long-term, elevated levels of cortisol can induce a condition in which glucocorticoid receptors on target cells and tissues, like white blood cells, may no longer respond sufficiently to the presence of cortisol.[7] The result is a condition in which the typical downregulating capacity of cortisol is not achieved and this loss homeostasis may lead to disease from excess immune activity.

While the HPA axis activation is triggered by exogenous stressors, cortisol is also released in a routine, circadian rhythm. This process is coordinated in the hypothalamus by the suprachiasmatic nucleus. Cortisol concentrations peak ~30 minutes after waking, slowly decline during the day, and reach a nadir during the middle of the night before rising again the early

morning hours. HPA axis dysregulation can be evaluated by examining changes to typical rhythms in cortisol concentrations. The amplitude of this diurnal rhythm has been found to be a proxy of HPA axis functionality and has been used to evaluate the role of chronic HPA axis dysregulation and its role in disease etiology.[8]

1.3 Preterm Birth

Preterm birth, defined as a live birth occurring before 37 weeks of gestation, occurs in approximately 10% of births in the United States. In terms of demographic characteristics, it occurs more often among minority women,[9,10] teenage mothers,[11,12] and mothers over 35 years old.[13,14] Behavioral risk factors include cigarette smoking,[15,16] alcohol consumption,[17,18] stress,[19,20] and long working hours.[21,22] Medical conditions might also put a woman at greater risk for PTB. These include sexually transmitted infections,[23] urinary tract infections,[24] high blood pressure, [25,26] in vitro fertilization,[27] diabetes,[28] and being underweight[29] or obese.[30]

Preterm birth can lead to a wide variety of adverse outcomes for the child. Among children under 5, preterm birth is the leading cause of mortality globally, leading to approximately 1 million deaths annually.[31] Perinatal neurological morbidities,[32] – including cerebral palsy[33] – chronic respiratory disease,[34] gastrointestinal complications,[35] pathological cardiovascular immaturity,[36] increased risk for serious infections,[37] and blindness[38] are all also attributable to preterm birth. By incurring medical costs, loss of productivity, and an added need for special education, it has previously estimated that each preterm birth in the United States generates an average total economic burden of $51,600. On aggregate, this sums to over $26 billion annually.[39]

Some tests have been developed to diagnose pregnant women who are at risk for a preterm birth. Placental alpha microglobulin-1, a protein found at high concentrations in amniotic fluid, has sensitivity and specificity above 90% in identifying a spontaneous preterm labor within 7 days.[40] Similarly, the presence of fetal fibronectin (fFN) – a fetal protein – has a very high negative predictive value of ~99% in ruling out proximal labor.[41] This property makes it helpful to avoid the use of potentially harmful and unnecessary interventions. Ultrasound is also used to identify cervical length as a predictor of preterm birth, but its accuracy as a diagnostic method has been mixed.[42]

Preterm birth can either occur spontaneously or through medical induction. While the majority of preterm births are spontaneous, approximately 15-20% are induced or elective.[43] Spontaneous preterm birth typically occurs through non-iatrogenic cervical dilation or premature rupture of membranes (PROM). By contrast, preterm labor might be medically indicated and be iatrogenically induced. Induction might be deemed necessary in cases where maternal or fetal wellbeing is in jeopardy, as in cases of severe preeclampsia, abruptio placentae, or fetal distress. Induction of vaginal labor can be stimulated medically, by administration prostaglandin or oxytocin, or physically through the artificial rupture of membranes.[44] Additionally, preterm birth may occur through a planned cesarean delivery.[45]

1.4 Preeclampsia

Preeclampsia occurs in approximately 2% to 8% of pregnancies. It is a complication of pregnancy that is characterized by hypertension and proteinuria in the mother that develops after 20 weeks of gestation. Severe cases of preeclampsia may also be accompanied by headache, visual disturbances, and abdominal pain.[46] When a preeclamptic woman begins to experiences

seizures, her condition then becomes eclampsia. The exact etiology and pathophysiology of preeclampsia are not entirely known. However, a primary element of the condition is abnormal placentation. During a normal pregnancy, uterine spiral arteries are typically remodeled into larger vessels that can accommodate increased blood flow to the placenta and fetus. However, in women with preeclampsia, this remodeling process is rendered incomplete and results in insufficient placental blood flow, which induces oxidative stress in the placental and maternal systems. One major byproduct of this biologic response is endothelial dysfunction that prevents vasodilation that typically occurs during pregnancy, which is thought to accommodate the systemic increased demand for blood supply. As a result, hypertension occurs; the prototypical symptom of preeclampsia.

Maternal morbidities, and even mortality, can result from preeclampsia. The maternal liver,[47] kidneys,[48] brain,[49] and cardiovascular system[50] are all susceptible to acute and chronic problems stemming from this complication. Preeclampsia and eclampsia are a leading cause of maternal mortality are responsible for approximately 1 of every 10 maternal deaths in the United States.[51] Preeclampsia also puts the infant at increased risk for adverse outcomes, including preterm birth, growth restriction due to hypoxia, and mortality.[52,53] Because of these potentially severe outcomes associated with preeclampsia, physicians may choose to induce labor, as giving birth is the only effective cure for preeclampsia.[54] While not allowing for a full term of gestation has considerable drawbacks, as was outlined above, the adverse outcomes of complications from preeclampsia may be even more serious in certain cases.

Women are at higher risk for this complication if they are having their first child, are having a non-singleton pregnancy, are obese, have a family history of preeclampsia, or are chronically hypertensive.[55] Counterintuitively, studies have reported that cigarette smoking

during pregnancy reduces the risk of developing preeclampsia.[56,57] However, among smokers in whom preeclampsia does develop, the risk for serious perinatal complications and death is markedly higher.[58]

1.5 Transportation-Related Air Pollution and Human Health

Ambient air pollution is a nearly ubiquitous environmental toxicant in urban settings, where motor vehicles are typically the primary source. In terms of specific pollutants, much focus has been placed upon particulate matter (PM), ground-level ozone (O_3), and oxides of nitrogen (NO_x). PM are made up of both liquid and solid particles and are often categorized by their diameters. PM_{10} is the largest category and comprises particles less than 10 µm across, which are capable of entry into the lower respiratory system. $PM_{2.5}$ includes particles less than 2.5 µm across, are considered "respirable," and can penetrate deep into the alveoli of the lungs. The smallest category of PM, ultrafine particles (UFP), are less than 0.1 µm in diameter. Due to their small size, UFPs are capable of translocation from the lung to nearly any distal tissue, which may confer added pathophysiological potential compared to the larger size fractions of PM.[59]

NO_x is comprised of nitric oxide (NO) and nitrogen dioxide (NO_2). NO_x is formed as both primary and secondary pollutants during the combustion process. NO_2 has previously been utilized as a marker for the complex mixture of traffic-related air pollution.[60] O_3 is formed when NO_x and volatile organic compounds (VOCs) react in the presence of sunlight.[61] PM, O_3, and NO_x in addition to oxides of sulfur (SO_x), carbon monoxide (CO), and lead are the six "criteria" air pollutants that the Clean Air Act mandated for regulation by the Environmental Protection Agency.[62]

Like ground-sources, air travel also generates a mixture of greenhouse gases and environmental toxicants. In addition to contributing pollutants like NO_x, particulate emissions due to aircraft have been recently identified as important near-airport determinants of air quality.[63–67] These local impacts are driven by different phases of aircraft movement, especially taxi, take-off, and landing. Other activities at the airport can contribute to ambient air pollution, including ground service vehicles (e.g. fuel trucks, baggage carts, and maintenance vehicles).[68]

The human health effects of transportation-related air pollution exposures have been well-documented. Chronic exposure to these pollutants can have deleterious effects on numerous bodily systems across the entire life span. Their effects range from very early in life, like increased risk of fetal loss[69,70] and preterm birth,[25,26,71] to very late, like increased risk of neurodegenerative disorders.[60,72] The induction of inflammation[73–75] and oxidative stress[76–79] have both been proposed as plausible mechanisms through which air pollution exposure can cause disease. Among countries that belong to the Organization for Economic Cooperation and Development (OECD), it has previously been estimated that these exposures lead to a total economic burden due to the morbidity and mortality of nearly $1 trillion annually.[80]

Generally, the risk of adverse health effects due to air pollution exposure tends to be small in magnitude, though this does not diminish their importance as a public health concern. For example, previous research found that risk of death due to a 10 µg/dl increase in PM_{10} exposure elevated the risk of mortality by 1%.[81] However, very large portions of the population are exposed to air pollutants which magnify the attributable risk of this exposure. When incorporating this large spatial distribution of air pollution, previous research has found that approximately 6% of annual deaths in developed nations are attributable to air pollution exposure.[82]

Air pollution – and its effects on human health – tends to impact communities of lower socioeconomic statuses. These communities are often located near important sources of air pollution, like freeways, heavy industry, and airports. Property values are negatively correlated with air pollution exposures[83] and individuals with lower socioeconomic status may have greater susceptibility to air pollution,[84] which can be conveyed through increased psychosocial stress,[85] poor diet,[86] cigarette smoking,[87] and limited access to healthcare.[88] Ironically, members of these communities are more likely to engage in behaviors that generate fewer fossil fuel emissions, like increased use of public transportation.[89]

Chapter 2 – Chronic exposure to inhaled, traffic-related nitrogen dioxide and a blunted cortisol response in adolescents

2.1 Abstract

Background

Chronic health effects of traffic-related air pollution, like nitrogen dioxide (NO_2), are well-documented. Animal models suggested that NO_2 exposures dysregulate cortisol function.

Objectives

We evaluated the association between traffic-related NO_2 exposure and adolescent human cortisol concentrations, utilizing measures of the cortisol diurnal slope.

Methods

140 adolescents provided repeated salivary cortisol samples throughout one day. We built a land use regression model to estimate chronic NO_2 exposures based on home and school addresses. We then generated model-based estimates of the association between cortisol and NO_2

exposure one year prior to cortisol sampling, examining changes in cortisol diurnal slope. The final model was adjusted other criteria pollutants, measures of psychosocial stress, anthropometry, and other demographic and covariates.

Results

We observed a decrease in diurnal slope in cortisol for adolescents exposed to the estimated 75th percentile of ambient NO_2 (high exposure) relative to those exposed at the 25th percentile (low exposure). For a highly exposed adolescent, the log cortisol was lower by 0.06 μg/dl at waking (95% CI: −0.15, 0.02), 0.07 μg/dl at 30 min post waking (95% CI: −0.15, 0.02), and higher by 0.05 μg/dl at bedtime (95% CI: 0.05, 0.15), compared to a low exposed adolescent. For an additional interquartile range of exposure, the model-based predicted diurnal slope significantly decreased by 0.12 (95% CI: −0.23, −0.01).

Conclusions

In adolescents, we found that increased, chronic exposure to NO_2 and the mixture of pollutants from traffic sources was associated with a flattened diurnal slope of cortisol, a marker of an abnormal cortisol response which we hypothesize may be a mechanism through which air pollution may affect respiratory function and asthma in adolescents.

2.2 Introduction

Exposure to air pollution in human studies has been consistently associated with a wide range of negative health outcomes.[90,91] Animal studies have suggested that air pollution may impact a major endocrine subsystem, the hypothalamic-pituitary-adrenal (HPA) axis, and alter the typical release of cortisol from the adrenal gland.[92,93] Dysregulation of this neuroendocrine subsystem has been associated with metabolic disorders,[94] cardiovascular dysfunction,[95] and

neuropsychiatric disorders.[96] Cortisol is also responsible for assisting in the regulation of immune and inflammatory responses in the airways,[97] but repeated, long-term exposure to high levels of cortisol may cause a counterregulatory response by the white blood cells that limits the inhibitory effects of cortisol and results in the promotion of inflammatory diseases like asthma.[7] Even though mechanistic evidence for air pollution's action on the HPA axis and cortisol has largely come from animal models,[98] there is an overlap between HPA axis-related diseases and diseases that have been associated with air pollution exposure, like depression.[99,100] To date, few studies of air pollution and cortisol response in humans exist, especially in children and adolescents.[101]

Cortisol is a steroid hormone produced in the adrenal gland and readily sampled from saliva.[8] Cortisol concentrations follow a diurnal rhythm where daily values peak approximately 30 to 45 minutes after waking, followed by a steady decline throughout the day. Lowest daily cortisol values typically occur overnight, with values cyclically increasing again in the hours prior to waking.[8]

Due to the time-dependent nature of the measure, cortisol analyses necessarily include multiple measurements during the day. Diurnal slope, or the change in cortisol values from post-waking peak to their nighttime low point, is a frequently used measure of HPA axis function. Flattened diurnal slopes are a marker of an abnormal cortisol response and have previously been associated with chronic exposures to psychosocial stress.[102] These flattened slopes are more generally described as having a lower post-waking cortisol peak and higher end-of-day values. Additionally, flattened diurnal slopes have been identified as a superior predictor of both psychosocial stress and potential HPA axis dysregulation relative to other measures of cortisol, like total daily cortisol output ("area under the curve") or cortisol awakening response.[8,103]

Here, we investigate the degree to which land use regression (LUR) modeled nitrogen dioxide (NO_2) exposure from traffic-related air pollution is associated with a flattened diurnal cortisol slope in adolescents ages 12 to 17 years who participated in the Los Angeles Family and Neighborhood Survey (LAFANS), Wave 2, that contained information on self-reported psychosocial stressors, demographic information, and collected repeated saliva cortisol samples from participants.

2.3 Materials and Methods

2.3.1 Sample Population

Participants were enrolled in the Los Angeles Family and Neighborhood Survey (LAFANS), Wave 2, a population-based study in Los Angeles County, California to study the complex, multilevel influence that neighborhoods and families have on child development.[104] Data were collected in two waves, the first conducted in 2000 and 2001 and the second from 2006 through 2008. Wave 1 sampled 3,090 households from 65 census tracts. Within each household sampled, adults and children were enrolled and consented/assented for their participation in the interviews. The second wave comprised of participants who responded in the first wave and remained in their neighborhood or had moved away but could still be traced, and new entrants into the original neighborhoods. Wave 2 re-interviewed 1,091 of the original 3,140 children who participated in Wave 1 and added 296 new neighborhood entrants under the age of 18, for a total of 1,387 children.

In addition to interviewing, Wave 2 introduced health assessments for a random subset of 492 participants between 3 and 17 years of age, which included anthropometry, spirometry, and salivary cortisol measurements. Older children, between the ages of 12 and 17, were asked a

more detailed battery of questions that included information on psychosocial stressors. Because both acute[105] and chronic stress[106,107] modulate the HPA axis and subsequent cortisol release, only adolescents were included in this analysis (n = 140) to allow for adequate covariate control. Data collection occurred with approval from the RAND Institutional Review Board. Subsequent data analyses were carried out with approvals from the RAND and the University of California, Los Angeles Institutional Review Boards.

