Title

Assessing risk and preventive factors for respiratory illness in children and adolescents: breastfeeding, prenatal and postnatal stressors in two population-based cohorts in Los Angeles, CA.

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Publication Date

2015

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Assessing risk and preventive factors for respiratory illness in children and adolescents: breastfeeding, prenatal and postnatal stressors in two population-based cohorts in Los Angeles, CA.

A dissertation submitted in partial satisfaction of the requirements

for the degree

Doctor of Philosophy in Epidemiology

by

Gretchen Elizabeth Bandoli

2015

ABSTRACT OF THE DISSERTATION

Assessing risk and preventive factors for respiratory illness in children and adolescents: breastfeeding, prenatal and postnatal psychosocial stressors in two population-based cohorts in Los Angeles, CA.

by

Gretchen Bandoli

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2015

Professor Beate Ritz, Chair

Respiratory diseases such as asthma, wheeze and reduced lung function physically and economically burden many individuals, and have biologic underpinnings to the prenatal and childhood timeframes via fetal programming and epigenetic mechanisms. This dissertation studies risk and preventive factors for respiratory illnesses during three distinct timeframes: the prenatal period, infancy, and childhood/adolescence. By using data that oversampled immigrant Latino families, we were afforded additional opportunities to study race/ethnicity and nativity as a confounder or effect measure modifier, further

tailoring our public health message to an important and growing population in our communities.

Our first study used longitudinal data from a population based nested case-control study in Los Angeles to analyze three different maternal stressors as well as paternal support during pregnancy to determine if these stressors carried differential risk of reported lifetime wheeze in the young offspring. We further examined whether Latina ethnicity modified those same associations. The risk of wheeze in the offspring was increased from high levels of pregnancy anxiety (aRR 1.40, 95% CI 1.07, 1.83), negative life events (aRR 1.36, 95% CI 1.06, 1.75), or low paternal support (aRR 1.41, 95% CI 1.02, 1.96). Additionally, the risk of lifetime wheeze was stronger in the offspring of Latina mothers than of White mothers for these same stressors.

Using data from the same sample in the second study, we assessed whether maternal nativity in a Latina population confounded or modified the association between exclusive breastfeeding and asthmatic symptoms. Using cross-sectional data restricted to Latinas, we found a 49% reduction in risk of asthmatic symptoms with $\geq$3 months of exclusive breastfeeding (aRR=0.51, 95% CI 0.28, 0.90). Foreign-born Latinas were more likely to initiate and continue breastfeeding for at least three months compared with US-born Latinas. We did not find evidence that maternal nativity confounded or modified the association, but rather predicted the woman's breastfeeding behavior.

In the third study, using cross-sectional data from the Los Angeles Family and Neighborhood Survey (L.A.FANS-2, 2006/8, n=584), we analyzed whether various

psychosocial stressors predicted lung function in youth ages 10-17 after adjusting for air pollution. No consistent results were seen between self-reported psychosocial stressors, caregiver stressors, or negative behaviors and lung function in youth. We observed a suggestion of reduced lung function in males from family fighting (FEV_1: -156.2ml, 95% CI -327.8, 15.5), absence of a father in the house (FEV_1: -176.2ml, 95% CI -322.7, -29.7) and the summary stress score (FEV_1: -45.6ml, 95%CI -97.6, 6.3), which were all stronger in older males ages 15-17. Additionally, feeing unsafe at school was associated with reduced lung function in younger participants ages 10-14 (FEV_1: -129.8ml, 95%CI -241.4, -18.2). None of the measures were associated with reduced lung function in females.

In conclusion, prenatal psychosocial stressors and breastfeeding behaviors are potentially modifiable, and are associated with respiratory illnesses. Further work is warranted looking at psychosocial stressors later in youth. Individually tailored messages, particularly to Latinas, who may have stronger effects from prenatal stressors or negative breastfeeding behavior by nativity status, should be a priority towards preventing childhood respiratory illnesses.

The dissertation of Gretchen Elizabeth Bandoli is approved.

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May-Choo Wang

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2015

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ABBREVIATIONS

Acute Otitis Media (AOM)

Behavioral Problems Index Internalizing scale (BPI-INT)

Environment and Child Health Outcome Study (ECHOS)

Environment and Pregnancy Outcomes Study (EPOS)

Forced expiratory flow (FEF)

Forced expiratory volume (FEV_1)

Forced vital Capacity (FVC)

Hypothalamus-pituitary-adrenal (HPA)

Glucocorticoid receptor (GR)

Inverse probability censoring weights (IPCW)

International Study of Asthma and Allergies in Childhood (ISAAC)

Los Angeles Family and Neighborhood Survey (L.A.FANS)

Negative Life Events (NLE)

Particulate Matter 2.5 micrograms ($PM_{2.5}$)

Pearlin Self-Efficacy Scale (PSE)

Perceived Stress Scale (PSS)

Risk Ratios (RR)

95% confidence intervals (CI)

Odds Ratios (OR)

ACKNOWLEDGEMENTS

I would like to thank my advisor, Beate Ritz, for her guidance and support throughout this program. Her unwavering commitment to the fundamentals and ethics of research, attention to detail, respect for students and commitment to her profession taught me as much outside of the classroom as inside. I will leave this program a better writer and researcher because of the time she spent with me.

I would also like to thank my committee, Drs. Cochran, Javanbakht and Wang for their guidance and support of this dissertation. Each brings her own strengths and subject matter expertise to my project, shaping its content and making it a stronger dissertation. I truly appreciated their capacities and professionalism, and learned a lot from each along the way.

I am appreciative of the financial support I received during my time at UCLA. The departmental fellowships from 2012-15, in addition to the Bixby Fellowship and Judith Blake award gave me the ability to complete this project in a timely manner.

As a child drawing on my father's chalkboard, I knew that I too wanted to be a professor. I would like to thank my family for their support, encouragement and sacrifice as they allowed me to chase my dream.

Chapter one is a version of Bandoli G, von Ehrenstein O, Flores M, Ritz B. Breastfeeding and Asthmatic Symptoms in The Offspring of Latinas: The Role of Maternal Nativity. Journal of Immigrant and Minority Health. 2015 January; [Epub ahead of print]. DOI 10.1007/s10903-015-0158-4. The co-authors Ondine von Ehrenstein and Marie Flores assisted in manuscript editing. Beate Ritz assisted in the project design, as well as manuscript editing.

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- Bandoli G, Lindsay S. Johnson DL, Kao K, Luo Y, Chambers CD. Changes in paternity and select perinatal outcomes: Causal or confounded? Journal of Obstetrics and Gynaecology 2012 Oct; 32(7): 657-662.
- Nguyen D, Bandoli G, Johnson DL, Chambers CD. Elevated Maternal Serum Alpha Fetoprotein Predicts Reduction In RA Disease Symptoms During Pregnancy But

Does Not Reduce Risk For Preterm Delivery. Presented as a poster at ACR/ARHP Annual Scientific Meeting, November 6-11 2010, Atlanta, GA.

- Bandoli G, Johnson DL, Jones KL, Lopez Jiminez J, Salas E, Mirrasoul N, Van Voorhees AS, Chambers CD. Potentially modifiable risk factors for adverse pregnancy outcomes in women with psoriasis. British Journal of Dermatology 2010 Aug; 163(2): 334-9.

Chapter I. Introduction and background

The purpose of this dissertation is to study three factors associated with the respiratory health of children and adolescents, and when possible, explore the associations by ethnicity and nativity. Briefly, the first project will examine different psychosocial stressors during the prenatal period and their associations with childhood wheeze, asthmatic symptoms and otitis media. This project will use data from the Environment and Child Health Outcome Study (ECHOS), a predominantly Latina cohort from a nested case control that oversampled preterm and low birth weight births from Los Angeles, CA. Using this same data set, the objective of the second project is to determine whether breastfeeding in a Latina population reduces the risk of asthmatic symptoms in the young offspring, and whether nativity modifies or confounds the association. Finally, the third project will use data from Los Angeles Family and Neighborhood Survey (L.A.FANS) to determine whether psychosocial stressors in youth are associated with reduced lung function.

1.1 Childhood outcomes: asthma, wheeze, lung function and otitis media

1.1.1 Childhood asthma

Asthma is a chronic lung disease that inflames and narrows the airways. Symptoms include wheezing, shortness of breath and coughing (1). Asthma is a broad term for what may be several disease phenotypes that arise from multiple etiologies (2). Diagnosis of asthma is difficult in young children, as many young children wheeze from colds and respiratory infections but do not subsequently develop asthma. However, the likelihood of asthma in young children with wheeze increases with allergies or parental asthma (1).

From the 1980's until its peak in 1995, asthma prevalence in children aged 0-17 years more than doubled, stabilizing in 2001 in the United States (3,4). In 2008, 9.3% of children in the US had asthma. Income and race/ethnicity are both associated with childhood asthma; there is higher prevalence of asthma among the poor than the near-poor or non-poor, and asthma prevalence is higher in non-Hispanic Black (14.6%) and multiracial (13.6%) children as compared with non-Hispanic White (8.6%) children, independent of poverty (5). Mexican-American children born in the US have similar rates to non-Hispanic White children (6). Although asthma generally is thought to be an allergic disease, a large percentage of cases are non-allergic, and although the etiologies of allergic and non-allergic asthma differ, clinical features are similar (7). Apart from genetics, multiple factors are thought to contribute to the risk of asthma, including sex (males), obesity, exposure to tobacco smoke, dietary factors and environmental factors including air pollution (8). Childhood asthma and wheeze present an enormous burden to the child, the families and to the healthcare system (9). Asthma is considered to be one of the costliest of chronic diseases due to the healthcare utilization and often lifetime duration, totaling $56B in 2007(10). Medications account for the largest proportion of the direct costs (41.3%), and school/work absenteeism of the child and parent are major contributors to the indirect costs (11).

1.1.2 Childhood wheeze

As previously described, not all types of wheeze in childhood eventually become asthma. Indeed, the major symptom 'wheezing' may get diagnosed as "asthma" in young children but its phenotype is heterogeneous; as many as six phenotypes have been identified in

longitudinal studies (infrequent (peak prevalence at 6 months and then declines, sporadic); transient early (peak prevalence of wheeze at 18 months and then declines); prolonged early (peak at 36 months, decline to low prevalence from 69 months); intermediate onset (low prevalence at age 18 months, peaks from 40 months onward); late onset (highest prevalence from 42 months) and persistent wheezing (highest prevalence from 6 months onward)) and are quite different in their risk for subsequent development of asthma (12). These phenotypes (and their consequences in diagnosing childhood asthma) cannot be established reliably until the child reaches age six (13). Recently, authors found that the six phenotypes in children age 0-7 differ in their risk factors as well; maternal atopy was related to all phenotypes, but was a stronger risk factor for intermediate onset and persistent wheeze. Maternal pregnancy anxiety also increased the risk of all types of wheezes, amongst their offspring, but was strongest in predicting persistent and prolonged early wheeze (60-155% increase in risk). Conversely, maternal anxiety during the first year of life generally increased the risk of all wheeze phenotypes, but was not as strong a risk factor as pregnancy anxiety (40-60% increase risk). Finally, while generally no association was reported between ever breastfeeding and wheeze, extended length of breastfeeding (three months or more) did protect against two types of wheeze- transient early and persistent (20% reduction in risk) (2). Whether or not the wheeze is outgrown with aging due to the enlarging of the airways or is a symptom of asthma, childhood wheeze presents a great burden to the child and family, and is often studied as a separate outcome from asthma, particularly in research studying children too young in which to diagnose asthma reliably.

1.1.3 Lung function

Lung function steadily increases through childhood and adolescence, plateauing in early adulthood and provides an objective measure of respiratory health and a predictor of cardiorespiratory morbidity and mortality (14). Those with lower lung function by early adulthood have increased risk of both all-cause mortality and ischemic heart disease mortality independent of smoking status (15). In addition to the long term health consequences, some children with reduced lung function develop asthma, and there is evidence that reduced lung function precedes asthma symptoms and may be decreased in asthmatic children as early as in the neonatal period (16). Factors associated with inflammation have been identified as risk factors for reduced lung function, including asthma, smoking, air pollution and respiratory infections (17). Lung function is assessed with spirometry, with forced vital capacity (FVC) and forced expiratory volume (FEV_1) measuring large airways, and peak and forced expiratory flow measures (PEF, FEF) measuring smaller airways which are more sensitive to ozone and tobacco smoke (14).

1.1.4 Otitis Media

Acute otitis media (AOM) is one of the most common childhood infections and a leading reason for antibiotic prescriptions in children (18). The highest prevalence is found in children ages 6-18 months, and it is more common in males (19). AOM is thought to result from an interaction between the microbial load and immune response. Known risk factors include genetics, young age and atopy, as well as siblings, daycare attendance and season

(18). The US health care expenditures for AOM exceed $5 billion/year, and sequelae of recurrent AOM include delayed speech and hearing damage(19).

Chapter II. Study 1: Prenatal maternal stress and the risk of wheeze in young offspring: examining stressors by maternal ethnicity.

2.1 Abstract

Background: Prenatal psychosocial stressors may increase the risk of wheeze in young offspring; yet little attention has been given to the modifying effects that maternal ethnicity may contribute to this relationship.

Methods: From a population-based cohort of 1,193 children, we assessed the effect of maternal prenatal stressors on the risk of lifetime wheeze in young offspring. We further studied whether maternal Latina ethnicity modified these associations.

Results: High levels of pregnancy anxiety (aRR 1.40, 95% CI 1.07, 1.83), negative life events (aRR 1.36, 95% CI 1.06, 1.75), or low paternal support (aRR 1.41, 95% CI 1.02, 1.96) were all associated with increased risk of lifetime reported wheeze in the offspring. The risk of lifetime wheeze was stronger in the offspring of Latina mothers than that of White mothers for these same stressors.

Discussion: Multiple maternal prenatal stressors are associated with increased risk of lifetime wheeze in young offspring, with slight effect modification by Latina ethnicity.

2.2 Background

2.2.1 Fetal programming

The time of pregnancy is recognized as a crucial period of fetal development impacting a child's health well beyond the immediate circumstances of the birth. The hypothesis known as "fetal programming" postulates that during critical periods of fetal development, certain stimuli or insults can have lifelong and even trans-generational effects (20). First proposed by and named as "Barker's hypothesis," research initially focused on fetal nutrition and the risk of ischemic heart disease (20). However, this hypothesis was largely expanded to encompass a variety of maternal/fetal exposures and subsequent health outcomes. One such exposure is maternal pregnancy stress and the risk of respiratory illness (primarily childhood wheeze and asthma) in the offspring. Relevant pathways that maternal stress events may affect have been summarized in two reviews (21,22); mainly it has been hypothesized that prenatal environmental conditions, including maternal stress, may alter the maturation of fetal immune networks, shifting the balance in favor of a Th2-biased allergic response and development of atopic wheeze. Additionally, prenatal stress exposure may affect the developing hypothalamus-pituitary-adrenal (HPA) axis through placental secretion of corticotrophin releasing hormone (CRH) and excess glucocorticoids have an impact on the developing immune system. Finally, pregnancy stress may change the epigenetic regulation of glucocorticoid receptors and alter HPA activity (21,23).

2.2.2 Previous literature investigating prenatal stress in pregnancy

Numerous studies over the past two decades, including one from our UCLA Environment and Pregnancy Outcomes Study (EPOS) cohort, have suggested that maternal stressors, including negative life events, perceived stress, chronic stress and acute stress in pregnancy, shorten gestation resulting in preterm birth and low birth weight infants (24,25). More recently researchers began investigating the association between maternal prenatal stress and asthma and wheeze in the offspring (26–32), with most studies concluding that prenatal stress increases the risk of these respiratory outcomes in the offspring (28–32). Previous reports have typically considered only one stressor or affective state per study (e.g.- maternal bereavement, negative life events, maternal demoralization, exposure to violence) (26–32) and/or simply adjusted for race/ethnicity (27,28) rather than evaluating possible modifying effects of race/ethnicity which may be more elucidating.

Different stressors (e.g.- chronic, acute, transient) may elicit different stress responses, with trauma hypothesized to have the greatest psychophysiologic alteration of the HPA axis (22). Stress exposures, perceptions, and responses may also vary culturally. Ethnic minorities and low-income women tend to report more chronic stress and discrimination, and less practical or emotional support from family and friends, which may influence coping mechanisms (33–35). It was recently observed that levels of maternal perceived stress, maternal negative life events and pregnancy stress differed by race within categories of federal poverty level (36), suggesting that racial differences in stress burden persist independent of income.

2.3 Hypothesis/aims

Here, we examine the influence of three different pregnancy stressors (pregnancy anxiety, acute stress from negative life events, chronic stress) and paternal support on wheezing in the offspring and examine the influence of maternal ethnicity and nativity on these associations. Using prospective data from a population-based cohort study that oversampled preterm and low birth weight children born in Los Angeles, CA in 2003, we examined whether pregnancy stressors increased the risk of lifetime wheeze in our population of young (3-4 year-old) children. Second, we assessed each pregnancy stressor and the risk of lifetime wheeze stratified by ethnicity and nativity to determine if ethnicity modified the relationships. Third, we examined whether the same pregnancy stressors increase the risk of additional respiratory outcomes; namely current wheeze (wheeze in the past 12 months), asthmatic symptoms (doctor-diagnosed asthma with dry cough and/or wheeze) and otitis media.

2.4 Study materials and methods

2.4.1.Subject selection

The UCLA Environment and Pregnancy Outcomes Study (EPOS) was originally designed to assess effects of air pollution on birth outcomes (37). The source population was identified among all live births from January 1, 2003 to December 31, 2003, to mothers who resided in one of 111 Los Angeles County ZIP codes (41% of all LA County births). After exclusions, the final birth cohort consisted of 58,316 eligible births (87% of the original total). A nested case-control study was then created by taking all cases of low birth weight (<2,500 g) or

preterm birth (<37 completed weeks gestation) and an equal number of randomly sampled controls (≥2,500-g weight and full term) from the set of 24 ZIP codes located in close proximity to South Coast Air Quality Management District air monitoring stations were selected. An additional 30 percent of cases and an equal number of controls were selected from the set of 87 ZIP codes containing major population centers and located close to major roadways. Of the 6,347 women sampled, 2,543 were interviewed (in English or Spanish) (40% response rate) 3-6 months post-partum and provided detailed information on pregnancy exposures and behaviors.

In 2006-2007, a longitudinal cohort of the original EPOS nested case-control study was created (Environment and Child Health Outcome Study (ECHOS)) primarily to study respiratory outcomes in the cohort of children. 1,201 women participated in the follow-up survey by phone or mail (49.3% of those who agreed to be re-contacted); the majority of attrition resulted from the inability to locate women 3-years after the first contact (38).

2.4.2 Outcome definitions

In the 2006-2007 interviews, we assessed respiratory health via maternal report according to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire for 6-7-year-olds (39). For the primary diagnosis of interest 'lifetime wheeze,' we asked "has your child ever had wheezing or whistling in the chest at any time in the past?" In sensitivity analyses, we defined 'current wheeze' as "wheeze or whistling in the chest in the past 12 months," 'asthmatic symptoms' as positive response to the question has a "doctor

diagnosed asthma with dry cough at night and/or wheeze," and 'otitis media' as three or more "doctor diagnosed ear infections over the child's life."