2.3.2 Saliva Cortisol

Parents of the participating children were trained by interviewers to gather saliva samples using absorbent, cellulose-cotton tipped sorbette swabs on the end of short plastic sticks, previously identified as practically advantageous relative to other saliva collection techniques.[108,109] This method harvested more than adequate amounts of saliva for laboratory assays of cortisol, remained stable at refrigerator temperatures for a week, was comfortable for the study subject, and could be accurately carried out with minimal training.

Parents were instructed to collect samples at three time points during a single day: immediately when the adolescent woke up, 30 minutes after waking, and at bedtime. Also known as “sponge-pops”, parents placed these into the adolescent’s mouth, under their tongue for 60 seconds in order to collect an adequate amount of saliva. Subsequently, the swabs were sealed in test tubes, stored in home refrigerators, and sent out the following day for laboratory analysis.

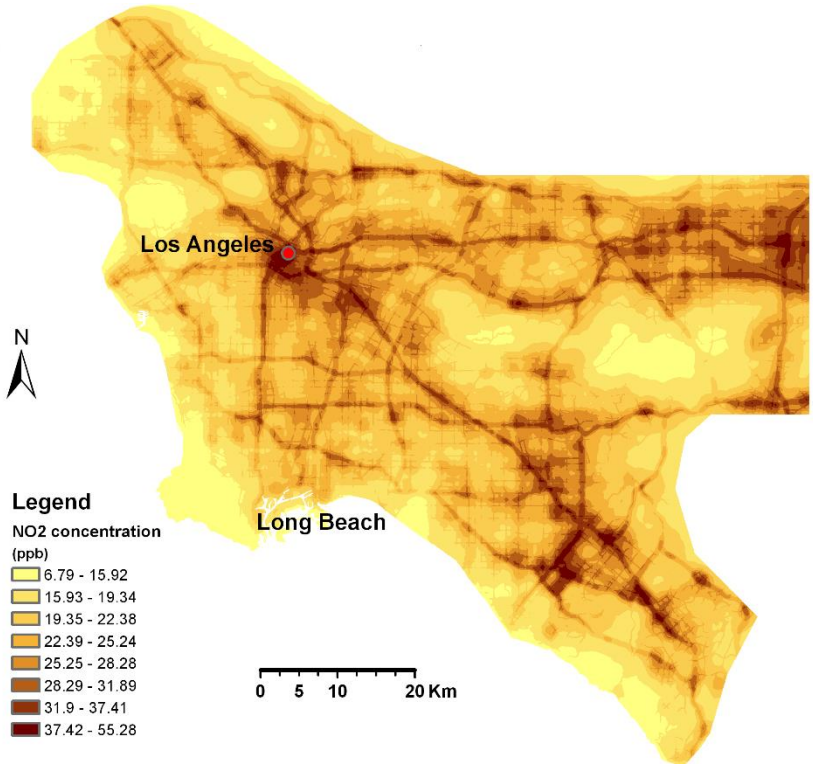
Participants were not allowed to provide samples if they ate or drank prior to the sample collection time point and were required to abstain from alcohol and dental work in the preceding 24 hours before the day of collection. Samples were also rejected if they were contaminated with blood or if cortisol values exceeded maximum assay sensitivity or had abnormally large intra-

assay differences. Detailed information on saliva collection protocols is available from the RAND Corporation and collection device manufacturer.[104,110] The second sample must have been collected between 15 and 60 minutes after waking to be included and the third sample taken at bedtime was only included if the subject was awake for at least 10 but no longer than 20 hours.

2.3.3 Exposure Assessment

An LUR model to estimate annual NO_2 exposures was created for Los Angeles County using data collected over two weeks from 201 passive air samplers (part number PS-100, Ogawa & Company USA, Inc, Pompano Beach, FL) placed in the LAFANS neighborhoods during both October 2006 and February 2007. The final prediction surfaces explained 85% in the variation of NO_2 concentrations over the two weeks. Detailed information about these air pollution estimates has been published previously.[111,112] The estimated NO_2 exposure was for the one year prior to the LAFANS, wave 2 data collection date and was not adjusted for seasonality. Figure 2.1 displays the final prediction surface for NO_2, a marker for the mixture of pollutants from traffic sources.

Figure 2.1 Chronic exposure to inhaled, traffic-related nitrogen dioxide and a blunted cortisol response in adolescents[113]



In addition to the unadjusted effect of NO_2, in adjusted models, we also controlled for $PM_{2.5}$ (fine particulate with aero-dynamic diameter ≤ 2.5 microns) and ozone exposure measures to isolate the role of near-source, traffic-related mixture of exposure, as represented by NO_2 in our LUR model from spatially more homogeneous, area-wide exposures. These two pollutants and our LUR traffic marker were not highly correlated in the Los Angeles region ($\rho < .70$). $PM_{2.5}$ and ozone exposure measures were generated via interpolation using a kriging algorithm with routinely collected, government ambient monitoring station data from 2002 and 2000, respectively.[112] Thus, $PM_{2.5}$ and ozone concentrations represent background levels for both pollutants and both are more homogeneously distributed across the LA basin. Air pollution exposure estimates were time-weighted for 3 locations: current home, any previous homes (within the preceding 12 months), and 1,080 hours spent at school per year.

2.3.4 Demographic, socioeconomic, and health characteristics

An adult household participant reported on the previous year's household income. Race/ethnicity of the child was reported by the adult in the home as being White, Black, Latino, Asian, Pacific Islander, or Native American. The latter two categories were collapsed into "Other" in this analysis due to small subgroup sizes. The household's adult also reported on smokers living in the home and the use of air conditioning. A previous analysis of LAFANS wave 2 data found that less than 2% of adolescents reported smoking,[114] which was deemed too low of a prevalence for inclusion in further analysis. Interviewers measured the height and weight of participants during study visits and recorded the child's use of medications for controlling asthma.

2.3.5 Psychosocial Stress and Neighborhood Cohesion

Three levels of stressors were considered as covariates in this analysis: neighborhood, family, and interpersonal. As described previously,[115] neighborhood-level stress was measured as a function of neighborhood cohesion, as reported by an adult living in the same household as the child participant. The adult was asked about the following scenarios: (a) this is a close-knit neighborhood, (b) there are adults kids can look up to, (c) people are willing to help their neighbors, (d) neighbors generally don't get along, (e) adults watch out that kids are safe, (f) people in the neighborhood don't share the same values, (g) people in the neighborhood can be trusted, (h) parents in neighborhood know kid's friends, (i) adults in a neighborhood know local kids, and (j) parents in the neighborhood know each other. The adult further reported on: (k) neighbors would do something if kids were skipping school and hanging out on a street corner, (l) would do something if a kid does graffiti, and (m) would scold kid if showing disrespect. Response options for (a) through (j) were: 1 to 5 or strongly agree to strongly disagree and

responses for (k) through (m) were: 1 to 5 or very likely to very unlikely. Summary scores were computed to generate a neighborhood stress score. Neighborhood cohesion may protect against the effects of stress[116] and stronger social bonds have been associated with steeper diurnal cortisol slopes.[117]

Family stress was measured as a composite of the adolescents' responses to six questions regarding the stability of their family's dynamics and relationships representing the degree to which the child experiences stressful situations in the home. Adolescents answered the following questions for the family stress score: (a) people in my family fight a lot, (b) people in my family hardly ever lose their tempers, (c) people in my family sometimes get so angry they throw things, (d) people in my family always calmly discuss problems, (e) people in my family often say mean things to each other, and (f) people in my family sometimes hit each other. Response options were: 1=True, 2=Sometimes True, and 3=Not True. Average of responses was computed to generate the family stress score. Family stress, like marital discord, has been identified as modulating cortisol level in children.[118]

Furthermore, participants were asked if they experienced any of the following events during the preceding 12 months: (a) someone tried to steal something from them by force or by threatening them, (b) something was stolen from them, (c) someone tried to sell them drugs or did sell them drugs, or (d) they saw someone get shot or shot at with a gun (1=Yes, 0=No). The average of responses forms the life events stress score. Such stressful experiences have been previously described as HPA axis dysregulators in younger populations.[119,120]

2.3.6 Statistical Analysis

We assessed the association between NO_2 exposure and the rate of change of salivary cortisol, measured as µg/dl, from daily peak (the second morning sample) to bedtime low using an unadjusted and adjusted repeated measures regression analysis (PROC MIXED; SAS 9.3, SAS Institute, Cary, NC). We used covariate-adjusted, model-based predictions to test the estimated difference per one interquartile range (IQR) increase in NO_2 exposure and associated changes in diurnal slope. Observed saliva cortisol values, as expected, were notably right-skewed, thus a log transformation was used to normalize this outcome variable. In a sensitivity analysis, we also stratified by gender due to gender-dependent differences in cortisol reactivity to exogenous stressors.[121]

Typical saliva cortisol concentrations are known to follow an "inverted J" shape with moderate wakeup values, a spike shortly after wakeup, and a slow decay throughout the remainder of the waking hours. Due to this expected non-linear shape, the modeled function of cortisol was allowed to vary at each observed time point. Therefore, time was handled nominally, with a NO_2 * time interaction term giving estimates for the effect of NO_2 exposure at each of the three time points measured. An estimated diurnal slope was calculated as the predicted difference between the post-waking cortisol peak and bedtime low. Point-wise and overall slope differences were tested using time-specific linear functions between subgroup-specific exposure quantities while covariates were fixed at their average values.

In addition to controlling for estimated $PM_{2.5}$ and ozone exposures, we adjusted for the three psychosocial stressors (neighborhood, family, and interpersonal), child's age, height, and weight, family income, race/ethnicity, child's use of medications to control asthma, cohabitation with cigarette smokers and use of air conditioning in the home. Cohabitating with a smoker and

the filtering effect of air conditioning use could mask the role of ambient air pollution. For model fitting, we focused on comparing within-subject covariance structures. Of the possible structures modeled, antedependence presented the best fit, offering the smallest Bayesian Information Criterion and performing better than the null independence model ($\chi^2 = 25.00$, $p < .0001$).

Secondary analyses will include participants under the age of 12 to examine the relationship of NO_2 and cortisol diurnal slope without being able to control for psychosocial factors lacking in LAFANS for this younger population. Further, we will evaluate the presence of statistical interactions between NO_2 and the three psychosocial stressors.

2.4 Results

Table 2.1 Descriptive and demographic data for participants ages 12-17 in the L.A.FANS-2 neighborhood and household survey in Los Angeles, CA, 2006-8

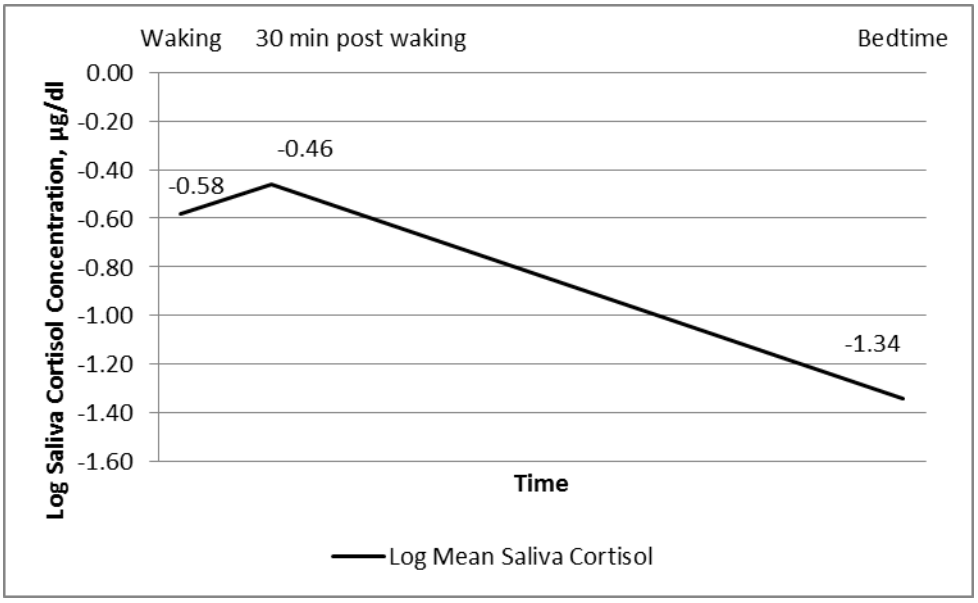
	Female (n = 73)	Male (n = 67)
Adolescent covariates		
Age, mean (sd)	14.2 (1.6)	14.4 (1.8)
BMI, mean (sd)	24.7 (6.5)	24.6 (5.7)
Asthma Medication User	3%	10%
Race		
Latino	69%	69%
White	15%	16%
Black	3%	2%
Asian	5%	0%
Other	8%	13%
Household covariates		
Cohabitates with smoker	22%	24%
Air Conditioning in the Home	47%	49%
Annual Family Income, median (sd)	$65,355 ($55,351)	$60,822 ($58,591)
Saliva Cortisol (μg/dl),		
At waking, mean (sd)	0.34 (0.24)	0.31 (0.18)
At 30 min post waking, mean (sd)	0.48 (0.29)	0.39 (0.23)

At bedtime, mean (sd)	0.08 (0.11)	0.07 (0.14)
Air Pollution Annual Exposure Estimates		
NO_2 (ppb) , mean (sd)	23.1 (4.8)	23.0 (3.6)
$PM_{2.5}$ ($\mu g/m^3$), mean (sd)	20.7 (2.6)	20.4 (2.9)
Ozone (ppb), mean (sd)	74.1 (19.6)	78.2 (21.2)
Psychosocial Stressors		
Stressful events, past 12 months, mean (sd)	0.43 (0.72)	0.60 (0.96)
Family stress score, mean (sd)	14.3 (1.8)	13.5 (3.1)
Neighborhood cohesion score, percent above LAFANS median	36%	34%

Ranges -- Age: 12-17; BMI: 15.9-44.6; Annual Family Income: $128-$258,500; Saliva Cortisol, Waking: 0.02 µg/dl-1.31 µg/dl; Saliva Cortisol, 30 min. Post-Waking: 0.03µg/dl-1.34µg/dl; Saliva Cortisol, Bedtime: 0.003µg/dl-0.40µg/dl; NO2: 6.6ppb-32.1ppb; PM2.5: 9.0µg/m3-23.5µg/m3; Ozone: 46.6ppb-130.2ppb; Stressful Events: 0-3, Family Stress Score: 8-18, Neighborhood Cohesion Score: 1.2-3.9.

Table 2.1 presents the distribution of exposure measures, demographics, and other covariates for males and females. Among the participants with valid saliva cortisol measurements (n=140), the mean age was 14.3 years and 52% were female. The majority were Latino, and less than a quarter of participants cohabitated with a smoker. Boys were about twice as likely to use asthma medication as girls; the overall prevalence of medication use was 9%. Adolescents reported experiencing an average of one stressful event in the past 12 months. Average NO_2 annual exposures from the LUR ranged from 6.2 ppb to 34.0 ppb, with a mean of 23.5 ppb and IQR of 5.3. Salivary cortisol levels when first waking up had a median of 0.26 µg/dl and 30 minutes after waking, they reached their maximum with a median of 0.36 µg/dl; at bedtime, the median cortisol had fallen to 0.04 µg/dl (Table 2.1). An empirical summary plot of the log-transformed means of saliva cortisol is presented in Figure 2.2.

Figure 2.2 Empirical mean summary plot of log saliva cortisol. Average cortisol profiles of participants achieved an expected “inverted J”-shaped curve.



We used a linear combination of coefficients to generate model-based, covariate-adjusted, and exposure-specific estimates of diurnal cortisol slopes. Slopes were compared between hypothetical 25th and 75th percentile exposures to NO_2. There was a decrease in diurnal slope, or the bedtime low minus the 30 minutes post waking peak value, in salivary cortisol for participants exposed to the 75th percentile of ambient NO_2 relative to those exposed to the 25th percentile. For an adolescent with an estimated exposure at the 75th percentile, the log cortisol was lower by 0.06 µg/dl at waking (95% CI: -0.15, 0.02), 0.07 µg/dl at 30 min post waking (95% CI: -0.15, 0.02), and higher by 0.05 µg/dl at bedtime (95% CI: -0.05, 0.15), compared to those at the 25th percentile (Table 2.2).

Table 2.2 Model-based Estimation & Tests of Diurnal Slopes, Log Saliva Cortisol in adolescents, ages 12-17 years for past year NO2, PM2.5, and Ozone exposures.

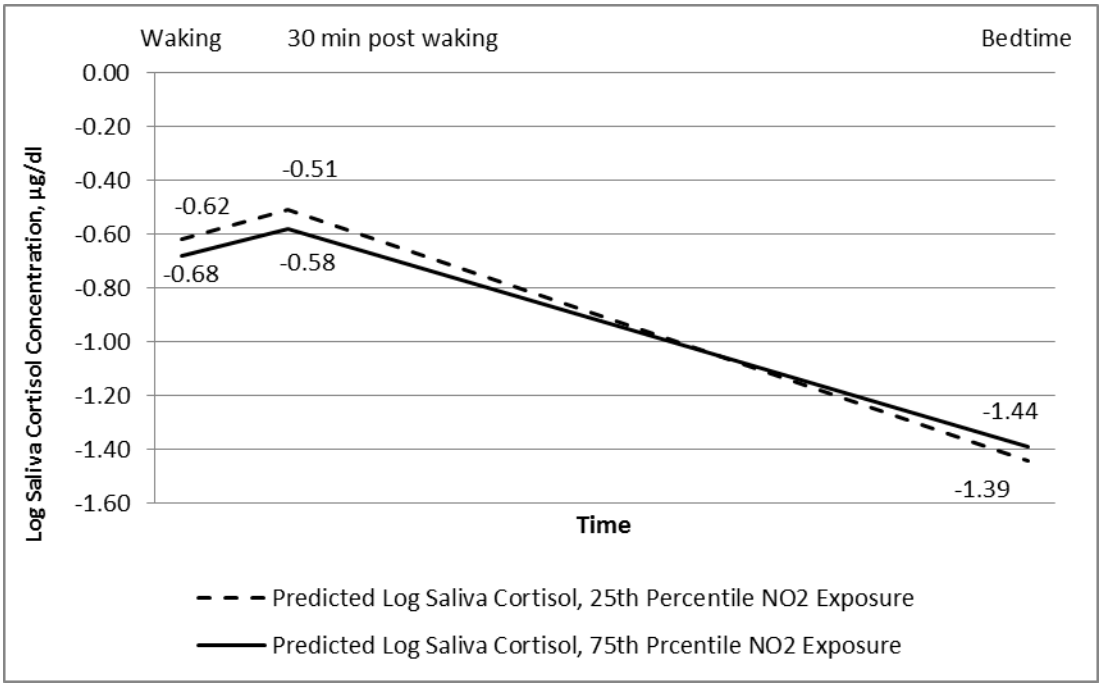
		Estimated Log Salivary Cortisol by Time			Test of Slopes
		Waking	30 Min Post-Waking	Bedtime	Slope (Post-waking Peak to Bedtime)
NO_2	25th percentile	-0.62	-0.51	-1.44	-0.93
	75th percentile	-0.68	-0.58	-1.39	-0.81
	Difference	**0.06**	**0.07**	**-0.05**	**-0.12**

	(95% CI)	**(-0.15, 0.02)**	**(-0.16, 0.02)**	**(-0.05, .0.15)**	**(-0.23, -0.01)**
$PM_{2.5}$	25^{th} percentile	-0.56	-0.46	-1.38	-0.92
	75^{th} percentile	-0.58	-0.47	-1.33	-0.86
	Difference (95% CI)	**-0.01 (-0.06, 0.03)**	**-0.01 (-0.06, 0.04)**	**0.03 (-0.03, 0.09)**	**-0.04 (-0.10, 0.02)**
Ozone	25^{th} percentile	-0.59	-0.48	-1.35	-0.87
	75^{th} percentile	-0.54	-0.45	-1.37	-0.91
	Difference (95% CI)	**0.05 (-0.04, 0.13)**	**0.03 (-0.07, 0.12)**	**-0.02 (-0.13, 0.09)**	**0.05 (-0.09, 0.18)**

Model is adjusted for PM2.5 and ozone exposures, three psychosocial stressors (neighborhood, family, and interpersonal), child's age, height, and weight, family income, race/ethnicity, child's asthma status, cohabitation with cigarette smokers and use of air conditioning in the home.

The diurnal slope of the low exposed (the 25^{th} percentile of estimated NO_2 exposure) was -0.93. In contrast, those with an added IQR of exposure to NO_2 (75^{th} percentile) had a predicted diurnal slope of -0.81, and the difference in slopes, 0.12, was statistically significant at alpha < .05 (95% CI: -0.23, -0.01). The model-based estimation results are presented in Table 2.2 and plotted in Figure 2.3. Table 2.2 also displays the model-based estimation results for an IQR difference of both past year $PM_{2.5}$ and ozone exposure on cortisol diurnal slope. The predicted difference in diurnal slope for those exposed to the 75^{th} vs 25^{th} percentile of $PM_{2.5}$ was -0.04 (95% CI: -0.10, 0.02) and for those exposed to the 75^{th} vs 25^{th} percentile of ozone was 0.05 (95% CI: -0.09, 0.18). Decreased waking cortisol was associated with an added IQR of ozone exposure (0.05, 95% CI: -0.04, 0.13).

Figure 2.3 Model-based predictions of log saliva cortisol by NO2 exposure in adolescents. Those exposed at the 75th percentile have a significant reduction in their diurnal slope, relative to those exposed at the 25th percentile.



In an unadjusted model, the crude association of a flattened diurnal slope was also significant (95% CI: -0.20, -0.03) with a difference in slopes of -0.11. The change in estimate was approximately 4%, suggesting that controlling for the covariates strengthened the associations. In a sensitivity analysis, when stratifying the analysis by gender, we found that males had a larger difference in slopes compared to females (-0.21, 95% CI: -0.46, 0.03). Further, we examined different time-weighted exposure estimates for NO_2 exposure and found that the difference in average one-year NO_2 exposures time-weighted for school attendance (used in this analysis) was 2% larger than and home-only estimates.

In secondary analyses, we included interaction terms between NO_2 exposure and the three types of psychosocial stressors to identify potential synergistic associations. However, for

family, neighborhood, and personal stressors, no statistically significant interaction was detected ($p = 0.50$, 0.31, and 0.41, respectively). We also evaluated the estimated effect of past year NO_2 exposure on diurnal cortisol slope among all participants less than 12 years of age with valid cortisol samples. However, for these children, we were not able to control for psychosocial stressors (family stress and stressful events) available for older participants and only included measures of neighborhood cohesion reported by an adult in the home. Model-based predictions indicated that there was no statistically significant difference in younger children modeled as exposed to the 75th percentile of NO_2 relative to those exposed at the 25th percentile (-0.02, 95% CI: -0.16, 0.11; data not shown).

2.5 Discussion

We found that past year NO_2 exposures as indicators of traffic-related air pollution, derived from a spatially well-defined LUR model, were associated with blunted diurnal slopes of salivary cortisol in adolescents living in Los Angeles. Using LAFANS interview data for subjects with three saliva collections over one day and annual average traffic-related air pollution at home and school, we for the first time report associations in adolescent humans that suggest a blunted cortisol response with exposure to traffic-related air pollution.

Previously, animal models consistently suggested that long-term exposure to inhaled air pollution can lead to chronic activation and dysregulation of the HPA axis leading to glucocorticoid resistance.[93] Inhaled particulate matter increases corticosterone levels in adult rats relative to controls,[92] while repeated ozone exposure not only increased corticosterone levels but induced antisocial behavior.[98] Nitric oxide (NO) and NO_2, are markers of the mixture of pollutants from automobile traffic exhaust.[122] These component gases have been associated with

changes in cortisol. In sheep, exogenous NO exposure was associated with the inhibition of cortisol production.[123] In a series of animal studies of dogs, guinea pigs, rats, mice, and rabbits, NO_2 exposure strained the pituitary and adrenal glands, which diminished cortisol availability.[124] Our results of flatter diurnal slopes associated with higher NO_2 exposures add to the existing literature[125,126] by suggesting that ambient traffic-related air pollution may have the potential to disrupt components of the endocrine system in human adolescents. If replicated, these findings may be especially relevant for younger populations as they might be more heavily exposed to air pollution while spending time outdoors due to their higher breathing rates and outdoor physical activities.[127] However, we did not find a flattened diurnal slope with either $PM_{2.5}$ or ozone exposures. While the $PM_{2.5}$ association was in the same direction as NO_2, it was of smaller magnitude and did not reach statistical significance, despite the aforementioned previous evidence for its role in cortisol response modulation. One possible explanation for our null result might be that our exposure estimates for NO_2 are much better indicators of localized exposure to the mixture of traffic-related air pollutants than the kriged $PM_{2.5}$ surface generated from government monitors. This might point to the greater relative importance of traffic-related air pollutants on the cortisol response compared with other sources in Los Angeles. Ozone is generally negatively associated with modeled NO_2 and traffic in the LAFANS neighborhoods.

Acute stress and acute exposure to air pollution have been shown to activate the HPA axis and stimulate the release of cortisol.[128,129] However, chronic exposure to stress and overactivation of the HPA axis results in diminished cortisol responses over time, a status known as hypocortisolism.[130,131] Chronic HPA axis activation in humans can result in long-term blunting of cortisol profiles where the morning peak values are lower and nighttime values are higher than normal.[132] A similarly flattened diurnal slope was observed in our participants

exposed to increased concentrations of NO_2 while controlling for multiple types of psychosocial stressors.

Associations between cortisol profiles and NO_2 exposure were somewhat stronger in males. This may be a chance finding or could be attributed to higher exposure to air pollution in male adolescents who may spend more time outside exercising. In LAFANS, boys reported playing sports as a social activity 35% more frequently than girls ($p = 0.001$). Boys also reported engaging in vigorous exercise 21% more frequently than girls. However, our LUR model-based NO_2 exposures for boys were only slightly (0.17 ppb) higher than for girls, but their higher physical activity rates might have resulted in the inhalation of more air pollutants.

We restricted our analysis to adolescents ages 12 through 17. Because psychosocial stress is a known activator of the HPA axis[105–107] and is associated with socioeconomic factors that are linked to air pollution exposure,[133] adequate confounder control for stress was necessary. For children between the ages of 3 and 11, LAFANS collected limited information on psychosocial stressors even though salivary cortisol was sampled in the same manner as for the adolescents. The results of a diminished association between NO_2 and diurnal cortisol slopes in these younger children may suggest the influence of uncontrolled confounding due to unmeasured psychosocial stress. Alternatively, there is evidence that infants and younger children are less responsive to external stimuli; a neuroprotective response that fades with increasing age.[134] It is also possible that the association between NO_2 exposure and cortisol diurnal slope in younger children was masked by the age-specific and rapid development of their neuroendocrine system. Similarly, we did not find a statistical interaction between NO_2 exposure and psychosocial stress on cortisol diurnal slope even though previous research reported this for adolescents.[135] Our analysis may have been underpowered to detect this association.

In a sensitivity analysis, evaluating different time-weighted exposure estimates for NO_2 exposure, we found that the difference in average one-year NO_2 exposures time-weighted for school attendance (used in this analysis) and home-only estimates was minimal. Using home-only estimates of NO_2, the change in cortisol slope coefficient in the adjusted model was only 2% smaller, indicating that home-only and school-weighted estimates of NO_2 exposure were very similar and that the time-weighted exposure estimate was sufficiently robust.

Our findings are noteworthy since they point towards a mechanism in which air pollution may affect respiratory function and asthma in adolescents; i.e. the blunting of the cortisol response due to chronic exposure to traffic-related air pollution. In terms of childhood asthma, some explanations have been that asthma is exacerbated by air pollutants as a result of damage to the epithelial tissue in the respiratory system.[136] Specifically, NO_2 has been implicated as leading to oxidative stress and the infiltration of inflammatory cells into the lungs[76] and asthma exacerbation.[117,137] In contrast to physical damage, if NO_2 has the ability to modulate the cortisol response, this offers an alternative mechanism through which air pollution may cause respiratory disease and exacerbate asthma. Such a pathway has been suggested in previous work among asthmatic children, which found that a blunted cortisol response was consistently associated allergic asthma,[138] which may be congruous with the theory that excess, chronic cortisol exposure leads to an impaired anti-inflammatory role of cortisol. Thus, we speculate that air pollution effects on inflammatory and respiratory diseases like asthma could be mediated by chronic adaptation of the endocrine system to such an exposure.