2.4.3 Exposure and covariate definitions

We previously described our stress measures and performed all summations and categorizations for this analysis in the same manner (25). In the baseline survey (EPOS), we asked women to recall three types of stressors pertaining to the pregnancy period: pregnancy anxiety, chronic stress, acute stress due to negative life events, as well as paternal support. These measures are subsets of validated stress measures selected for their brevity and their ability to predict adverse birth outcomes (24,40,41).

Pregnancy anxiety was operationalized by: "I was fearful about the health of my baby or about losing my baby during pregnancy." Responses were provided via four-point Likert scales (not at all, moderately, somewhat, very much).

Chronic stress was estimated using four questions from the Perceived Stress Scale (42), a validated instrument measuring perception of stress: 1) ability to control things, 2) difficulties piling up, 3) confidence in ability to handle problems, and 4) how often things were going the respondent's way. Responses were given on a five-point Likert scale (never, almost never, sometimes, fairly often, very often). We calculated cumulative totals from the four questions and categorized the scores as low (4-8), moderate (9-12), and high (13+) chronic stress.

Acute stress was assessed in terms of six major negative life events that occurred during pregnancy (1) loss of car/job/home, 2) serious arguments with partner, 3) close acquaintance with health, drug or legal problems, 4) anyone close having died, 5) having been threatened with physical harm, or 6) having been exposed to discrimination due to race/ethnicity. We summed the negative life events as 0 events, 1 event, and 2+ events.

Paternal support was operationalized in three questions: "does your partner show you respect/care," "criticize you," and "support you financially," answered on a five-point Likert scale (never, almost never, sometimes, often, almost always). We summed the answer to the three questions and defined low support (3-8), moderate support (9-11) and high support (12+).

Covariates collected from the 2003 birth certificates include maternal age and race/ethnicity, gestational age at delivery and sex of the child. The 2003 EPOS survey provided information on maternal education and maternal pregnancy smoking. In 2006-2007 follow-up interviews, we collected data on current smoking in the residence, maternal history of atopy, maternal nativity, and months of exclusive breastfeeding.

2.4.4 Statistical analyses

We estimated risk ratios (RR) for the pregnancy stressors on reported wheeze, asthmatic symptoms and otitis media at age 3-4 years using Poisson regression models with robust error variance and a log link function (43). We analyzed the stressors individually in separate models due to the correlation between stressors. Multivariate analysis was conducted including potential confounders previously described. There were too few

respondents (n=6) among those with wheeze who affirmed current smokers in the house to include in adjusted models, however, exclusion of those who currently smoked from adjusted models did not change estimates by >10% (44). Similarly, we were missing 11.6% of responses about household income, however, its inclusion in adjusted models did not change the effects by >10%. In our data, income had a correlation of 0.63 with maternal education, thus only maternal education was used in adjusted models.

We adjusted models stratified by ethnicity using propensity scores to account for the limitations of small strata. Propensity scores were created by regressing covariates from the fully adjusted models on each individual stressor in a multinomial logistic regression, with inclusion of the predicted probabilities of exposure in the final model. Stratification by race/ethnicity was limited to White mothers and Latina mothers; strata for Black/African American or Asian/Other individuals were too small for analysis (n=70 and 105 respectively). Within the Latina stratum, we further stratified by maternal nativity (US-born vs. foreign-born).

In sensitivity analyses, inverse probability censoring weights (IPCW) were applied to assess the impact of attrition in the cohort. Within the EPOS (baseline) study, maternal age, race/ethnicity and education were all associated with the probability of being censored, and were regressed on a censoring variable to create censoring weights. In a separate sensitivity analysis examining each stressor and lifetime wheeze, the sample was re-weighted to adjust the prevalence of preterm births in the sample (39.7%) to equal 10% as observed in the general population.

Finally, risk ratios for current wheeze, asthmatic symptoms and otitis media were calculated for each individual factor adjusting for the variables listed above.

The UCLA Office of the Human Research Protection Program and the California State Committee for the Protection of Human Subjects approved this research; informed consent was obtained from the women.

2.5 Results

Of the 1,193 women in the ECHOS sample, a majority were Latina (59.6%) or non-Latina White (25%). Of the Latina mothers, 68.1% were foreign-born, predominantly in Mexico. Ages of the offspring ranged from 2.3-5.8 years, with a median age of 3.5 years. Of all women in the sample, 25.5% of the offspring (n=304) had a lifetime history of wheeze, and 14.1% (n=168) had wheezed within the last 12 months. Children with a lifetime history of wheeze were more likely to be born to Black/African American or US-born Latina women, to have been born preterm, and more frequently had a mother with a history of atopy. Frequencies of maternal pregnancy stress variables also differed as displayed in Table 2.1.

In multivariate adjusted models (Table 2.2), the risk of lifetime wheeze in the offspring was increased when the mother reported high pregnancy anxiety, high numbers of negative life events, or low paternal support in separate models. Level of chronic stress also increased the risk of lifetime wheeze, but confidence intervals crossed the null, suggestive of a weak effect. IPCW analysis did not appreciably change the results.

When stressors were individually analyzed in models stratified by ethnicity (Figure 2.1), the risk of lifetime wheeze was higher in the offspring of Latina mothers than the offspring of White mothers when having reported high pregnancy anxiety, 2+ negative life events, or low paternal support in pregnancy, although the confidence intervals of the estimates largely overlapped, implying only a suggestion of effect measure modification. The risk of lifetime wheeze from high levels of prenatal chronic stress was higher in the offspring of White mothers than in offspring of Latinas. Further stratification among Latinas by nativity (data not shown) resulted in no appreciable differences in the risk of wheezing in the offspring between foreign-born and US-born Latinas resulting from the stressors, with the exception of low paternal support, where offspring of US-born Latinas had higher risk for wheeze (aRR 1.87, 95% CI 1.04, 3.36) than those of foreign-born Latinas (aRR 1.42, 95% CI 0.79, 2.54).

In sensitivity analyses (Table 2.3) for current wheeze (within the last 12 months) we estimated similar sized effects as for lifetime wheeze for all factors except for paternal support, where low paternal support had a stronger association with current wheeze in the offspring. Point estimates for associations between the three stressors and paternal support and asthmatic symptoms in the offspring indicated increased risk from each of the stressors, but all confidence intervals crossed the null. Finally, 2+ negative life events and low paternal support were weakly associated with an increased risk of three or more infections with otitis media, as confidence intervals crossed the null.

When preterm birth was down-weighted to represent 10% of the sample, point estimates did not change by greater than 10%; confidence intervals became slightly wider (Table 2.2).

2.6 Discussion

Using measures on three types of stress and paternal support during pregnancy, we found that a woman's anxiety about the health of the baby during pregnancy, negative life events, and low paternal support in pregnancy were all associated with an increased risk of lifetime wheeze in the offspring. The strength of the association with lifetime wheeze in the offspring did not differ by the type of stressor. However, upon examination by ethnicity, Latina mothers tended to have greater magnitude risk estimates for wheeze in their offspring resulting from pregnancy stressors.

Our interest in examining ethnicity as an effect modifier stemmed from a recent analysis suggesting that the perception and vulnerability to stress may vary by race/ethnicity. In the analysis, levels of maternal perceived stress, maternal negative life events and pregnancy stress differed by race/ethnicity within income categories (36) suggesting that racial/ethnic differences in stress burden persist independent of income. While our sample sizes within strata were small, we too found evidence for differences in risk of wheeze to the offspring of White and Latina mothers. Latina mothers had stronger risk of wheeze in their offspring from pregnancy anxiety, 2+ negative life events, and low paternal support when compared with White mothers. Additionally, among Latinas, US-born Latinas had stronger associations between low paternal support and wheeze in the offspring than

foreign-born Latinas. One explanation for our findings with respect to paternal support is that compared with both non-Latina White and foreign-born Latinas, US-born Latinas were less likely to be married or living with a partner, more likely to be teenage mothers, and less likely to breastfeed. Although we adjusted for these factors in our models, these patterns suggest there may be other unmeasured and less healthy behaviors during pregnancy, and the additional stress of low paternal support may then be even more detrimental to health in pregnancy and of young offspring among the US-born Latinas.

In our attempt to analyze ethnicity as a potential effect modifier, it should be noted that these stress measures are subsets of validated scales, selected for their ability to predict birth outcomes. In their current form, they were not validated in Latinas and may not have the same ability to predict wheeze in the offspring. This may have resulted in added variability in our estimates, attenuating results. Future studies with validated stress measures in Latinas would be beneficial to more precisely estimate the risk of reported wheeze in their offspring and any explore effect modification by ethnicity.

The few studies that have examined the risk of asthma from prenatal stressors found stronger evidence of an increased risk of asthma in older children (age 7+) (29) and males (26). Our attenuated findings of prenatal stressors and asthmatic symptoms may reflect the difficulty of diagnosing asthma at the young age of our children. In addition, 39.6% of those with asthmatic symptoms in our sample had mothers with atopy, and our wide confidence intervals may reflect heterogeneity in those with asthmatic symptoms and potentially different fetal programming mechanisms that result from prenatal stress in atopic and non-

atopic respiratory disease (22). Finally, we saw suggestions of an increased risk of otitis media from 2+ negative life events and low paternal support. Otitis media results from infection with the hypothesized pathway of HPA alteration in the developing fetus resulting in compromised immune function (45). Little has been published on prenatal stress and infections in human offspring, however, researchers did find an increased risk of hospitalization from any type of infection prior to age 15 in the offspring of mothers who suffered prenatal bereavement (RR 1.31, 95% CI 1.27, 1.35) (46). While our observations for otitis media are only suggestive, more research targeting this outcome may be warranted.

It was not possible in our sample to consider the effect of postnatal psychosocial stressors as we did not ask about postnatal maternal stress in follow up interviews. A recent study found prenatal and postnatal stressors to be correlated (ρ=0.56-0.6 in first 3 years of life) (28), and one could hypothesize that alteration to the HPA axis from prenatal stress could prime the offspring for vulnerability to postnatal stress, further increasing the risk of childhood wheeze. However, given the biologic plausibility of the fetal programming hypothesis and work that has been done to elucidate the role of prenatal stress on immune function in animal models (47,48) and in human cord blood mononuclear cells (49), it is convincing that the mental health and wellbeing of the mother during the prenatal time frame independently contributes to the respiratory health in her offspring.

Strengths of this study include the large population of immigrant Latinas, allowing us to investigate this often-understudied group to examine effect measure modification by

ethnicity and nativity, which, to our knowledge, has not been explored previously. Additionally, using three types of pregnancy stressors and paternal support allowed us to test whether different aspects or types of stress had differential effects on the risk of wheeze, which our data did ultimately not support.

Limitations in our study include that our stressors were recalled 3-6 months postpartum. This allows for the possibility of recall bias if wheezing occurred in the first 3-6 months; however, the similar magnitude in risk ratios observed with current wheeze (in the past 12 months) in sensitivity analyses increased our confidence in the time sequence of events. Another limitation is our single-time point collection of respiratory outcomes, prohibiting the ability to distinguish between transient, persistent, or early or late-onset wheeze. Wheezing phenotypes are not reliably established until the age of six, and are quite different in their risk for subsequent development of asthma (12,13). There was also the potential of selection bias, as we were unable to locate 51% of our sample between 2003 and 2006. However, our analyses utilizing IPCW did not meaningfully change our estimates of interest. Finally, our cohort was at higher risk than the general population as preterm birth may be on the causal path to childhood wheeze. In sensitivity analysis re-weighting the cohort to mirror the population prevalence of preterm birth, estimates remained stable with slightly wider confidence intervals, suggesting that the increased risk of wheeze from prenatal stressors still persists in our sample without the over-contribution from those with higher risk.

New Contribution to the Literature

This work adds to the literature by examining different maternal prenatal stressors and the risk of lifetime wheeze in their offspring, and further exploring differences in the magnitude of risk between Whites and Latinas. As both asthma and wheeze have higher prevalence in minorities and disproportionately affect children (50), the identification of potentially modifiable risk factors such as maternal prenatal stress is of great public health importance. Further, the identification of stressors that may be more detrimental to select races/ethnicities could aid in targeted approaches to reducing maternal stress during this crucial development period.

2.7 Tables and figures

Table 2.1. Demographic and pregnancy characteristics by child wheeze status among respondents to the Environment and Child Health Outcomes Study in Los Angeles County, California, 2006 (n=1193).

	Lifetime Wheeze	
	Yes n=304 (25.5)	No n=889 (74.5)
Maternal age at child's birth		
< 20	18 (5.9)	57 (6.4)
20-24	54 (17.8)	155 (17.4)
25-34	174 (57.2)	476 (53.5)
> 34	58 (19.1)	201 (22.6)
Maternal education		
< 11 years	62 (20.4)	256 (28.8)
12 years	65 (21.4)	209 (23.5)
>13 years	172 (56.6)	404 (45.4)
missing	5 (1.6)	20 (2.5)
Maternal race/ethnicity		
White	79 (26.0)	219 (24.6)
Latina	168 (55.3)	543 (61.4)
Foreign-born	101 (60.1)	383 (70.5)
Black	31 (10.2)	39 (4.4)
Asian/Other	23 (7.6)	82 (9.2)
missing	3 (1.0)	6 (0.7)
Preterm birth		
Preterm (<37 weeks)	137 (45.1)	312 (35.1)
Sex of child		
Male	184 (60.5)	421 (47.4)
Maternal pregnancy smoking		
Nonsmoker	193 (63.5)	600 (67.5)
Former smoker	93 (30.6)	254 (28.6)
Pregnancy smoker	18 (5.9)	35 (3.9)
Current smoker in house		
Yes	6 (2.0)	19 (2.1)
missing	1 (0.3)	0 (0.0)
History of maternal asthma, eczema, hayfever		
Yes	107 (35.2)	162 (18.2)
Annual income		
<$10,000	48 (15.8)	137 (15.4)

$10-30,000	51 (16.8)	161 (18.1)
$30-50,000	64 (21.1)	170 (19.1)
<$50,000	105 (34.5)	318 (35.8)
missing	36 (11.8)	103 (11.6)
Confident of normal birth		
Not at all	27 (8.9)	76 (8.5)
Moderately	73 (24.0)	176 (19.8)
Somewhat	46 (15.1)	105 (11.8)
Very much	158 (52.0)	520 (58.5)
missing	0 (0.0)	12 (1.3)
Fearful about health of baby		
Not at all	85 (28.0)	293 (33.0)
Moderately	71 (23.4)	210 (23.6)
Somewhat	80 (26.3)	236 (26.5)
Very much	67 (22.0)	142 (16.0)
missing	1 (0.3)	8 (0.9)
Chronic stress composite score		
Low (4-8)	151 (49.7)	481 (54.1)
Medium (9-12)	107 (35.2)	293 (33.0)
High (13+)	41 (13.5)	94 (10.6)
missing	5 (1.6)	21 (2.3)
Negative life events		
None (0)	125 (41.1)	463 (52.1)
Moderate (1)	95 (31.3)	244 (27.4)
High (2+)	79 (26.0)	169 (19.0)
missing	5 (1.6)	13 (1.5)
Paternal support composite score		
Low (3-8)	27 (8.8)	45 (5.1)
Medium (9-11)	48 (15.8)	108 (12.1)
High (12+)	226 (74.3)	714 (80.3)
missing	3 (1.0)	22 (2.5)
Months exclusive breastfeeding (mean, sd)	3.1 (3.8)	3.6 (3.8)

Table 2.2. Crude, adjusted and inverse probability of censor weighted risk ratios for lifetime wheeze by stressor among respondents to the Environment and Child Health Outcomes Study in Los Angeles County, California, 2006 (n=1193).

	n (case)/ n (non-case)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)[1]	IPCW adjusted risk ratio (95% CI)[2,3]	Adjusted risk ratio (95% CI) weighted for PTB[4]
Fearful about health of baby					
Not at all	85/293	Reference	Reference	Reference	Reference
Moderately	71/210	1.12 (0.85, 1.48)	1.21 (0.92, 1.60)	1.21 (0.91, 1.62)	1.17 (0.84, 1.62)
Somewhat	80/236	1.13 (0.86, 1.47)	1.04 (0.80, 1.36)	0.98 (0.74, 1.29)	0.94 (0.69, 1.28)
Very much	67/142	1.43 (1.09, 1.87)	1.40 (1.07, 1.83)	1.47 (1.11, 1.94)	1.38 (1.00, 1.91)
Chronic stress (PSS)					
Low	151/481	Reference	Reference	Reference	Reference
Moderate	107/293	1.12 (0.90, 1.39)	1.15 (0.93, 1.43)	1.11 (0.89, 1.40)	1.16 (0.90, 1.49)
High	41/94	1.27 (0.95, 1.70)	1.22 (0.91, 1.63)	1.18 (0.86, 1.63)	1.01 (0.68, 1.50)
Negative life events					
None	125/463	Reference	Reference	Reference	Reference
Moderate (1)	95/244	1.32 (1.05, 1.66)	1.30 (1.04, 1.63)	1.28 (1.00, 1.63)	1.16 (0.88, 1.52)
High (2+)	79/169	1.50 (1.18, 1.90)	1.36 (1.06, 1.75)	1.33 (1.02, 1.74)	1.15 (0.84, 1.57)
Paternal support					
High	226/714	Reference	Reference	Reference	Reference
Moderate	48/108	1.28 (0.99, 1.66)	1.24 (0.95, 1.62)	1.20 (0.90, 1.59)	1.25 (0.92, 1.69)
Low	27/45	1.56 (1.13, 2.15)	1.41 (1.02, 1.96)	1.34 (0.94, 1.59)	1.34 (0.90, 2.03)

[1]Adjusted for maternal race, maternal age, maternal education, preterm birth, month's exclusive breastfeeding,

maternal atopy, child sex, pregnancy smoking and individually adjusted for each stressor.

[2]Inverse probability censor weights (maternal age, race and education). Additionally, model is adjusted for all covariates in previous model.