Our study has several strengths, including that the estimated NO_2 exposure was modeled for the year prior to collecting interview and saliva cortisol data, establishing a measure of chronic exposure prior to testing salivary cortisol. Further, the LAFANS study covered a range

of interview topics with information on several psychosocial stressor domains. Our analysis benefited from having a robust set of psychosocial covariates to assess adolescent's experiences in and outside their homes. Another strength is that the LAFANS cohort sampling scheme overrepresented poorer families. Lower socioeconomic status is associated with increased traffic-related air pollution exposures in the home in Los Angeles[115] and other North American Cities[133], thus we were able to examine associations across a wide range of NO_2 exposures.

A limitation of our study is that the three cortisol samples were taken only on one study day. To reduce the within-subject variation of saliva cortisol levels across different days, samples should be collected on multiple days with a greater number of samples taken on each day. Studies indicated that four to six saliva collections over two to three study days are needed to minimize within-subject variance,[8] though these suggestions came from studies focused on older populations.[139] In the LAFANS study, parents of participants were trained by interviewers and were provided with timers to ensure saliva collection happened at specific times. Lacking multi-day cortisol or more comprehensive daily data resulted in the analysis strategy we used; i.e. using nominal time points (waking and bedtime) instead of clock time (i.e. 8:00 am or 10:15 pm). Since we only had access to one day of cortisol data, we had to assume that the collection day represented a typical circadian cycle for the participant and that associated flattened diurnal slopes reflected long-term dysregulation instead of acute modification. Cortisol was the only relevant endocrine biomarker collected for this analysis. Future studies on this topic would benefit greatly from additional biomarker sampling of the HPA axis, like corticotropin-releasing hormone or adrenocorticotropic hormone, to make broader conclusions about the role of chronic air pollution exposure on neuroendocrine functioning. Further, other non-traffic-related sources of NO_2 are not accounted for in our LUR exposure model. But, due to the great relative

importance of traffic-related air pollution on human health in Los Angeles relative to other cities,[140] this likely played only a minor role. Lastly, psychosocial stressor information was collected at the same time as saliva cortisol samples, thus we have to assume that the stress measures reflect past and chronic stressors.

2.6 Conclusion

A blunted cortisol response is associated with a wide variety of serious short- and long-term adverse health outcomes. While psychosocial stress has previously been linked to changes in normal cortisol patterns, recent work in animals suggested that air pollution exposure has similar effects. Our findings corroborate these conclusions, suggesting that chronic exposure to ambient NO_2 may flatten the diurnal salivary cortisol slopes in adolescents. This points towards an important mechanism through which traffic-related air pollution may impact human health and it warrants future studies of the influence of traffic pollutants on the neuroendocrine system.

Chapter 3 – Preterm Birth among Infants Exposed to In Utero Ultrafine Particles from Aircraft Emissions

3.1 Abstract

Background

Ambient air pollution is a known risk factor for adverse birth outcomes, but the role of ultrafine particles (UFPs) is not well understood. UFP emissions from aircraft are spread across large residential areas downwind of airports, possibly causing a considerable reproductive health burden. This analysis evaluates whether UFPs from jet aircraft emissions increase rates of preterm birth (PTB) among pregnant mothers living downwind of Los Angeles International Airport (LAX).

Methods

This population-based study uses birth records, provided by the California Department of Public Health, to ascertain birth outcomes and a novel, validated geospatial UFP dispersion model to estimate in utero exposure profiles. All mothers who gave birth from 2008-2016 while living within 15 km of LAX were included in this analysis (N = 174,186).

Results

There was a significant association between in utero exposure to aircraft-related UFP and PTB. The odds ratio for PTB in the fourth quartile of in utero UFP exposure compared to the first was 14% (95% CI 1.08 – 1.20), when controlling for maternal demographic characteristics, as well as exposure to nitrogen dioxide and airport-related noise.

Conclusion

This study reveals an association between in utero exposure aircraft-associated UFPs in pregnant women and PTB. Our results suggest that emissions from aircraft play an independent etiologic role in producing PTBs, possibly due to their ability to translocate to numerous organs and carry known toxicants. These findings are of public health concern as UFP exposures downwind of airfields are common and may affect large, densely populated residential areas.

3.2 Introduction

Approximately 1 in 10 babies in the US are born preterm[141], increasing the infant's risk for developing complications such as respiratory problems, infections, developmental delays, and vision or hearing impairments.[142] Prematurity is also the leading cause of neonatal mortality[143] and generates an annual economic burden in the US of ~$26 billion.[39]

Exposure to ambient air pollution during pregnancy has previously been identified as a risk factor for adverse birth outcomes (ABOs), including preterm birth (PTB).[25,144–151] The effect of transportation-related combustion sources of ambient air pollution on birth outcomes have been extensively studied, but not for aircraft emissions. During landing, takeoff, and taxiing, aircraft generate pollutant plumes that are blown downwind of airports, potentially adversely affecting the health of residents. The pollutants include particulate matter (PM) – especially ultrafine particles (UFPs) from jet engines – volatile organic compounds (VOCs), oxides of sulfur (SO_x), and nitrogen (NO_x).[152–155] PM has traditionally been measured and regulated in terms of mass concentration of particles with aerodynamic diameter less than 10 μm (PM_{10}) or less than 2.5 μm ($PM_{2.5}$). Ultrafine or nanoparticles, which are less than 0.1 μm in diameter, are not routinely monitored or regulated. They account for little mass but make up the majority of

particles in terms of number and surface area.[156] UFPs may have more impact on reproductive health than particulates with larger aerodynamic diameters, such as $PM_{2.5}$[157–159] and PM_{10}[25,151], due to their greater mobility within the body and greater surface area.

Recent studies report adverse air quality impacts from landing jets over large areas downwind of major airports.[160–166] For example, jets approaching LAX Airport in Los Angeles (LA), California produce ground-level UFP concentrations more than twice the nearby ambient levels at distances up to 16 km away from the airport.[161] Here, we evaluated whether UFPs from jet aircraft emissions increase rates of PTB near LAX based on an AERMOD dispersion model for UFPs we built and validated with spatially extensive ground-level measurements.

3.3 Materials and Methods

3.3.1 Sample population and health outcome

We identified all mothers who gave birth from 2008 through 2016 while living within 15 km of LAX using birth certificates obtained from the California Department of Public Health (CDPH). Our health outcome, PTB, was defined as a live birth occurring before 37 gestational weeks (yes/no). We excluded birth records with implausible gestational ages (< 20 or > 50 weeks, n = 686), implausible birth weights (< 500 or > 5,000 g, n = 1,181), non-singleton pregnancies (n = 6,407), or incomplete data (n = 14,236) leaving 174,186 births. This study was approved by the University of California Los Angeles Institutional Review Board and the California Health and Human Services Agency's Committee for the Protection of Human Subjects.

3.3.2 Exposure assessment – Ultrafine Particles

We utilized an AERMOD meteorological dispersion model to predict downwind UFP number concentrations from LAX flight activity. The model used several line sources oriented at 3% slope to simulate the aircraft descent path in addition to a ground-level area source at the airport, similar to the traditional Federal Aviation Administration (FAA) version of AERMOD. However, unlike the FAA model, our model adjusted the line source geometry slightly downward to represent the effect of plume entrainment and downward motion of interacting wingtip vortices produced by aircraft during descent.[167]

The modeled concentrations were validated using UFP measurements taken by a mobile instrumented platform using real-time condensation nucleus counters over seven non-consecutive days spanning two seasons.[161] Measurements were taken along six transects downwind of LAX nearly perpendicular to the prevailing wind. Figure 3.1 displays the typical daytime pattern of measured UFP concentrations.[161] Background UFP concentrations were determined by taking the 5^{th} percentile concentration north and south of the transect impact zones and subtracted to eliminate the contribution of roadway vehicles.[161] AERMOD predictions and the background-subtracted, measured UFP concentrations showed a coefficient of determination of 0.54 assuming a zero intercept.

Figure 3.1. Measured UFP concentrations downwind of LAX on December 3, 2013, with the area above 65 dB average noise in gray.[23]

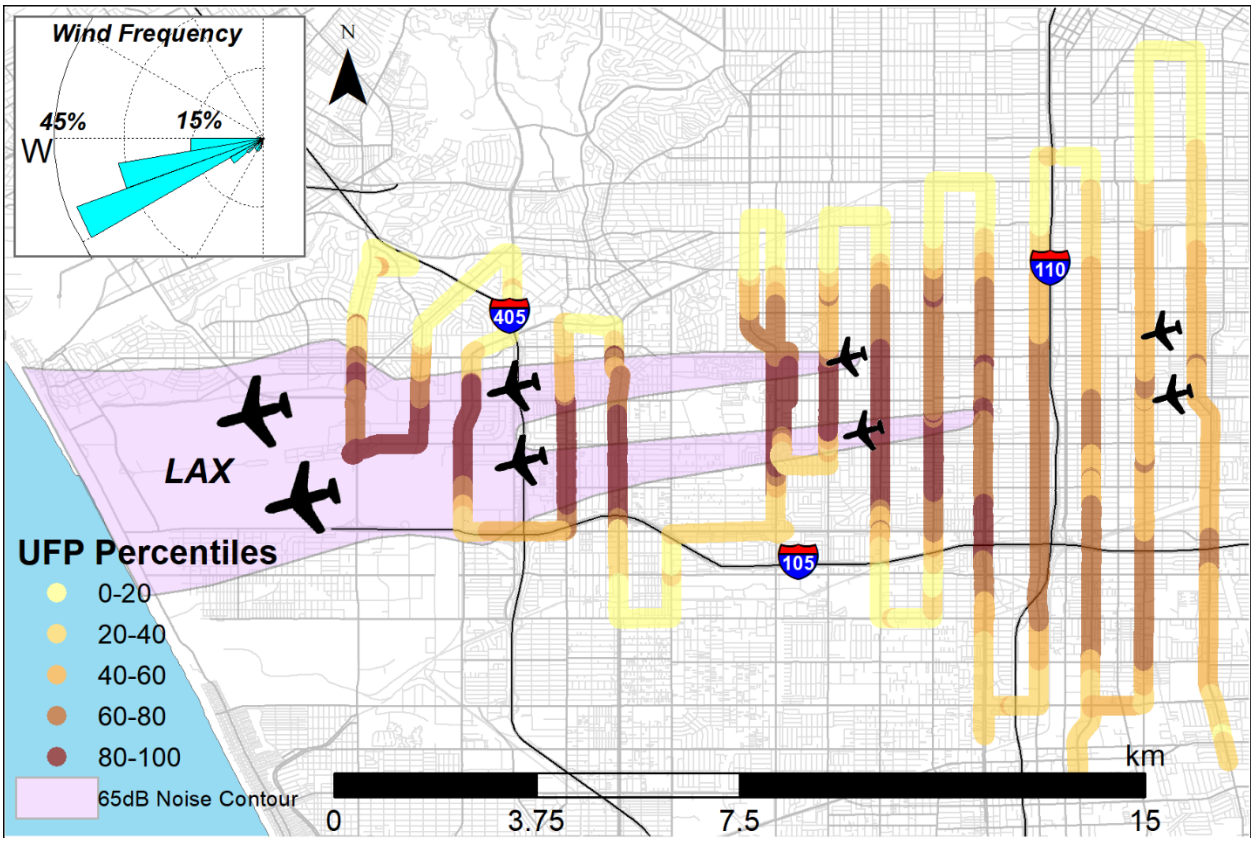
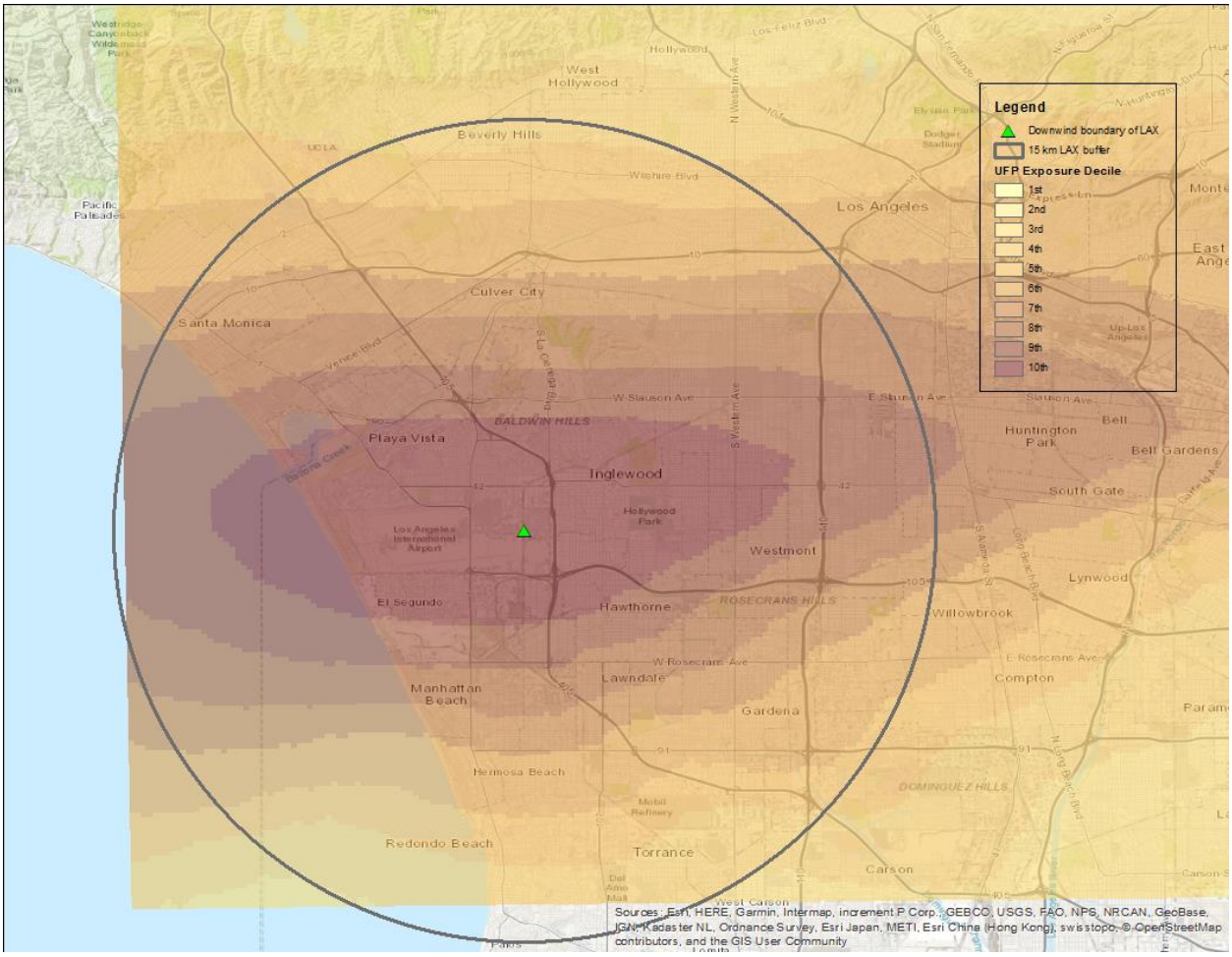


Figure 3.2 displays the results of the long-term average AERMOD UFP concentration predictions and the 15 km population buffer centered at the downwind boundary of LAX. A constant average UFP emission rate across jets was assumed while taking into account the average diurnal variability and annual variation in flight activity.

Figure 3.2 Estimated UFP exposure deciles from AERMOD results



Using this UFP dispersion model, we geocoded average UFP exposures per trimester and per pregnancy period using the maternal home address reported on the birth certificate. For sensitivity tests, we also evaluated non-circular, ellipsoid exposure buffers with semi-minor axes of 10, 12 and 14 km and semi-major axes of 22.5, 18.8, and 16.1 km, respectively, in order to preserve the original exposure buffer area of ~707 km^2. These ellipses were aligned with the prevailing daytime wind direction of 263 degrees, the angle of the runways.

3.3.3 Covariates

We controlled for NO_2 concentrations as a ground-level vehicle traffic surrogate for combustion emissions similar to previous studies[111,112]. Briefly, with a Land Use Regression (LUR) model we estimated annual NO_2 exposures for LA County using data collected over two weeks from 201 passive air samplers (part number PS-100, Ogawa & Company USA). Final predicted concentration surfaces explained 85% in the variation of measured NO_2 concentrations.

The analysis also included the known PTB risk factors[14,168–171] listed in the birth certificates including parental age; mother's race/ethnicity (Hispanic (any race), non-Hispanic black, non-Hispanic White, non-Hispanic White, and non-Hispanic Asian and non-Hispanic Other (including Native American and Hawaiian/Pacific Islander); maternal educational attainment; maternal nativity (US- or foreign-born); and maternal smoking (yes/no by trimester).

Noise monitors within the communities surrounding the airport routinely record noise from overhead flights and generate publicly reported community noise equivalent levels (CNELs). The areas above an annual average of 65 dB, the acceptable CNEL limit for individuals living near an airport according to the California Department of Transportation,[172] are shown in Figure 3.3. We included CNEL values at each mother's residence as a dichotomous variable, either above or below 65 dB.

To further control for confounding by neighborhood socioeconomic status (SES), we also adjusted for a composite score of SES based on seven indicator variables.[173] Mothers were assigned a quartile SES index (5 = high, 1 = low) based on their census tract's median household income, median rent, median house value, percent living 200% below poverty level, percent of blue-collar workers, percent unemployed, and education index.

3.3.4 Statistical Analysis

We assessed the association between quartiles of residential location-specific aircraft UFP concentrations during pregnancy and PTB using logistic regression (SAS 9.3, SAS Institute, Cary, NC). In covariate-adjusted models, we estimated the odds ratio for PTB in each quartile of UFP exposure relative to the lowest quartile. To evaluate the role of maternal nativity and race/ethnicity we conducted stratified analyses.

3.4 Results

Demographic factors by PTB status for the infants born within a 15 km radius of LAX between 2008 and 2016 are shown in Table 3.1. Most mothers were Hispanic with a high school degree or less. Mean age at delivery was 29 years. PTB occurred in 8.7% of all births and was more common in Black and Hispanic mothers, mothers with less education, and in male births.

Table 3.1 Maternal and Infant Demographics by Gestational Age

Total N = 174,186	< 37 weeks (n = 15,134)	≥ 37 weeks (n = 159,052)
Gestational Age, mean weeks (sd)	34.5 (2.8)	39.7 (1.4)
Birth Weight, mean grams (sd)	2598 (752)	3348 (444)
Parity, mean children (sd)	2.3 (2.3)	2.1 (2.4)
Quintile of SES Index, mean (sd)	1.9 (1.3)	2.2 (1.4)
Infant Sex, percent male	54.7%	45.3%
Maternal Age		
<20	8.7%	7.3%
20-24	19.7%	19.3%
25-29	22.7%	23.1%
30-34	24.5%	27.3%
35+	24.4%	22.0%
Maternal Race		
White	12.2%	18.7%
Black	20.0%	14.1%
Hispanic	59.5%	56.3%
Asian	6.1%	8.6%
Others	2.3%	2.2%
Maternal Education		
High School Graduate or Less	58.9%	51.3%
Some College to Bachelor's Degree	32.6%	36.4%
More than a Bachelor's Degree	8.6%	12.3%
Maternal Nativity		
US-Born	71.4%	70.0%
Foreign-Born	28.6%	30.2%
High Noise at Residence, > 65 dB CNEL	5.2%	4.2%
Cigarette Smoking, ever during pregnancy	1.0%	0.6%

In an unadjusted model, the highest quartile of pregnancy average UFP exposure was associated with a 43% increase in odds of giving birth to a preterm baby compared with the lowest quartile in logistic regression models. Controlling for demographic factors as well as traffic pollution and noise, the odds ratio for PTB in the upper quartile of UFP exposure was 14% (95% CI 1.08 – 1.20) (Table 3.2), with the odds increasing in each exposure quartile (P trend < .001). When we stratified by maternal race/ethnicity and nativity, we found the strongest

associations among foreign-born women, particularly among Asian and Hispanic women (Table 3.4). Exposure to the highest quartile of traffic-related NO_2 relative to the lowest was associated with a 15% increased odds of PTB (95% OR: 1.09 – 1.22). Additionally, exposure to > 65 dB CNEL was associated with an odds ratio of 1.10 (95% CI 1.01 – 1.19). Maternal exposure to high noise, traffic-related NO_2, and UFPs were only very weakly correlated (Table 3.3). When UFP is removed from the model (data not shown), the odds ratio for the association between noise and PTB increased slightly to 1.16 (95% CI 1.08 – 1.26).

Table 3.2 Logistic Regression Modeling Results estimating the association between UFP exposure on the odds of PTB

Variable	Adjusted Model[1] (95% CI)	Adjusted Model[2] (95% CI)	Adjusted Model[3] (95% CI)
UFP			
Quartile 1	Ref.	Ref.	Ref
Quartile 2	1.01 (0.96 – 1.07)	1.03 (0.98 – 1.08)	1.03 (0.98 – 1.08)
Quartile 3	1.05 (1.00 – 1.10)	1.08 (1.02 – 1.13)	1.08 (1.02 – 1.13)
Quartile 4[4]	1.11 (1.05 – 1.16)	1.16 (1.10 – 1.22)	1.14 (1.08 – 1.20)
Maternal Age			
<20	1.12 (1.04 – 1.20)	1.11 (1.04 – 1.19)	1.11 (1.04 – 1.19)
20-24	0.99 (0.94 – 1.04)	0.99 (0.94 – 1.04)	0.99 (0.94 – 1.04)
25-29	Ref.	Ref.	Ref.
30-34	1.10 (1.04 – 1.15)	1.10 (1.05 – 1.15)	1.10 (1.05 – 1.15)
35+	1.42 (1.35 – 1.49)	1.42 (1.35 – 1.50)	1.42 (1.35 – 1.50)
Maternal Educational Attainment[5]	0.93 (0.92 – 0.95)	0.94 (0.92 – 0.95)	0.94 (0.92 – 0.95)
Quintile of SES Index	0.95 (0.93 – 0.97)	0.96 (0.94 – 0.98)	0.96 (0.94 – 0.98)
Maternal Race			
White	Ref.	Ref.	Ref.
Black	1.78 (1.65 – 1.92)	1.80 (1.67 – 1.93)	1.80 (1.67 – 1.93)
Hispanic	1.23 (1.14 – 1.32)	1.23 (1.14 – 1.32)	1.23 (1.14 – 1.32)
Asian	1.06 (0.98 – 1.15)	1.05 (0.97 – 1.14)	1.05 (0.97 – 1.14)
Other	1.43 (1.27 – 1.62)	1.43 (1.27 – 1.62)	1.43 (1.27 – 1.62)
Ever smoked cigarettes during pregnancy	1.62 (1.37 – 1.93)	1.62 (1.36 – 1.92)	1.62 (1.36 – 1.92)
NO_2			
Quartile 1	-	Ref.	Ref.
Quartile 2	-	1.10 (1.05 – 1.15)	1.10 (1.05 – 1.16)
Quartile 3	-	1.10 (1.05 – 1.16)	1.11 (1.05 – 1.15)
Quartile 4	-	1.15 (1.09 – 1.21)	1.15 (1.09 – 1.22)
Exposed to > 65 dB CNEL	-	-	1.10 (1.01 – 1.19)

[1] Adjusted for Maternal Age, Maternal Educational Attainment, SES, Maternal Race, and Cigarette Smoking

[2] Adjusted for all variables in Model 1 and NO_2

[3] Adjusted for all variables in Model 2 and noise

[4] The mean particle number concentrations in Quartile 4 is 25,000 particles/cc. This estimate of the long-term average is based on model comparisons with seven sampling days between August 2013 and July 2014 and therefore is only approximate.

[5] Educational attainment was recorded in 9 ordinal categories: No formal education, 8th grade or less, 9th grade through 12th grade with no diploma, High school graduate or GED, Some college credit with no degree, Associates degree, Bachelor's degree, Master's degree, Doctorate or professional degree

In additional sensitivity analyses, we explored exposure to UFP at different times during pregnancy and found that the per trimester effect estimates were nearly identical to those for the entire pregnancy. However, the UFP averages for the trimesters and pregnancy were highly correlated and it was not possible to assess trimester-specific exposures in the same model. We also modified the aspect ratio of the exposure area, generating an ellipsoid buffer, but observed only minor changes in effect estimates (Table 3.5). When stratified by quintile of SES, there was a modest increase in the odds of PTB associated with UFP exposure with decreasing SES, though there was not a strictly linear trend (Table 3.6). Lastly, we estimated the association between UFPs and very PTB (< 32 weeks gestation), and the odds ratio for the highest quartile (1.13) of exposure was very similar to the overall estimate, but the CI was wider (95% CI 0.98 – 1.31).

3.5 Discussion

We found that in utero exposures to jet-specific UFP emissions, derived from a spatially validated AERMOD dispersion model, increased the odds of PTB among mothers living within 15 km of LAX. This is the first study to report such associations for an ABO among residents living within the incoming flight paths of a major airport. Interestingly, the effect estimates for UFPs and PTB were stronger among foreign-born Hispanic and Asian women, possibly because these women are less likely to be employed during pregnancy compared with US-born mothers,[174] thus they spent more time at their residence during pregnancy which may result in greater exposure and/or reduced exposure misclassification and explain the stronger effect sizes we estimated.

We also found associations between PTB and with vehicle traffic-related air pollution using an LUR model as reported previously for earlier birth years,[71] but without the dose-

response seen for LAX UFPs. These results are corroborated by other population-based birth outcome studies.[175] Importantly, our results indicate that concomitant exposure to UFP from aircraft independently elevate the odds of PTB beyond the risk due to traffic-related air pollution and aircraft noise alone. Whether noise was included or excluded from our models, the effect estimate for jet UFP exposure remained the same. While exposure to airport-related noise does appear to be associated with an increased risk for PTB, especially for those living very close to the airport (see Figure 3.3), aircraft-based UFP exposures are a consistent predictor of PTB that impacts the much larger population living downwind of the LAX airfield. In fact, in 2010, over 1.9 million residents lived within the 15 km buffer.[176] Aircraft movements at LAX have been previously estimated to generate an average particle number concentration equivalent to 280-790 km of freeway, which represents emissions equivalent to 19%-53% of the total freeway length in all of LA County.[161]

Importantly, this study isolates airplane-specific UFPs from traffic-related UFPs. A previous study in California implicated vehicle traffic UFPs in PTBs from 2000 to 2008.[177] However, the CALINE4 traffic model used to estimate exposures could not include the contributions of UFPs from air traffic sources. Compared with the sharp UFP gradients resulting from vehicle traffic, UFP emissions from jets, particularly landing planes, show unusually large impact areas with relatively little small-scale spatial variability (e.g., almost no change over 100s of meters).[178] This allows for more accurate exposure estimates compared with ground-source UFP concentrations from roadways, which typically have sharp downwind concentrations gradients[179] Furthermore, due to the consistency of daytime on-shore breeze directions at LAX, the location of elevated UFPs concentrations downwind to the east of LAX is very stable,[161,178]

producing relatively large contrasts in concentrations between residences inside the area of impact compared with those located outside.

Several aspects of UFP may help explain their effect on gestational age at birth. Inhaled UFPs penetrate the lung mucosa and can translocate to other parts of the body as their size facilitates movement across cell barriers, entrance into the bloodstream, and relocation to distal tissues.[59] Additionally, UFPs escape the usual clearance mechanisms by phagocytes, which remove larger particles like PM_{10} and $PM_{2.5}$.[180] Murine cell-based experiments have linked UFP exposures with increased oxidative stress response and inflammation,[181,182] mechanisms that have been implicated in PTB.[74,183] For example, at concentrations occurring in ambient Los Angeles air, one experiment found large increases in measures of oxidative stress such as heme oxygenase expression, intracellular glutathione depletion, and reactive oxygen species generation (via dithiothreitol assay) in exposure to quasi-UFP size fraction (<0.15 μm) compared with fine or coarse PM fractions.[181] In humans, intrauterine inflammation is common in PTB,[184] and PTB is associated with an unusually large presence of pro-inflammatory immune cells and tumor necrosis factor alpha.[185] *In vivo* murine experiments showed that exogenous administration of interleukin (IL)-1 leads to initiation of preterm labor.[186]

Another important physiochemical property of UFPs that may increase their pathogenic potential is their large particle surface area. Dependent on sources, they may carry adsorbed or condensed air toxics such as polycyclic aromatic hydrocarbons (PAHs).[187] In fact, UFPs are responsible for up to 30% of the PAHs deposited in the lung.[188] UFP plumes from aircraft emissions have been directly associated with the presence of elevated levels of PAHs[63] and research in the LA area has found that UFPs contain much higher PAH content than fine (<2.5 μm) and coarse (2.5 – 10 μm) particles.[181] With respect to aircraft-based PAHs, a study of

emissions within the plane loading area of a major airport showed that the particle-bound PAHs were comprised of ~80% high molecular weight compounds with high toxicity.[189] Altogether, there is ample evidence that UFPs, especially those originating from aircraft, carry pathogenic PAHs linked to inflammation[190,191] and PTB.[192]

Another source of aviation-related emissions located in the study area is the Santa Monica Municipal Airport (SMO) (~7.5 km north of LAX) but the private planes using this airfield are smaller, utilizing Avgas, which contains tetraethyl lead.[193] In utero lead exposure is a known cause of ABOs.[194] To account for potential lead exposures in areas near this municipal airport, we excluded births within a 2-5km distance from SMO, but this did not change our effect estimates for UFPs.