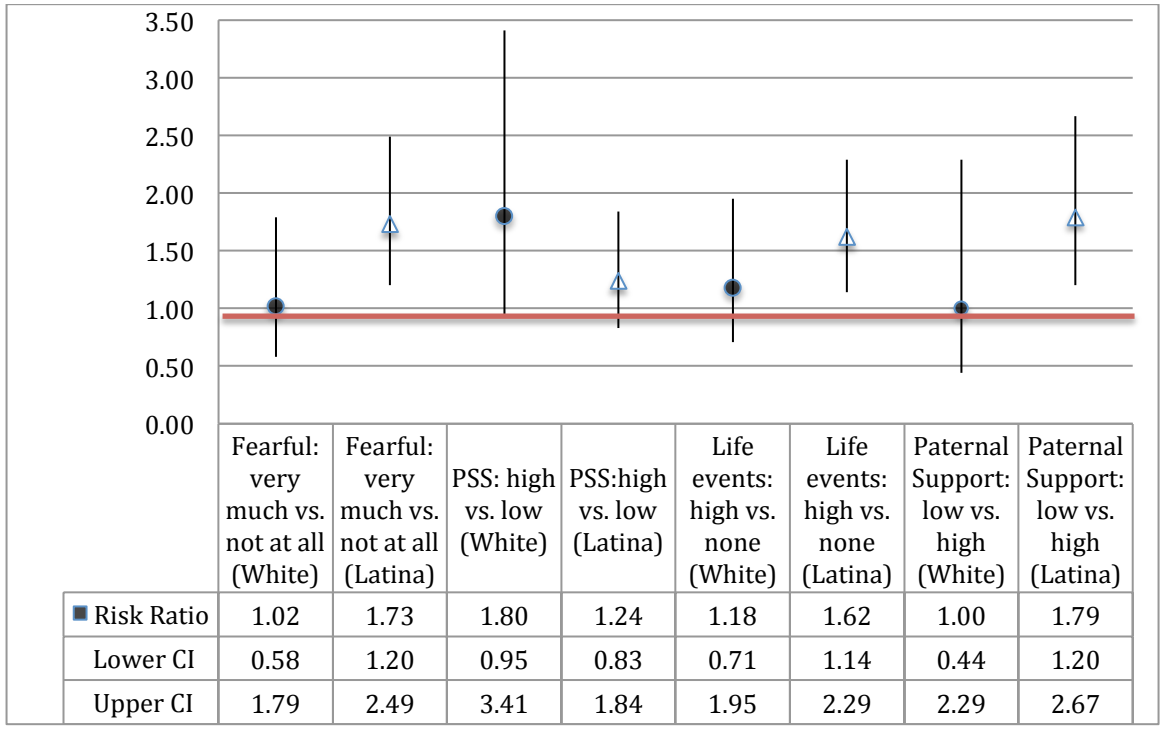
[3]Weighted sample n=2434.

[4]Weighted to adjust PTB to 10% of sample

Table 2.3. Crude and adjusted risk ratios for current wheeze, asthmatic symptoms and otitis media by stressor among respondents to the Environment and Child Health Outcomes Study in Los Angeles County, California, 2006 (n=1193).

	Current wheeze (yes=168)		Asthmatic symptoms (yes=106)		Otitis media (yes=129)	
	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)[1]	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)[1]	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)[1]
Fearful about health of baby						
Not at all	Reference	Reference	Reference	Reference	Reference	Reference
Moderately	0.95 (0.63, 1.43)	1.03 (0.68, 1.55)	1.12 (0.70, 1.89)	1.22 (0.73, 2.05)	1.15 (0.84, 1.59)	1.18 (0.85, 1.62)
Somewhat	1.17 (0.81, 1.70)	1.04 (0.72, 1.50)	1.23 (0.76, 2.01)	1.07 (0.67, 1.71)	1.27 (0.94, 1.72)	1.16 (0.85, 1.57)
Very much	1.45 (0.99, 2.14)	1.45 (1.00, 2.14)	1.43 (0.85, 2.41)	1.39 (0.83, 2.35)	0.99 (0.68, 1.43)	0.96 (0.66, 1.39)
Chronic stress (PSS)						
Low	Reference	Reference	Reference	Reference	Reference	Reference
Moderate	1.02 (0.75, 1.39)	1.03 (0.76, 1.41)	0.75 (0.49, 1.15)	0.75 (0.49, 1.14)	1.17 (0.91, 1.49)	1.42 (1.11, 1.82)
High	1.23 (0.81, 1.87)	1.14 (0.76, 1.72)	1.33 (0.80, 2.21)	1.11 (0.67, 1.86)	0.95 (0.64, 1.42)	1.18 (0.78, 1.77)
Negative life events						
None	Reference	Reference	Reference	Reference	Reference	Reference
Moderate (1)	1.28 (0.92, 1.79)	1.23 (0.89, 1.70)	1.28 (0.84, 1.95)	1.21 (0.80, 1.83)	0.89 (0.67, 1.18)	0.92 (0.69, 1.22)
High (2+)	1.44 (1.01, 2.05)	1.22 (0.85, 1.76)	1.24 (0.77, 1.98)	0.96 (0.58, 1.57)	1.16 (0.87, 1.54)	1.22 (0.91, 1.64)
Paternal support						
High	Reference	Reference	Reference	Reference	Reference	Reference
Moderate	1.37 (0.93, 2.00)	1.35 (0.92, 1.96)	1.56 (0.97, 2.50)	1.54 (0.95, 2.45)	0.92 (0.64, 1.32)	0.98 (0.68, 1.41)
Low	2.06 (1.35, 3.13)	1.82 (1.15, 2.87)	1.96 (1.09, 3.51)	1.54 (0.84, 2.81)	1.19 (0.77, 1.84)	1.45 (0.93, 2.27)

[1]Adjusted for maternal race, maternal age, maternal education, preterm birth, month's exclusive breastfeeding, maternal atopy, child sex, pregnancy smoking and individually adjusted for each stressor.



	Fearful: very much vs. not at all (White)	Fearful: very much vs. not at all (Latina)	PSS: high vs. low (White)	PSS:high vs. low (Latina)	Life events: high vs. none (White)	Life events: high vs. none (Latina)	Paternal Support: low vs. high (White)	Paternal Support: low vs. high (Latina)
Risk Ratio	1.02	1.73	1.80	1.24	1.18	1.62	1.00	1.79
Lower CI	0.58	1.20	0.95	0.83	0.71	1.14	0.44	1.20
Upper CI	1.79	2.49	3.41	1.84	1.95	2.29	2.29	2.67

Figure 2.1. Risk of lifetime wheeze by race/ethnicity. Adjusted risk ratios for lifetime wheeze stratified by race among respondents to the Environment and Child Health Outcomes Study in Los Angeles County, California, 2006 (n=1193). Risk ratios are adjusted with propensity scores for maternal age, maternal education, preterm birth, months of exclusive breastfeeding, maternal atopy, child sex, and pregnancy smoking, and individually adjusted for each stressor.

Chapter III. Study 2: Assessing nativity: breastfeeding and asthmatic symptoms in the offspring of Latinas

3.1 Abstract

Background: Previous research has generally found exclusive breastfeeding to protect against asthma in young children. However, maternal nativity in a Latina population has not been assessed as a potential confounder or effect modifier.

Methods: Using cross sectional data restricted to Latina mothers (n=704) from a birth cohort in Los Angeles interviewed in 2003 and 2006, we estimated risk ratios (RR) for exclusive breastfeeding and asthmatic symptoms in the offspring.

Results: 56 children (8 %) had asthmatic symptoms at age 3.5 years. We found a 49% reduction in risk of asthmatic symptoms with $\geq$3 months of exclusive breastfeeding (aRR=0.51, 95% CI 0.28, 0.90). Foreign-born Latinas were more likely to initiate and continue breastfeeding for at least three months compared with US-born Latinas.

Discussion: Three or more months of exclusive breastfeeding was associated with a reduced risk of asthmatic symptoms in the offspring of Latinas, and we did not find evidence that maternal nativity confounded or modified this association.

3.2 Background

3.2.1 Breastfeeding

Breastfeeding has been investigated as a protective factor against asthma. One hypothesis is that this association is mediated through breastfeeding's protective effects on early respiratory illness (51). Moreover, it has recently been found that asthma and allergy risks are lower when the degree of microbial biodiversity in the gut is higher; notably, exclusive breastfeeding has been hypothesized as one mechanism to establish a higher level of microbial diversity in infancy (52).

3.2.2 Breastfeeding and asthma research

Early studies from the 1980 and 1990's summarized in a meta-analysis of 12 prospective studies reported that exclusive breastfeeding is protective of asthma; 3 months of exclusive breastfeeding reduced the risk of asthma in young children age 1-5 by 30% (OR = 0.70, 95% CI 0.60 - 0.81). Associations were stronger among those with a maternal history of atopy (53). A subsequent meta-analysis in 2007 added three additional prospective studies and confirmed the results for young children aged 1-5, but not for older children (>10 years) (51). Some more recent studies questioned the results for younger children as well. A randomized study of breastfeeding promotion did not find reduced rates of asthma (54), nor did a very large (n=200,000) observational study of 6-7 year olds (55). A longitudinal study of 1,037 children born in New Zealand between 1972-1973 found that breastfeeding during infancy increased risk of asthma at each assessment between ages 9 to 26 years with no differences by maternal history of atopy nor by duration of breastfeeding (56). A

new meta-analysis of breastfeeding and asthma (defined from medical charts or parental report) found a 22% reduction in the pooled odds ratio, with the strongest protection observed in children 0-2 years old, slightly weaker protection in 3-6 year olds, and protection bordering on null in children aged 7 and up. The role of maternal atopy was not assessed (57). The authors of the recent meta analysis concluded that additional work should to be done to analyze potential confounders and mediators such as daycare attendance and early respiratory illness, and to explore potential difference by ethnicity in the relationship of breastfeeding and childhood asthma (57–59).

To our knowledge, there are no studies to date examining the role of characteristics associated with immigration and acculturation that may influence both breastfeeding behaviors and the risk of asthma in the offspring of Latina immigrant and Latina native-born populations living in the US. Overall, Latinas in the US have breastfeeding initiation rates (79.8%) comparable with white women (60). However, within Latinas, nativity predicts breastfeeding behavior, with foreign-born Latinas having higher initiation and duration of breastfeeding than US-born Latinas (61). Additionally, within foreign-born Latinas, longer time spent in the US has been shown to lower both breastfeeding initiation and duration among foreign-born immigrant Latinas (61,62). Asthma rates in Latino children may also differ by the mother's nativity, with a higher prevalence reported in children of US-born Latinas (63) than foreign-born Latinas.

3.3 Hypothesis/aims

We hypothesized that associations between breastfeeding and asthma symptoms in young offspring of Latinas may be confounded or modified by maternal nativity. In order to study this association, we used cross sectional data from a cohort study with oversampling of preterm and low birth weight children in Los Angeles, CA. In analyses restricted to Latinas and their offspring, we examined whether exclusive breastfeeding reduces the risk of asthmatic symptoms in our population of young (3.5 year old) children born to Latina women, and assessed possible effect measure modification by maternal nativity.

3.4 Study materials and methods

3.4.1 Subject selection

The ECHOS cohort was described previously in section 2.3.1. For this analysis, we included a subset of the ECHOS cohort who self-identified as being of Latina ethnicity (n=704).

3.4.2 Outcome definitions

In the 2006-2007 interviews, asthmatic symptoms were assessed via maternal report according to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire for 6-7 year olds (39). We asked all questions in the core questionnaire wheezing module, in addition to "has a doctor said your child has asthma?" "age at doctor diagnosed asthma," and "has your child visited the emergency room because of asthma?" We here will define our outcome as 'doctor diagnosed asthma' combined with 'dry cough at

night occurring in the past 12 months' and/or 'any history of wheezing or whistling in the chest.'

3.4.3 Exposure and covariate definitions

Mothers reported the number of months of both total (any breastfeeding) and exclusive breastfeeding (breastfeeding without formula or food supplementation) in the follow up interview (2006/7). We categorized exclusive breastfeeding as 0 months, 1-2 months, ≥3 months, and < 3 vs ≥3 months in sensitivity analysis and stratified analysis assessing effect measure modification.

In EPOS interviews (3-6 months postpartum), mothers reported duration of total (any) breastfeeding (or ongoing if currently breastfeeding) which were categorized into 0 months, 1-2 months, ≥3 months.

Covariates collected from the 2002 birth certificates and from the 2003 follow-up survey interview included maternal age, maternal education, maternal nativity, income, maternal pregnancy smoking, preterm birth, antibiotics in breast milk, insurance type, and work outside of the home in pregnancy. In the 2006-2007 follow-up interviews, we collected data on smoking in the residence, both maternal and paternal history of atopy, pets in the home before age 1, daycare before age 1, doctor diagnosed bronchitis and doctor diagnosed severe cold or flu before age 1, number of residents in the household under age 18, maternal birthplace and preferred language if the participant identified as Latina/Hispanic (as a proxy for acculturation), and years lived in the US among the foreign-born Latinas.

3.4.4 Statistical analyses

We estimated risk ratios (RR) for the effect of exclusive breastfeeding on the child's asthmatic symptoms using Poisson regression models with robust error variance and a log link function (43). Multivariate analysis was conducted including potential confounders added sequentially. Retained covariates (on the basis of previous literature (58) or changing the effect estimate by >10%) included preterm birth, maternal education, maternal age, maternal pregnancy smoking, parental history of atopy, and income. Maternal nativity, insurance type, pets in the home, daycare, antibiotics in breast milk, doctor diagnosed bronchitis, doctor diagnosed severe cold/flu before age 1, number of other residents in home under 18, and work outside of the home did not change the effect estimate for exclusive breastfeeding and were removed from the multivariate analysis. There were too few respondents who affirmed smokers in the house, thus the variable could not be included.

Information for income was missing in 16.2% of responses, thus multiple imputations were performed utilizing standard SAS procedures with 5 imputation datasets to replace all missing values. The effect estimate for exclusive breastfeeding did not change appreciably (<5%), thus to maintain a sufficient sample size the imputed datasets were used in final multivariate models and for propensity score adjustment. Propensity scores were calculated by regressing exclusive breastfeeding on all aforementioned retained covariates in a multinomial logistic regression, with inclusion of the predicted probabilities of

exposure in the final model. Fully adjusted models and propensity score adjusted models are both reported.

Effect measure modification was assessed by examining risk ratios in stratified analyses. Maternal nativity was assessed for our main hypothesis, and preterm birth and maternal history of atopy were assessed in sensitivity analyses. Risk estimates for the stratum with a positive maternal history of atopy did not converge due to the small sample size and number of covariates for adjustment; however, we were able to estimate the risk in all strata using propensity score adjustment. Dichotomous breastfeeding (<3 months vs. $\geq$3 months) was used as the exposure due to small cell sizes in the strata.

In additional sensitivity analyses, we explored the risk of asthmatic symptoms and exclusive breastfeeding using <3 months of exclusive breastfeeding as the reference group. We also explored predictors of breastfeeding initiation and duration using Poisson regression with robust error variance and a log link function adjusting for nativity, education, age, daycare attendance prior to age 1 year and work outside the home during pregnancy. In a model restricted to foreign-born Latinas only, we also included years lived in the US (continuous).

Finally, in an attempt to validate our cross sectional ECHOS data with longitudinal EPOS breastfeeding estimates collected at 3-6 months postpartum, we compared the percentages of respondents between EPOS and ECHOS who reported months of total breastfeeding, and compared the unadjusted risk estimates for asthmatic symptoms in those with 3+ months

of total breastfeeding as reported by respondents during EPOS interviews and ECHOS interviews.

The UCLA Office for Protection of Research Subjects and the California State Committee for the Protection of Human Subjects approved this research; informed consent was obtained from the women.

3.5 Results

Table 3.1 provides demographic characteristics for our study participants. In the ECHOS sub-sample of children born to Latina mothers (n=704), 56 (8.0%) had asthmatic symptoms (doctor diagnosed asthma with wheeze (n=28) or dry cough (n=3) or both (n=25). Children with asthmatic symptoms were more likely to be born to US-born women, to women who smoked prior to pregnancy, and were exclusively breastfed for shorter durations.

When examining demographic characteristics by nativity (supplemental table 3.4) several factors differed; in particular US-born Latinas were younger, had more years of formal education and were more likely to have given birth to a child who developed asthmatic symptoms than foreign-born Latinas.

Foreign-born Latinas were more likely to initiate breastfeeding (RR 1.19 95% CI 1.07, 1.32) and more likely to breastfeed for a minimum of 3 months (RR 1.45 95% CI 1.15, 1.80) as

compared with US-born Latinas after adjusting for age, education, daycare and work outside the home in pregnancy. Years lived in the US did not predict breastfeeding initiation or duration in foreign-born Latinas (data not shown).

The children's risk of asthmatic symptoms in relation to 3+ months of exclusive breastfeeding was reduced by 49% (RR=0.51, 95% CI 0.28, 0.90) in multivariate models adjusted using propensity scores (Table 3.2). We did not find evidence of confounding or effect measure modification by maternal nativity (data not shown). The reduction in risk of asthmatic symptoms was not as strong when the reference group included women who breastfed for <3 months (Table 3.2).

In sensitivity analyses, there was a suggestion of effect measure modification by maternal history of atopy with the reduced risk of asthmatic symptoms from breastfeeding being lower among children of mothers without a history of atopy; however the number of mothers with history of atopy was small (Table 3.3). There was no effect measure modification observed by preterm birth (data not shown).

Finally, there was 78.2% concordance in reporting total breastfeeding between EPOS and ECHOS. This was strongest in the category of 3+ months (95.2%) and weakest in the category of 1-2 months (41.9%). Crude risk ratios for asthmatic symptoms with 3+ months of total (any) breastfeeding using EPOS (longitudinal) data were RR=0.57 (95% CI 0.31, 1.05) and ECHOS (cross sectional) data RR=0.53 (95% CI 0.30, 0.92).

3.6 Discussion

Using cross sectional data from a cohort study restricted to Latinas, exclusive breastfeeding for 3 or more months was associated with a reduced risk of asthmatic symptoms in their offspring by 49% in adjusted models. We found no evidence that risk reduction from breastfeeding was modified or confounded by nativity of the mother.

We were interested in maternal nativity in Latinas as immigration and acculturation may be related to both asthma risk in the offspring and breastfeeding in this dominant minority in the US. While breastfeeding initiation and duration in Latinas is comparable to whites (60), there is considerable heterogeneity of breastfeeding within Latinas by nativity: US-born Latinas initiate less and breastfeed for shorter time than foreign-born Latinas (61,62,64). Furthermore, time lived in the US as a measure of acculturation is a negative predictor of breastfeeding, with increasing time of residency in the US leading to less breastfeeding (61,65). Similarly in our sample, US-born Latinas were less likely to initiate breastfeeding and had shorter duration of exclusive breastfeeding than foreign-born Latinas. However, among our foreign-born (75.6% Mexican origin) Latinas, we did not observe any reduction in the initiation or duration of exclusive breastfeeding with years lived in the US in either crude models or models adjusted for socio-demographic variables. Although the median time lived in the US among our immigrant Latinas was 15 years, breastfeeding practices remained similar for recent and long-time immigrants. One possible explanation for this is the relative homogeneity in our Latina foreign-born immigrant population: 80% had a 12^{th} grade education or less, and of those reporting income, 80% earned $30,000 or less a year. Although low education and income are

generally negative predictors for breastfeeding in White women, they have been reported to not be as strong of determinants for breastfeeding behaviors in Latinas (61), and in our sample may represent a group who resisted such "negative acculturation" despite the duration lived here, and have retained breastfeeding behaviors from their home countries.