Our study has several strengths. The UFP dispersion model allowed us to assess exposure profiles in a large population encompassing tens of thousands of births. Due to the daytime wind directions at LAX being very consistent throughout the entire year, the locations at which UFP exposures occur downwind of LAX are quite stable,[161,178] allowing for accurate exposure estimation at residences across the years. Further, the outcome data were derived from birth records, reported and recorded in a uniform manner in California. UFP exposures have received limited research attention and this project addresses impacts of aircraft movements that could have profound public health impacts given the ever-growing demand for air travel. In the US, there are over 40,000 daily flights[195] servicing nearly 400 primary airports.[196] UFP emissions from these aircraft are spread across large residential areas. Resulting health effects from perinatal exposures may be responsible for large economic and health burdens. Due to the noise from airports, many of the UFP impacted areas are low SES with especially vulnerable populations. Low neighborhood SES was associated with higher levels of aircraft-related UFP

exposures (Table 3.7) and a higher risk of PTB with UFPs in separate analyses for each level of neighborhood SES (Table 3.6). Our results indicate that low SES communities are over-represented in housing stock located directly downwind of this highly trafficked airport. In addition, since lower household income has been shown to be inversely correlated with air conditioner use,[197] the proximity might be magnifying air pollution exposures due to the opening of windows in homes lacking air conditioning which can result in increased indoor UFP concentrations.[198]

This study has some limitations including a semi-ecologic exposure assessment as we are measuring estimated UFP exposures at the home address provided on the birth certificate. We cannot account for time spent at work or elsewhere. Further, we could not account for time spent at different homes during pregnancy. It has been previously estimated that 9%-32% of mothers move during their pregnancy,[199] though mobility is likely nondifferential with respect to case status.[200] This could lead to an underestimation of the association of UFP exposure with PTB. Finally, our assumption of a constant per-aircraft UFP emission rate did not account for possible changes in relative emission factors over the study period. Unfortunately, there is not adequate information to quantify historical trends for jet UFP emission factors.

3.6 Conclusion

An increased odds of PTB was associated with in utero exposure to higher concentrations of aircraft-associated UFPs in women living near LAX. These UFPs are capable of translocation to numerous organs and carry known toxicants like PAHs on their surface. While in utero air pollution exposure from particulate matter – especially from traffic-related combustion sources – are known risk factors for PTB, our results suggest that emissions from aircraft play an independent etiologic role in producing ABOs. These findings are of great public health concern

as UFP exposures downwind of airfields are common and may affect large densely populated residential areas.

3.7 Supplemental Tables & Figures

Table 3.3 Correlation between air pollutants and noise

	UFP	NO_2	Noise
UFP	1.00	-0.22	0.55
NO_2		1.00	-0.13
Noise			1.00

Table 3.4 Adjusted logistic regression results*, stratified by race/ethnicity and maternal Nativity, 4th vs 1st Quartile

Race/Ethnicity	Maternal Nativity	Total N	4^{th} Quartile n	OR (95% CI)
White	Foreign-born	5,881	498	1.36 (0.90 – 2.03)
	US-born	25,710	3,777	0.90 (0.75 – 1.08)
Black	Foreign-born	1,873	594	0.90 (0.53 – 1.54)
	US-born	23,641	9,062	1.20 (1.02 – 1.40)
Hispanic	Foreign-born	36,548	10,236	1.21 (1.07 – 1.36)
	US-born	62,041	17,118	1.12 (1.02 – 1.23)
Asian	Foreign-born	7,416	952	1.61 (1.18 – 2.19)
	US-born	7,170	911	1.09 (0.79 – 1.49)
Other	Foreign-born	579	170	1.07 (0.39 – 2.94)
	US-born	3,327	885	0.53 (0.42 – 0.94)

* Adjusted for NO2, Maternal Age, Maternal Educational Attainment, SES Index, Maternal Race, Noise and Cigarette Smoking.

Table 3.5 Adjusted logistic regression results* with modified elliptical exposure buffers, quartiles of UFP exposure

Semi-Major Axis, km	Semi-Minor Axis, km	4th vs 1st Quartile (95% CI)	3rd vs 1st Quartile (95% CI)	2nd vs 1st Quartile (95% CI)
14	16.1	1.14 (1.08 - 1.21)	1.08 (1.03 - 1.14)	1.04 (0.98 - 1.09)
12	18.8	1.12 (1.06 - 1.18)	1.07 (1.02 - 1.13)	1.02 (0.97 - 1.08)
10	22.5	1.11 (1.05 - 1.17)	1.07 (1.02 - 1.13)	1.03 (0.98 - 1.08)

* Adjusted for NO2, Maternal Age, Maternal Educational Attainment, SES Index, Maternal Race, Noise and Cigarette Smoking.

Table 3.6 Adjusted logistic regression results* stratified by quintile of SES Index, quartiles of UFP exposure

		4th vs 1st Quartile (95% CI)	3rd vs 1st Quartile (95% CI)	2nd vs 1st Quartile (95% CI)
Quintile of SES	5 (High)	0.92 (0.74 - 1.14)	0.95 (0.79 – 1.15)	0.75 (0.59 – 0.94)
	4	1.03 (0.86 - 1.23)	1.07 (0.90 – 1.26)	0.96 (0.85 – 1.09)
	3	1.22 (1.00 - 1.49)	1.20 (0.99 – 1.47)	1.03 (0.87 – 1.22)
	2	1.02 (0.89 - 1.17)	0.99 (0.86 – 1.14)	1.00 (0.87 – 1.15)
	1 (Low)	1.26 (1.16 - 1.36)	1.16 (1.08 – 1.24)	1.13 (1.05 – 1.21)

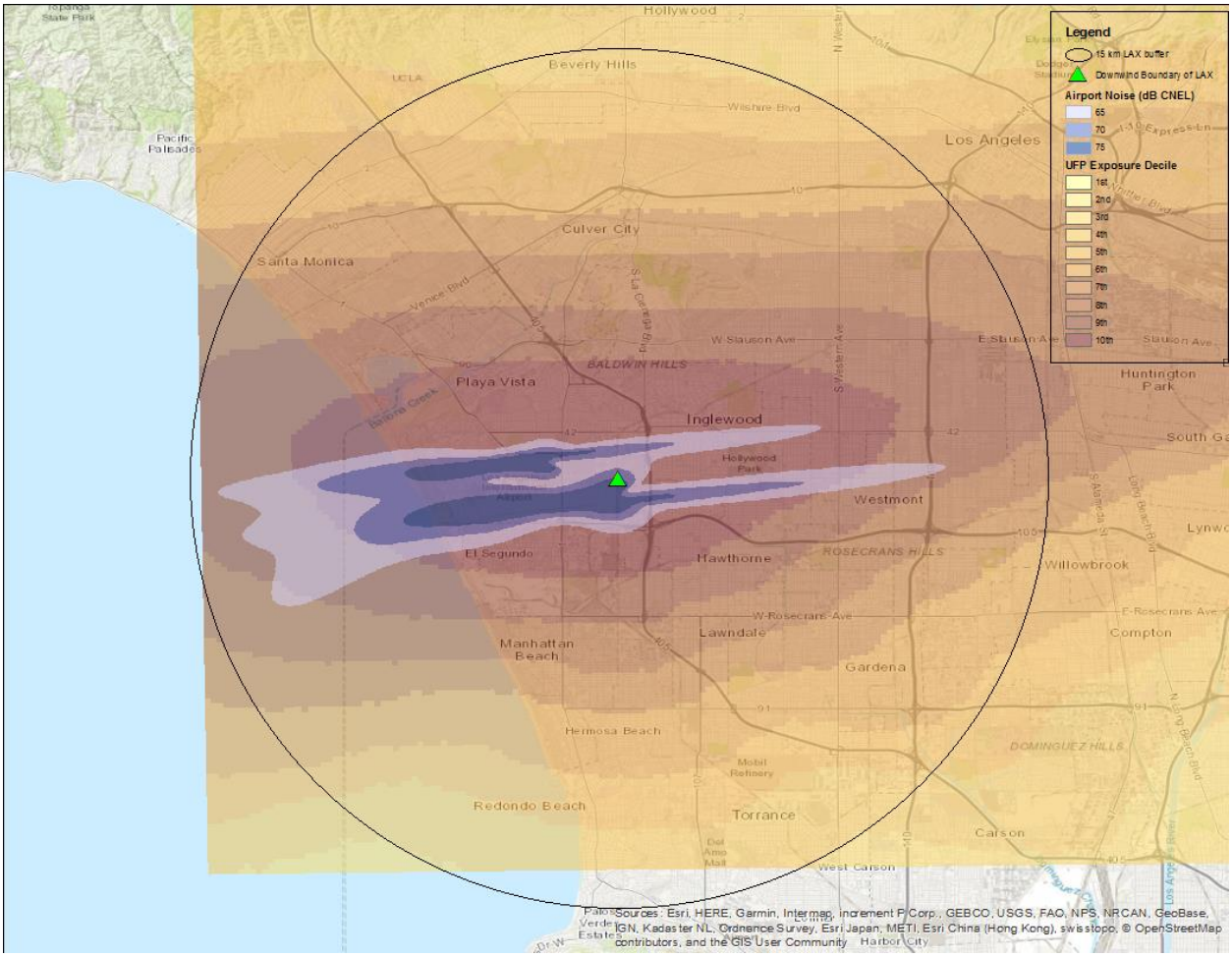
* Adjusted for NO2, Maternal Age, Maternal Educational Attainment, SES, Maternal Race, Noise and Cigarette Smoking.

Table 3.7 Percent of mothers in quartiles of UFP exposure stratified by quintile of SES index*

		Quintile of SES Index					
		1st (Low)	2nd	3rd	4th	5th (High)	Total
Quartile of UFP exposure	1st	36%	11%	8%	21%	23%	100%
	2nd	51%	13%	12%	19%	4%	100%
	3rd	66%	13%	7%	8%	6%	100%
	4th	57%	20%	10%	8%	5%	100%

* Pearson Correlation coefficient: -.27, p<.0001

Figure 3.3 UFP exposures and airport noise exposures



Chapter 4 – Pregnancy-induced hypertensive disorders partially mediate the relationship between aircraft-related in utero ultrafine particle exposures and preterm birth

4.1 Abstract

Background

In utero exposure to ambient air pollution is a known risk factor for preterm birth (PTB), but the mechanisms underlying this relationship are not well understood. Recent research has shown that exposure to ultrafine particles (UFP) is associated with increased risk for both PTB and hypertensive disorders, while some have posited that the underlying biological mechanism

between UFPs and PTB may involve pregnancy-induced hypertension (PIH). Here we examine this mechanism using mediation analyses.

Methods

Using birth registry data, all births among women living within 15 km of Los Angeles International Airport (LAX) who were born between January 1st, 2008 and December 31st, 2016 were included in this analysis (N = 173,414). Exposure to aircraft-related UFPs were estimated using an AERMOD dispersion model and relevant covariate and outcome data were listed on the birth record. We used a weighted marginal structural models approach to estimate the total, direct, and indirect effects of UFP on PTB through the proposed mediator, PIH.

Results

The tenth decile of UFP exposure versus the first was associated with a 15% greater natural direct effect (95% CI 1.12 – 1.18), a 2% greater natural indirect effect (95% CI 1.00 – 1.05), and a 17% total effect (95% CI 1.07 – 1.27). In this top decile, 12.8% of the total effect was mediated through the natural indirect effect. There was a 1.38-times greater odds (1.12 – 1.68) of iatrogenic PTB versus spontaneous term birth comparing the tenth decile of UFP exposure to the first, while this association was 12.2% mediated through PIH.

Conclusion

We have identified PIH as a potential mediator of the relationship between in utero aircraft-related UFP exposures and PTB. Thus, exposure to ambient particulate matter air pollution may lead to the initiation of hypertensive disorders and subsequent increased risk for adverse birth outcomes.

4.2 Introduction

In utero exposure to ambient air pollution is a known risk factor for preterm birth (PTB), but the mechanisms underlying this relationship are not well understood. Recent research has shown that exposure to ultrafine particles (UFP) is associated with increased risk for both PTB[177,201] and hypertensive disorders.[202–204] Additionally, pregnancy-induced hypertensive disorders (PIH) are known risk factors for PTB.[205–207] Understanding whether PIH has a potential mediating role in the UFP-PTB relationship may indicate a mechanism underpinning this association.

PIH includes both gestational hypertension and preeclampsia, which occur in approximately 6-10% of pregnancies.[208] Gestational hypertension is defined by incident hypertension (systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) >90 mmHg) that develops during pregnancy, after 20 weeks of gestation. Preeclampsia is defined as gestational hypertension with proteinuria (>300 mg of protein in 24 h).[209] PIH is a leading cause of morbidity and mortality for the mother and infant; approximately 15% of PTB cases[210] and approximately 15% of maternal deaths in developed countries are directly attributable to preeclampsia and eclampsia.[211] Risk of adverse outcomes increases among women with severe subtypes of preeclampsia, i.e. more extreme elevations of blood pressure and/or proteinuria with the presence of symptoms like headache, vomiting, or visual disturbances.[210] Among severe preeclampsia cases, there is added risk of serious maternal morbidities, like stroke,[212] and adverse birth outcomes, like PTB.[206]

Increased risk of both PIH and PTB have been associated with in utero exposure to ambient air pollution. In particular, UFP exposures are related to increased risk of hypertension,[205–207] while plumes of aircraft-related UFP emissions have also been found to

increase risk of PTB.[201] More specifically, ambient air pollution has been suggested as an etiologic factor in the development of both gestational hypertension and preeclampsia,[71,158,213,214] and for PTB.[25,26] Researchers have previously posited that the underlying biological mechanism may involve PIH[71] and here we are proposing to examine this mechanism using mediation analyses. Specifically, we will use marginal structural models to examine whether and to what extent the relationship between in utero exposure to aircraft-related UFPs and PTB is mediated by PIH. We use a novel, validated AERMOD dispersion model to estimate UFP exposures and comprehensive birth records compiled by the California Department of Public Health to ascertain health outcomes.

4.3 Methods

4.3.1 Sample

All births among women living within 15 km of Los Angeles International Airport (LAX) who were born between January 1st, 2008 and December 31st, 2016 were included in this analysis. Subjects were identified from birth certificates provided by the California Department of Public Health. Women were excluded if they had a diagnosis of chronic hypertension (n = 1,022). Records of non-singleton births (n = 6,364), implausible gestational age (< 20 weeks or > 50 weeks, n = 684), or implausible birth weight (< 500 g or > 5,000 g, n = 1181) were excluded, leaving 173,414 records for analyses. This study was approved by the University of California Los Angeles Institutional Review Board and the California Health and Human Services Agency's Committee for the Protection of Human Subjects.

4.3.2 Pregnancy outcomes and complications

PTB status was defined dichotomously as a live birth less than 37 weeks gestation recorded on the birth certificate. Pregnancy complications and the presence of chronic hypertension were recorded in the Medical Data Supplemental Worksheet VS 10A. The presence of PIH includes both incident gestational hypertension and preeclampsia and was also coded dichotomously. Information on labor was recorded on the birth record, including whether the labor was induced or spontaneous and whether the baby was delivered via cesarean section or vaginally.

4.3.3 Exposure assessment

To estimate in utero exposure profiles, we utilized a modified AERMOD UFP dispersion model, which has been described previously.[201] Briefly, this meteorological dispersion model predicts downwind UFP number concentrations due to flight activity at LAX. The dispersion model also incorporates the effects aircraft descent into the airfield and the downwash imparted by wingtip vortices, which increase UFP concentrations at the ground-level. A mobile monitoring platform was deployed across two seasons underneath the LAX approach pattern, validating the modeled UFP concentrations. AERMOD predictions and measured UFP concentrations showed a coefficient of determination of 0.54. The dispersion model generated monthly average UFP estimates with 1 km x 1km spatial resolution which was smoothed using inverse distance weighted interpolation. Mothers address at birth was collected on the birth certificate and geocoded. Using the smoothed UFP estimates, monthly average UFP exposure estimates were assigned for the gestational period and averaged across the pregnancy. Finally, mothers were categorized into deciles of UFP exposure.

4.3.4 Covariates

We adjusted for demographic factors available on the birth record. Routinely collected variables include mother's race/ethnicity, age, educational attainment, and cigarette smoking during pregnancy. To further control for socioeconomic stats (SES), we adjusted for a composite, census tract-level measure of SES.[173] The composite variable was comprised of the census tract's median household income, median rent, median house value, percent living 200% below poverty level, percent of blue-collar workers, percent unemployed, and education index.

We also adjusted for two other environmental factors: exposure to traffic-related nitrogen dioxide (NO_2) and airport-related noise. NO_2 is a surrogate marker for ground-source combustion emissions[111,112] and exposure to this pollutant was estimated with a Land Use Regression model (LUR) that has been described previously.[113] Briefly, an LUR was developed using data on roadway networks, traffic volumes, land use patterns and satellite-derived vegetation greenness and soil brightness while 201 monitors were deployed across two seasons in Los Angeles County for validation purposes. The final modeled values explained 86% of the variance in measured NO_2 and quartiles of exposure, based upon annual average LUR estimates, were assigned to mothers at their home address.

Airport noise is routinely measured by government monitors located in neighborhoods proximal to LAX. From this monitoring network, data on average annual noise exposures (CNELs) are generated and mothers were considered exposed to airport-related noise if they lived in areas that experience average > 65 dB CNEL.

4.3.5 Statistical methods

To examine the underlying associations between aircraft-specific UFPs, PIH and PTB, we first conducted multiple logistic regression analyses, adjusting for known confounders. We also adjusted for noise and NO_2 in all models to isolate the role of aircraft-related UFPs apart from other environmental pollutants. We used these models to generated three key estimates: the conditional OR of PTB due to PIH, the conditional OR of PTB due to UFP exposure, and the conditional OR of PIH due to UFP exposure. UFP was categorized into deciles of exposure, while PIH and PTB were both dichotomous variables. These estimates were adjusted for age, maternal educational attainment, maternal race, cigarette smoking, quintile of census tract SES, quartile of NO_2 exposure, and exposure to airport-related noise.

We then conducted a mediation analysis to estimate how much of the UFP-PTB association is mediated through PIH. In order to estimate this, we modeled the total UFP-PTB effect and the natural direct and indirect effects using a weighted marginal structural models approach,[215,216] a method grounded in the potential outcomes counterfactual framework.[217] In this analysis, we defined deciles of UFPs as the exposure, PIH is the mediator, and PTB is the outcome. We estimated the total effect of UFP exposure on PTB, as well as the natural direct and natural indirect effects. We also estimated the proportion mediated as the ratio of natural log of the indirect effect to the natural log of total effect. The natural direct effect represents the change in odds of PTB between categories of exposure to UFP, while allowing for PIH status to remain at its observed value between subjects. In other words, it is the estimated effect of exposure to UFPs on PTB, had UFPs estimated effect on PIH been blocked. By contrast, the natural indirect effect represents the change in odds of PTB setting UFP to the reference value, but comparing levels of PIH under exposure and reference values. This means it is the estimated effect of UFPs

on PTB relayed entirely through the effect of UFPs on PIH.[218] Finally, the proportion mediated is interpreted as the degree to which the mediating pathway through PIH explains the overall association between UFP and PTB.

To estimate these natural direct and indirect effects, we first created a new data set, replicating each observation in the data set 10 times – once for each potential decile of UFP exposure. Second, two sets of weights are calculated. The first weight addresses confounding, creating a pseudo-population wherein the confounding variables are not associated with the exposure. This weight is the inverse probability of exposure conditional on all confounders, i.e. age, maternal educational attainment, maternal race, cigarette smoking, quintile of census tract SES, quartile of NO2 exposure, and exposure to 65 dB of airport-related noise. The second weight is the ratio of the probability of the mediator conditional on exposure in a given decile (possibly counter to fact) and all confounders to the probability of the mediator conditional on the observed exposure and all confounders. Finally, a logistic regression model is fit, regressing PTB on observed value of UFP exposure and the unobserved replicates of UFP exposure, which is then weighted by the product of the aforementioned weights.

We also conducted mediation analyses for subgroups. Using the same marginal structural models approach, we examined different outcomes among PTB: any iatrogenic PTB versus spontaneous PTB, induced vaginal labor PTB versus spontaneous PTB, and cesarean section PTB versus spontaneous PTB.

4.4 Results

Most mothers in this analysis were Hispanic and were between 30-34 years of age (Table 4.1). Infants born preterm were more likely to be born to a mother living in an area with lower

SES and higher exposure to airport-related noise. PTB birth occurred in 8.6% of pregnancies and PIH complicated 2.3% of pregnancies. PIH was more common in PTB versus term births (6.3% vs 1.9%), while labor was induced for 28.4% of the PIH cases and 6.2% of the PTB cases. Iatrogenic births were more common in PTB than term births (47.4% vs 38.9%) and in PIH cases compared to non-cases (69.4% vs 38.9%), while cesarean section was more common than induced vaginal labors among all births.

Table 4.1 Maternal and Infant Demographics by Gestational Age

Total N = 173,414	< 37 weeks (n = 15,006)	≥ 37 weeks (n = 158,408)
Gestational Age, mean weeks (sd)	34.5 (2.8)	39.7 (1.4)
Birth Weight, mean grams (sd)	2600 (751)	3348 (444)
Parity, mean children (sd)	2.3 (2.3)	2.1 (2.3)
Quintile of SES Index, mean (sd)	1.9 (1.3)	2.2 (1.4)
Pregnancy Induced Hypertension, No. (%)	939 (6.3)	2977 (1.9)
Infant Sex		
Male, No. (%)	8208 (54.7)	80 454 (50.8)
Female, No. (%)	6796 (45.3)	77 954 (49.2)
Maternal Age		
<20, No. (%)	1322 (8.8)	11 647 (7.4)
20-24, No. (%)	2976 (19.8)	30 674 (19.4)
25-29, No. (%)	3418 (22.8)	38 232 (24.1)
30-34, No. (%)	3670 (24.5)	43 169 (27.3)
35+, No. (%)	3620 (24.1)	34 686 (21.9)
Maternal Race		
White, No. (%)	1828 (12.2)	29 583 (18.7)
Black, No. (%)	2989 (20.0)	22 316 (14.1)
Hispanic, No. (%)	8938 (59.6)	89 367 (56.4)
Asian, No. (%)	903 (6.0)	13 612 (8.6)
Others, No. (%)	348 (2.3)	3530 (2.2)
Maternal Education		
High School Graduate or Less, No. (%)	8855 (59.0)	81 328 (51.3)
Some College to Bachelor's Degree, No. (%)	4868 (32.4)	57 575 (36.4)
More than a Bachelor's Degree, No. (%)	1283 (8.6)	19 505 (12.3)

Maternal Nativity		
US-Born, No. (%)	10 705 (71.3)	110 574 (69.8)
Foreign-Born, No. (%)	4301 (28.7)	47 834 (30.2)
High Noise at Residence, > 65 dB CNEL, No. (%)	775 (5.2)	6663 (4.2)
Cigarette Smoking, ever during pregnancy, No. (%)	156 (1.0)	911 (0.6)
Pregnancy Induced Hypertension, No. (%)	945 (6.3)	3 010(1.9)
Mode of delivery		
Cesarean, No. (%)	6 429 (42.8)	50 852 (32.1)
Induced Vaginal, No (%)	687 (4.6)	10 720 (6.8)
Spontaneous Vaginal, No. (%)	7 890 (52.6)	86 116 (61.1)

In adjusted logistic regression models, there was a 71% increased odds of PIH (95% CI 1.43 – 2.05) and a 15% increased odds of PTB (95% CI 1.06 – 1.25) in the highest decile of UFP exposure compared to the lowest. Similarly, the odds of PTB among women who experienced PIH was 339% greater (95% CI 3.14 – 3.65) than in women who did not have PIH. Exposure to traffic-related NO_2 and airport-related noise were also associated with PTB. The fourth versus the first quartile of NO_2 exposure was associated with a 21% increased odds (95% CI 1.15 – 1.28) of PTB and exposure to > 65 dB CNEL of airport-related noise was associated with a 9% increased odds (95% CI 1.00 – 1.20) of PTB.

Table 4.2 Logistic Regression Results for the adjusted total association between UFP exposure and PTB compared to all term birth

Variable	Adjusted Model[a] OR (95% CI)
UFP	
Decile 1	Ref
Decile 2	1.02 (0.94 – 1.11)
Decile 3	0.99 (0.91 – 1.07)
Decile 4	1.00 (0.92 – 1.08)
Decile 5	1.06 (0.97 – 1.15)
Decile 6	1.04 (0.96 – 1.13)
Decile 7	1.10 (1.02 – 1.20)
Decile 8	1.10 (1.02 – 1.20)
Decile 9	1.14 (1.05 – 1.24)

Decile 10	1.15 (1.06 – 1.25)
Maternal Age	
<20	1.11 (1.04 – 1.19)
20-24	0.99 (0.94 – 1.05)
25-29	Ref.
30-34	1.10 (1.04 – 1.15)
35+	1.39 (1.33 – 1.47)
Maternal Educational Attainment[b]	0.94 (0.92 – 0.95)
Quintile of SES Index	0.96 (0.95 – 0.98)
Maternal Race	
White	Ref.
Black	1.74 (1.62 – 1.88)
Hispanic	1.21 (1.12 – 1.30)
Asian	1.04 (0.96 – 1.14)
Other	1.40 (1.24 – 1.59)
Ever smoked cigarettes during pregnancy	1.64 (1.38 – 1.95)
NO_2	
Quartile 1	Ref.
Quartile 2	1.13 (1.07 – 1.19)
Quartile 3	1.14 (1.08 – 1.20)
Quartile 4	1.21 (1.15 – 1.28)
Exposed to > 65 dB CNEL	1.09 (1.00 – 1.20)

[a]Adjusted for Maternal Age, Maternal Educational Attainment, SES, Maternal Race, and Cigarette Smoking

[b]Educational attainment was recorded in 9 ordinal categories: No formal education, 8th grade or less, 9th grade through 12th grade with no diploma, High school graduate or GED, Some college credit with no degree, Associates degree, Bachelor's degree, Master's degree, Doctorate or professional degree

In the mediation analysis results (Table 4.3), the tenth decile of UFP exposure versus the first was associated with a 15% greater natural direct effect (95% CI 1.12 – 1.18), a 2% greater natural indirect effect (95% CI 1.00 – 1.05), and a 17% total effect (95% CI 1.07 – 1.27). In this top decile, 12.8% of the total effect was mediated through the natural indirect effect. The total and direct effects reflected evidence of a dose-response relationship, with increased deciles of

UFP exposure associated with increased odds of PTB. However, this relationship was not strictly monotonic. By contrast, the estimated indirect effect odds remained relatively constant between categories of exposure.

Table 4.3 Marginal Structural Model Mediation Results for the total, indirect, and direct association between UFP exposure at PTB compared to all term birth

Variable	OR (95% CI)
Total Effect	
Decile 1	Ref.
Decile 2	1.03 (0.95 – 1.11)
Decile 3	1.00 (0.92 – 1.09)
Decile 4	1.01 (0.93 – 1.10)
Decile 5	1.07 (0.99 – 1.16)
Decile 6	1.06 (0.97 – 1.15)
Decile 7	1.12 (1.04 – 1.22)
Decile 8	1.11 (1.03 – 1.21)
Decile 9	1.15 (1.06 – 1.25)
Decile 10	1.17 (1.07 – 1.27)
Direct Effect	
Decile 1	Ref.
Decile 2	1.02 (0.99 – 1.05)
Decile 3	0.99 (0.96 – 1.01)
Decile 4	1.00 (0.97 – 1.02)
Decile 5	1.05 (1.03 – 1.08)
Decile 6	1.03 (1.01 – 1.06)
Decile 7	1.10 (1.07 – 1.13)
Decile 8	1.10 (1.07 – 1.13)
Decile 9	1.13 (1.11 – 1.16)
Decile 10	1.15 (1.12 – 1.18)
Indirect Effect	
Decile 1	Ref.
Decile 2	1.01 (1.01 – 1.01)
Decile 3	1.02 (1.02 – 1.02)
Decile 4	1.02 (1.02 – 1.02)
Decile 5	1.02 (1.02 – 1.02)
Decile 6	1.02 (1.02 – 1.03)
Decile 7	1.02 (1.02 – 1.03)
Decile 8	1.01 (1.01 – 1.02)
Decile 9	1.02 (1.01 – 1.02)
Decile 10[a]	1.02 (1.02 – 1.02)

[a]Proportion mediated, 10th Decile versus 1st:
ln(1.02)/ln(1.17) = 12.8%

We then conducted subgroup analyses among preterm births by type of delivery (Table 4.4). Among infants born preterm, the total, natural direct, and natural indirect effects were all stronger among births after iatrogenic versus spontaneous labor. The tenth decile of UFP exposure vs the first was associated with a total effect of OR 1.38 (95% CI 1.12 – 1.68), natural direct effect OR of 1.31 (95% CI 1.07– 1.61) and natural indirect effect OR of 1.04 (95% CI 1.04 – 1.04). This association was 12.2% mediated through PIH. However, PTB only represented 8.6% of the overall births and therefore confidence intervals for these estimates were wide relative to the overall findings.