Foreign maternal nativity has previously also been studied as a protective factor for asthma in Mexican-Americans. In a predominantly Mexican-American sample of Latinos in Los Angeles, CA, 0-17 year old children of immigrant mothers exhibited a lower odds ratio of asthma (OR 0.64, 95% CI 0.44-0.94) than those born to US-born mothers (63). While our data was initially suggestive of a lower risk of asthmatic symptoms in offspring of foreign-born Latinas (crude RR= 0.67, 95% CI 0.41, 1.12), the results were attenuated in multivariate models that included exclusive breastfeeding (RR=0.79, 95%CI 0.44, 1.41). The previous study of LA children did not adjust for breastfeeding (63). This suggests breastfeeding may influence risk of asthmatic symptoms while maternal nativity may only be an indicator of breastfeeding practices.

Some studies have found either no or an increased risk of asthma with breastfeeding (56,66,67). These inconsistencies may be due to differences in phenotypes and related to the age of the child. The protective effect of breastfeeding appears to attenuate in older children, with the most pronounced effects found in children under the age of 3 (58,66,68). Indeed, wheezing that may get diagnosed as "asthma" in young children is heterogeneous; as many as 6 wheezing phenotypes have been identified in longitudinal studies, and are quite different in their risk for subsequent development of asthma (12). These phenotypes cannot be established reliably until the child reaches age 6 (13); thus given our single time

point of assessment, what is classified by health care providers as asthma at this young age may in fact be transient wheeze. Given that we found stronger protection for those without a maternal history of atopy, our results may be strongly influenced by transient wheezers in our population. However, our findings relied on few women reporting atopy (n=84; 11.9% of the sample) and confidence limits overlapped largely for both estimates.

Categorizations used for breastfeeding and the choice of reference group may also result in heterogeneous effects. A large cluster randomized study conducted in Belarus, found no association between breastfeeding intervention and asthma at age 6.5, but both the intervention and control groups included a substantial proportion of women who breastfed, thus these null results are difficult to interpret (69). We observed stronger reduction in risk of asthmatic symptoms from exclusive breastfeeding in analysis using 0 months of exclusive breastfeeding as the reference as compared to a reference of <3 months of exclusive breastfeeding. This suggests that any duration of exclusive breastfeeding reduces the risk, and including short duration of exclusive breastfeeding in the reference group as done in previous studies may underestimate the protective benefits that any breastfeeding offers.

Strengths of this study include the large proportion of immigrant Latinas, enabling us to study the association of breastfeeding and asthmatic symptoms in an understudied population, and to simultaneously investigate the role of maternal nativity. Also, we have a sample rich in covariate information linked to birth certificate data for multivariate adjustment, including detailed duration of exclusive breastfeeding, daycare attendance, parental atopy, pets, and child bronchitis/cold and flu history. These latter covariates

allowed us to explore the hypothesis that the benefits from breastfeeding might be due to a reduction in virus-associated wheeze (59,67). However, including both bronchitis and severe cold/flu prior to one year in our models did not change the estimate for breastfeeding.

Limitation to our study include the young age of children studied, as wheeze and "doctor diagnosed asthma" may in fact be transient wheeze and thus may not be consistent with actual chronic asthma in later childhood. Additionally, the ISAAC questionnaire was not validated for children aged 3-4 in our sample. Another potential limitation is maternal recall of breastfeeding; women reported duration of breastfeeding when the child was 3.5 years old, and there may be correlation between the self-reported outcome and exposure. However, there is evidence that women recall breastfeeding quite well (70), and as this study was not specifically aimed at studying breastfeeding or asthma and a range of questions were administered, the likelihood of strongly correlated self-report is reduced. Additionally, using total breastfeeding estimates collected in both EPOS and ECHOS interviews, we found high concordance in breastfeeding reporting (95.2% in those reporting 3+ months and 78.2% in those reporting no breastfeeding between the two interviews), which resulted in very similar risk estimates between total breastfeeding and asthmatic symptoms in the both the longitudinal and cross sectional data. Finally, this cohort contains a large portion of preterm births (38.6%), which may limit generalizability. However, sensitivity analyses re-weighting preterm birth to 10% of the population did not meaningfully change our estimates. In post-hoc sensitivity analysis, we excluded births prior to 36 weeks of gestation to determine whether our observed association was biased

by those very preterm that may not be able to breastfeed and be at a higher risk of asthmatic symptoms. The association between breastfeeding and asthmatic symptoms changed minimally (RR 0.45, 95% CI 0.22, 0.92; n=524).

New contributions to the literature

Our study suggests that duration of breastfeeding may need to be considered in Latino populations, and that maternal nativity (i.e. US-born status) may be a risk factor for asthma at least in part because it is related to breastfeeding behavior. Also of interest, we found that breastfeeding practices did not change with length of residency in foreign-born (predominantly Mexican) Latinas in Los Angeles. This suggests that there are factors that determine breastfeeding practices in this population that if better understood could be also be used to design and target programs that promote this beneficial behavior among US-born Latinas.

3.7 Tables

Table 3.1. Demographic and Pregnancy Characteristics by Child Asthmatic Symptoms among Latina respondents to the Environment and Child Health Outcomes Study in Los Angeles County, California, 2006 (n=704).

	Asthmatic symptoms[a]	
	Yes	No
	n=56 (8.0)	n=648 (92.0)
Maternal Age		
< 20	5 (8.9)	57 (8.8)
20-24	11 (19.6)	164 (25.3)
25-29	18 (32.1)	171 (26.4)
30-34	16 (28.6)	161 (24.9)
≥ 34	6 (10.7)	95 (14.7)
Maternal Education		
< 8 years	8 (14.3)	119 (18.7)
9-11 years	10 (17.9)	158 (24.8)
12 years	16 (28.6)	195 (30.6)
13-15 years	16 (28.6)	96 (15.1)
≥ 16 years	6 (10.7)	69 (10.8)
Maternal nativity		
Foreign-born	33 (58.9)	446 (68.8)
Income		
<$10k	18 (32.1)	138 (21.3)
$10k-<$30k	16 (28.6)	261 (40.3)
$30k-<$50k	10 (17.9)	77 (11.9)
≥$50k	5 (8.9)	65 (10.0)
missing	7 (12.5)	107 (16.5)
Maternal pregnancy smoking		
Nonsmoker	35 (62.5)	486 (75.0)
Former smoker	19 (33.9)	148 (22.8)
Pregnancy smoker	2 (3.6)	14 (2.2)
Preterm birth		
Preterm (<37 weeks)	26 (46.4)	246 (38.0)
Antibiotics in breastmilk		
Yes	5 (8.9)	56 (8.6)
Insurance		
Public	35 (62.5)	444 (68.5)
Work outside of the home in pregnancy		
Yes	32 (57.1)	332 (51.2)
missing	1 (1.8)	4 (0.6)

Smoking inside of the home		
No	56 (100.0)	636 (98.1)
Yes	0 (0.0)	9 (1.4)
Yes, child not at home	0 (0.0)	3 (0.5)
History of maternal asthma, eczema, hayfever		
Yes	11 (19.6)	73 (11.3)
History of paternal asthma, eczema, hayfever		
Yes	5 (8.9)	47 (7.2)
Pets before age 1		
Yes	12 (21.4)	130 (20.1)
missing	0 (0.00)	2 (0.3)
Daycare before age 1		
Yes	6 (10.7)	35 (5.4)
missing	1 (1.8)	16 (2.5)
Doctor diagnosed bronchitis		
Yes	14 (25.0)	48 (7.4)
Doctor diagnosed severe cold/flu before age 1		
Yes	31 (55.4)	177 (27.4)
missing	0 (0.00)	2 (0.31)
Exclusive breastfeeding (months)		
$\geq$ 3 months	19 (33.9)	310 (47.8)
missing	0 (0.0)	8 (1.2)
Exclusive breastfeeding (months)		
0 months	30 (53.6)	224 (34.6)
1-2 months	7 (12.5)	106 (16.4)
$\geq$3 months	19 (33.9)	310 (47.8)
missing	0 (0.0)	8 (1.2)
Number of residents under age 18 (mean, sd)	1.18 (1.2)	1.37 (1.2)

[a] Defined by doctor-diagnosed asthma with wheeze and/or dry cough.

Table 3.2. Crude, multivariate and propensity adjusted risk estimates for asthma with exclusive breastfeeding in a Latina population from the Child Health Outcomes Study in Los Angeles County, California, 2006 (n=704).

	N case/ non-case	Crude model[a] (n=696)	N case/ non-case	Multivariate model imputed (n=704)[a,b]	Propensity adjusted model (n=704)[a,c]
Exc. breastfeeding (months)					
0 Months	30/224	Reference	30/224	Reference	Reference
1-2 months	07/106	0.52 (0.24, 1.16)	7/108	0.49 (0.22, 1.07)	0.47 (0.21, 1.05)
≥ 3 months	19/310	0.49 (0.28, 0.85)	19/316	0.52 (0.29, 0.91)	0.51 (0.28, 0.90)
Exc. breastfeeding (months)					
< 3 months	37/330	Reference	37/331	Reference	Reference
≥ 3 months	19/310	0.57 (0.34, 0.98)	19/317	0.62 (0.36, 1.06)	0.62 (0.36, 1.07)

[a] RR (95% CI).

[b] Multivariate model adjusted for preterm birth, maternal age, maternal education, pregnancy smoking, parental history of asthma/eczema/hayfever, and income.

[c] Propensity scores include all covariates in the multivariate model.

Table 3.3. Effect measure modification of risk ratios of breastfeeding and asthmatic symptoms by maternal history of asthma/eczema/hayfever in a Latina population from the Child Health Outcomes Study in Los Angeles County, California, 2006 (n=704).