We further compared induced vaginal PTB and cesarean section PTB to spontaneous PTB. Among induced vaginal PTB births, there was an increased odds of PTB associated with increased UFP exposure (Total Effect OR 1.70, 95% CI 1.04 – 2.78) compared to spontaneous births in the highest versus lowest deciles of UFP exposure. Compared to the same reference group, the odds of cesarean section PTB was 33% greater (95% CI 1.08 – 1.64). These total effects were 12.8% and 13.8% mediated through PIH, respectively.

Table 4.4 Marginal Structural Model Mediation Results by Delivery Type

	Odds of Iatrogenic PTB vs. Spontaneous PTB OR (95% CI)	Odds of Induced Vaginal PTB vs. Spontaneous PTB OR (95% CI)	Odds of Cesarean Section PTB vs. Spontaneous PTB OR (95% CI)
Total Effect			
Decile 1	Ref.	Ref.	Ref.
Decile 2	1.10 (0.92 - 1.32)	1.47 (0.92 - 2.37)	1.07 (0.89 - 1.29)
Decile 3	1.02 (0.86 - 1.22)	2.02 (1.28 - 3.17)	0.95 (0.80 - 1.14)
Decile 4	0.93 (0.79 - 1.11)	1.48 (0.93 - 2.35)	0.90 (0.76 - 1.07)
Decile 5	1.09 (0.92 - 1.28)	1.49 (0.94 - 2.35)	1.06 (0.89 - 1.25)

Decile 6	1.13 (0.96 - 1.33)	1.54 (0.98 - 2.42)	1.09 (0.92 - 1.29)
Decile 7	1.19 (1.01 - 1.40)	1.33 (0.84 - 2.11)	1.17 (0.99 - 1.39)
Decile 8	1.14 (0.96 - 1.36)	1.55 (0.98 - 2.46)	1.11 (0.93 - 1.32)
Decile 9	1.17 (0.98 - 1.39)	1.48 (0.91 - 2.40)	1.14 (0.95 - 1.36)
Decile 10	1.38 (1.12 - 1.68)	1.70 (1.04 - 2.78)	1.33 (1.08 - 1.64)
Direct Effect			
Decile 1	Ref.	Ref.	Ref.
Decile 2	1.08 (0.9 - 1.3)	1.52 (0.95 - 2.44)	1.05 (0.87 - 1.27)
Decile 3	0.99 (0.83 - 1.18)	2.02 (1.28 - 3.17)	0.92 (0.77 - 1.10)
Decile 4	0.9 (0.76 - 1.07)	1.47 (0.93 - 2.34)	0.87 (0.73 - 1.03)
Decile 5	1.04 (0.88 - 1.23)	1.47 (0.93 - 2.31)	1.01 (0.85 - 1.20)
Decile 6	1.08 (0.91 - 1.27)	1.52 (0.97 - 2.39)	1.04 (0.88 - 1.23)
Decile 7	1.14 (0.96 - 1.35)	1.33 (0.84 - 2.10)	1.12 (0.94 - 1.33)
Decile 8	1.11 (0.93 - 1.32)	1.58 (1.00 - 2.49)	1.07 (0.90 - 1.28)
Decile 9	1.13 (0.95 - 1.35)	1.49 (0.92 - 2.40)	1.10 (0.92 - 1.32)
Decile 10	1.31 (1.07 - 1.61)	1.67 (1.02 - 2.72)	1.27 (1.03 - 1.57)
Indirect Effect			
Decile 1	Ref.	Ref.	Ref.
Decile 2	1.02 (1.02 - 1.02)	1.03 (1.02 - 1.04)	1.02 (1.01 - 1.02)
Decile 3	1.04 (1.03 - 1.04)	1.06 (1.04 - 1.08)	1.03 (1.03 - 1.04)
Decile 4	1.04 (1.03 - 1.04)	1.06 (1.04 - 1.08)	1.03 (1.03 - 1.04)
Decile 5	1.04 (1.04 - 1.05)	1.07 (1.05 - 1.09)	1.04 (1.03 - 1.04)
Decile 6	1.05 (1.04 - 1.05)	1.08 (1.05 - 1.10)	1.04 (1.04 - 1.05)
Decile 7	1.04 (1.04 - 1.05)	1.07 (1.05 - 1.09)	1.04 (1.03 - 1.04)
Decile 8	1.03 (1.02 - 1.03)	1.05 (1.03 - 1.06)	1.02 (1.02 - 1.03)
Decile 9	1.03 (1.03 - 1.04)	1.05 (1.04 - 1.07)	1.03 (1.02 - 1.03)
Decile 10	1.04 (1.04 - 1.05)	1.07 (1.05 - 1.09)	1.04 (1.03 - 1.04)
Proportion Mediated, 10^{th} decile	12.2%	12.8%	13.8%

4.5 Discussion

We found that the relationship between in utero airport-related UFP exposures and PTB was partially mediated by PIH. To our knowledge, this is the first study to report this mediating effect of PIH. The overall effect estimates of UFP exposures were stronger among women who had induced labor compared to spontaneous labor.

One plausible mechanism for the relationship between exposure to UFPs and PIH is the initiation of inflammation. Exposure to ambient air pollution has been shown to induce a systemic inflammatory response.[219–221] Importantly, aircraft-related UFPs are uniquely capable of being a catalyst for inflammation. Previous research found that interleukin 6, a biomarker for systemic inflammation, was elevated in serum of individuals highly exposure to aircraft-related UFPs near LAX.[222] This corroborates earlier reports that UFP exposure stimulates a pro-inflammatory response that may even be stronger than that due to larger particulate pollutants,[223] possibly since UFPs are capable of translocation into distal tissues after inhalation and can escape clearance by the immune system.[180] UFPs are capable of transplacental transfer, i.e. particles up to 240 nm in diameter have been shown to cross the placental barrier,[224] possibly inducing inflammation directly in uteroplacental tissues. Because UFPs also resist the usual removal processes, long-term and chronic activation of immune cells may prime the body for an heightened inflammatory response,[225] which could manifest itself as PIH.

While pregnancy is typically associated with a pro-inflammatory response, previous research has described an excess degree of inflammation in cases of preeclampsia.[226,227] Pathologically, preeclampsia is linked to dysfunction of the maternal endothelium, which may be caused by an infiltration of pro-inflammatory leukocytes.[228] Inflammation has been also identified as a key promoter in the pathogenesis of hypertension.[229,230]

PIH, particularly preeclampsia, is a leading risk factor for PTB. In cases of mild preeclampsia, PTB occurs in approximately 12-14% of births.[231,232] Preeclampsia is also a major risk factor for maternal morbidity and mortality. As a result, early induction of labor or cesarean delivery[233,234] might be indicated for mothers with PIH. When comparing PTB with induced versus spontaneous labor, we found the estimated magnitude of effect of UFP exposure to be

markedly stronger among women with iatrogenic labor. This held true when comparing women with either induced vaginal PTB or cesarean PTB to spontaneous PTB. Among mothers with PIH, iatrogenic births were approximately twice as common as in women without PIH. Women experiencing PIH are encouraged to carry their pregnancies until 37 weeks of gestation to diminish the chance of adverse neonatal outcomes. However, more severe cases of preeclampsia may require an iatrogenic induction of a preterm birth,[235] since labor is an effective cure for preeclampsia[236] delivering the child prior to 37 weeks might be required to avoid adverse fetal and maternal outcomes.[237]

Unexpectedly, the estimated proportion mediated in these secondary analyses among PTB did not change appreciably. Given the contrasts we examined between iatrogenic and spontaneous labor, we hypothesized that the proportion mediated through PIH would increase, especially given its indication for delivering a baby before term. We hypothesize this might be explained by PIH likely being underreported in this cohort due to the data collection method. Previous research found that the sensitivity value of birth registry data for the diagnosis of PIH was 56%.[238] Due to this possible underreporting, we do not see change in the proportion mediated. However, more pronounced overall effects among women for whom birth was iatrogenic versus spontaneous still suggests that PIH is indeed a critical pathway through which UFP exposure leads to PTB.

The observed dose-response relationship for the direct but not indirect effect of UFP on PTB also suggests that additional factors apart from the mediating effect of PIH that connect UFP exposure with PTB including placental implantation errors early in pregnancy.[39,239] Alternatively, air pollution exposures may stimulate and dysregulate the hypothalamus-pituitary-adrenal gland (HPA) neuroendocrine axis,[240,241] and trigger the parturition process.

The strengths of this study include our exposure model for aircraft-related UFPs in a large population. The validated AERMOD exposure model, calibrated for monthly air traffic and wind patterns, allows for a spatially and temporally resolved exposure assignment across pregnancy. Additionally, birth records are comprehensive and provide ample sample size to assess UFP impact in a well-defined area over almost a decade. The marginal structural models approach to mediation analysis also has advantages. First, it enables the estimation of direct and indirect effects without specifying a model conditional on covariates. Models conditioning on covariates can inadvertently lead to collider stratification bias, whereas marginal structural models rely upon weights rather than conditioning for model specification. Further, without conditioning on covariates, marginal effect estimates more closely approximate causal population effects rather than associations in observed data.[217] Finally, other mediation analysis techniques often estimate the controlled direct effects, which fix the mediator value at a common value for all subjects, which has value for assessing policy implications. By contrast, the natural direct and indirect effects are more appropriate estimands for understanding disease mechanisms, which is our research question of interest.[242]

This analysis had some limitations. The medical supplement to the birth record combined gestational hypertension and preeclampsia into one composite variable. Therefore, we were unable to differentiate between the mediating role of these to hypertensive disorders. Further, mothers' exposure profiles were based on their recorded home address at birth and we could not account for time not spent at this location (i.e. working, traveling, etc.). As was previously discussed, PIH is likely underreported in this cohort as the birth record might not accurately reflect the mother's medical record. Pregnancy complications reported on the birth record are not as reliable as a mother's medical record and might only reflect more severe cases of PIH.[71] There

is no evidence that this underreporting is differential with respect to PTB status and could be moving our effect estimates closer to the null. As a result, these results may represent a relatively conservative estimate for mediation by PIH.

4.6 Conclusion

PIH is a major risk factor for PTB and exposure to in utero UFPs increases the risk of PIH. We have identified PIH as a potential mediator of the relationship between in utero aircraft-related UFP exposures and PTB. Thus, exposure to ambient particulate matter air pollution, here UFPs from aircraft exhaust, may lead to the initiation of hypertensive disorders, possibly by stimulating an inflammatory response. Our results also suggest that UFP exposures during pregnancy influenced both spontaneous and iatrogenic PTB, while controlling for demographic characteristics and exposure to other air pollutants. Large populations are living downwind of major airports and experience chronic exposure to UFPs. Our findings suggest that PIH is part of the mechanism of PTB from UFP exposures.

Chapter 5 – Public Health Importance

5.1 Traffic-related air pollution and children's health

Exposure to traffic-related air pollution is almost unavoidable among populations living in urban settings. Among American cities, Los Angeles stands out as uniquely problematic in this domain. The U.S. Department of Transportation estimates that 40% of all American imports are routed through the Ports of Long Beach & Los Angeles, which are the busiest container ports in the country.[243] This trade leads to thousands of daily truck trips, which share the road with many thousands more automobile-dependent Angelinos, generating a disproportionately high

amount of air pollution in the region. In Los Angeles, traffic contributes approximately five times more to overall particulate pollution compared to the rest of the United States.

These emissions tend to overly impact communities and children living near high-volume roads, like freeways.[244] Children are also potentially exposed to traffic-related air pollution not only while at home. The Los Angeles Unified School District has 90 schools located within 500 feet of a freeway, while 37 of those schools are within 100 feet.[245] Approximately 60,000 children attend these schools.[246] Moreover, 169 childcare facilities serving nearly 10,000 children are also with the same 500 feet buffer distance.[247] Given our findings and the wealth of literature on the insidious effect of air pollution exposure on children's health, effective policies for limiting these exposures to our most vulnerable populations are critical. Currently, such strategies include the prohibition of construction of schools within 500 feet of freeways[248] and the installation of filtration systems.[249]

5.2 Aircraft-related UFPs and PTB

Much like road travel, Los Angeles is a leader in air travel. LAX has approximately 700,000 annual aircraft movements, transporting 90,000,000 passengers and over 2,000,000 tons of freight.[250] Moreover, the runways of LAX and the airspace around it might only be getting busier. Since 2010, the number of passenger enplanements increased an average of 5% per year and aircraft movements increased 3% per year.[250] As air travel continues to become more financially attainable and common for Americans,[251] the emissions from these trips grows as well.[252] Given their large-scale impacts, UFP emissions from aircraft are having a sizable impact on reproductive health as a result. From our findings, it only takes 91 women exposed to the top quartile of UFP concentrations to generate 1 PTB case.

New aircraft jet engines are far more efficient now than their introduction into commercial aviation in the middle of the 20th century.[253] However, these gains in efficiency have been outpaced by the increased demand for air travel, resulting in a net increase in aircraft-related emissions.[253] Unless radical technological improvements are implemented, aircraft will likely increase in importance as sources of air pollution exposure in the coming years. Moreover, routine monitoring of emissions near airports stands to improve, especially since some critical pollutants like UFPs are neither routinely measured nor regulated.[63]

Similarly, rates of preterm birth had been steadily declining until 2014, but then subsequently rose in 2015 and 2016.[254] Improvements in rates had been partially attributed to the decline in births among young mothers, especially teenagers.[255] To regain traction in the improvements of PTB rates, it may be critical to protect pregnant mothers from exposure to these ever-growing aircraft-related emissions. Previously proposed mitigation strategies for reducing airport-related emissions involve moving towards a fuel supply with lower sulfur content, electrification of ground service vehicle fleets, and utilizing only one engine during taxiing. Holistic implementation of such policies could prevent up to 65% of adverse health effects due to airport-related emissions.[256]

Chapter 6 – References

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