Exclusive breastfeeding (in months)	N case/ non-case	Crude model[a]	N case/ non-case	Multivariate model[a,b]	Propensity adjusted model[a,c]
Positive maternal history (n=84)					
< 3 months	07/ 40	Reference	07/ 40	Reference	Reference
≥ 3 months	04/ 33	0.73 (0.23, 2.29)	04/ 33	n/a[d]	0.72 (0.23, 2.22)
Negative maternal history (n=620)					
< 3 months	30/ 290	Reference	30/ 291	Reference	Reference
≥ 3 months	15/ 277	0.55 (0.30, 1.00)	15/ 284	0.57 (0.32, 1.06)	0.59 (0.32, 1.10)

[a] RR (95% CI).

[b] Multivariate model adjusted for preterm birth, maternal age, maternal education, pregnancy smoking, parental history of asthma/eczema/hayfever, and income.

[c] Propensity scores include all covariates in the multivariate model.

[d] Model did not converge due to small cell sizes in multivariate model.

Supplemental table 3.4: Demographic and Pregnancy Characteristics by maternal nativity status in the Latina subset of the Environment and Child Health Outcomes Study in Los Angeles County, California, 2006 (n=704).

	Maternal Nativity	
	US-born n=225 (32.0)	Foreign-born n=479 (68.0)
Maternal Age		
< 20	36 (16.0)	26 (5.4)
20-24	73 (32.4)	102 (21.3)
25-29	69 (30.7)	120 (25.1)
30-34	35 (15.6)	142 (29.7)
≥ 34	12 (5.3)	89 (18.6)
Maternal Education		
< 8 years	3 (1.3)	124 (25.9)
9-11 years	41 (18.2)	127 (26.2)
12 years	88 (39.1)	123 (25.7)
13-15 years	60 (26.7)	52 (10.9)
≥ 16 years	30 (13.3)	45 (9.4)
missing	3 (1.3)	8 (1.7)
Income		
<$10k	31 (13.8)	125 (26.1)
$10k-<$30k	85 (37.8)	192 (40.1)
$30k-<$50k	36 (16.0)	51 (10.7)
≥$50k	42 (18.7)	28 (5.9)
missing	31 (13.8)	83 (17.3)
Pregnancy smoking		
Nonsmoker	139 (61.8)	382 (79.8)
Former smoker	73 (32.4)	94 (19.6)
Pregnancy smoker	13 (5.8)	3 (0.6)
Preterm birth		
Preterm (<37 weeks)	90 (40.0)	182 (38.0)
History of maternal asthma, eczema, hayfever		
Yes	47 (20.9)	37 (7.7)
Insurance type		
Public	110 (48.9)	369 (77.0)
Breastfeeding initiation		
Yes	158 (70.2)	405 (84.6)
Exclusive breastfeeding (months)		
≥ 3 months	75 (33.3)	254 (53.0)
missing	1 (0.4)	7 (1.5)
Work outside the home in pregnancy		

Yes	147 (65.3)	217 (45.3)
missing	2 (1.0)	3 (0.6)
Daycare under 1		
Yes	21 (9.3)	20 (4.2)
missing	7 (3.1)	10 (2.0)
Asthmatic symptoms* in offspring		
Yes	23 (10.2)	33 (6.9)
Years lived in US (mean, sd)	N/A	15.0 (8.1)
Months of exclusive breastfeeding (mean, sd)	2.17 (3.0)	3.60 (4.3)

* Asthmatic symptoms include doctor-diagnosed asthma with wheeze and/or dry cough.

Chapter IV. Study 3: Psychosocial stressors and lung function in youth: an examination by stressor, age and sex.

4.1 Abstract

Background: Previous research on the impact of psychosocial stressors on children and adolescent's lung function is limited, and has primarily relied either on parental stress measures or parental-reported stressors of the child, which may be a poor proxy for perceived stress in youth, particularly older youth. The present study explores both the individual and caregiver's measures of self-reported stressors to predict lung function in youth ages 10-17 years after adjusting for the effects of air pollution.

Methods: Using spirometry measures of FVC, FEV_1 and FEF_{25-75} from 584 youth from the Los Angeles Family and Neighborhood Survey, we performed multivariate linear regression with robust standard errors to assess the effects of several self-reported psychosocial stressors (family fighting, unsafe neighborhood and school), negative internalizing behaviors (Behavioral Problems Index-Internalizing), absence of a father, caregiver Pearlin Self Efficacy and a summary stress score in models stratified by sex and age, adjusting for $PM_{2.5}$ and potential confounders.

Results: No consistent results were seen between self-reported stressors, parental stressors, or negative behaviors and lung function in youth. We observed a suggestion of reduced lung function in males from family fighting (FEV_1: -156.2ml, 95% CI 327.8, 15.5), absence of a father in the house (FEV_1: -176.2ml, 95% CI -322.7, -29.7) and the summary stress score (FEV_1: -45.6ml, 95%CI -97.6, 6.3), which were all stronger in older males ages 15-17. Additionally, feeing unsafe at school reduced lung function in younger, but not older, youth (FEV_1: -129.8ml, 95% CI-241.4, -18.2). None of the measures were associated with reduced lung function in females.

Conclusions: This research informs a very limited literature on psychosocial stressors and lung function in youth. Although we were unable to consistently show associations between selected psychosocial stressors and lung function, further exploration of gender differences in youth psychosocial stressor response on lung function may be warranted.

4.2 Background

Recently, researchers have begun investigating whether psychosocial stressors, previously associated with asthma and wheeze (71–76), are also associated with decreased lung function (17,77,78). Lung function, measured with spirometry, steadily increases throughout childhood and adolescence, plateauing after puberty. Individuals with lower lung function by early adulthood have increased risk of both all-cause mortality and ischemic heart disease mortality independent of smoking status (15). Other factors

associated with inflammation including asthma, smoking, and respiratory infections increase risk of impaired lung function (17). Chronic perceived stress may alter a child's organ development through the differential expression of genes involved in the hypothalamus-pituitary-adrenal (HPA) axis (22,23). The HPA axis' altered reactivity to psychosocial stressors may also modulate immune function later in life (22), potentially heightening inflammatory activity (79) and generating susceptibility to environmental insults such as air pollution.

4.2.1 Previous literature of psychosocial stressors and childhood/adolescent lung function

The literature examining psychosocial stressors and lung function in children and adolescents is limited and inconsistent. Of the three previous studies, one study in East Boston did not account for air pollution but found that the child's exposure to violence as measured by interparental conflict (spousal psychological or physical attacks reported by the parent) was associated with reduced lung function in 6-7 year old girls only, while the child's exposure to community violence (as reported by the parent) was associated with reduced lung function in boys only (17). Another study of children ages 11-13 years conducted in the United Kingdom found that neither self-reported racism nor $PM_{2.5}$ or PM_{10} air pollution predicted lung function (78). The third study from Southern California reported that maternal psychosocial stress did not independently predict lung function, but maternal psychosocial stress modified the impact of air pollution on lung function impairment in 11 year-old children. This last analysis relied solely on maternal stress assessed with a 4-question Perceived Stress Scale (PSS) (77). Measures of parental stressors (PSS) or those reported by the parents (exposure to violence) may not reflect the

psychosocial stress that youth perceive. Particularly as a child ages into adolescence, it is important to capture their own perception, as peer networks may alter their perceived stress and their social positions and the roles they occupy in the family might change considerably. Additionally, given the heterogeneity of perceived stressors and coping mechanisms that are influenced by the ethnic culture, sex and socio-economic status (SES), utilizing measures for different types of potential stressors is crucial in identifying where vulnerabilities exist.

4.3 Hypothesis/aims

Here, we use data from the Los Angeles Family and Neighborhood Survey (L.A.FANS-2), a population based cohort from Los Angeles County, CA that collected several self-reported psychosocial stressors from youth and their primary caregivers. Using cross-sectional data in a study that over-sampled low-income families, we explored whether self-reported psychosocial stressors (family fighting, unsafe neighborhood or school), negative internalizing behaviors (Behavioral Problems Index-Internalizing: BPI-INT), absence of a father in the home, low caregiver self-efficacy (Pearlin Self Efficacy (PSE)) or a summary stress score predict lung function in youth ages 10-17 after adjusting for $PM_{2.5}$ air pollution exposure and other potential confounders. We further stratified models by sex and age to explore possible modification by age or gender.

4.4 Study materials and methods

4.4.1 Subject selection

Los Angeles Family and Neighborhood Survey 2

We used data from the Los Angeles Family and Neighborhood Survey wave 2 (80,81). Briefly, L.A.FANS was conducted in two waves. The first wave (L.A.FANS-1) sampled 3,090 households from 65 neighborhoods in Los Angeles County in 2000-2001, interviewing 3,140 children ages 0-17. Households were sampled from three neighborhood strata: very poor, poor and not-poor with oversampling of very poor and poor census tracts and of households with children, with an overall response rate of 89%. In 2006-2008, L.A.FANS-2 re-interviewed L.A.FANS-1 participants and added additional households within the sampled neighborhoods. Excluding children who participated in the Wave 1 survey who were more than 18 years old when the Wave 2 survey re-enrolled Wave 1 participants, there were 1,091 children who were re-interviewed (64% response rate); also, 296 additional children from new families were added to the sample, for a total of 1,387 children. To minimize lung function measurement issues in younger children and allow us to assess older youth's self-reported psychosocial stressors, we included only those between ages 10-17 years in our analyses and with a reproducible spirometry curve (n=584).

4.4.2 Outcome definitions

Of the 1,387 children in L.A.FANS-2, 1,070 children aged 5-17 years participated in spirometry assessments via EasyOne™ portable spirometers, which measured forced vital

capacity (FVC), forced expiratory volume after 1 second (FEV_1), and forced expiratory mean flow between 25% and 75% of FVC (FEF_{25-75}). Of the 775 children with at least one acceptable curve for analysis utilizing ATS guidelines (82), 584 children were between 10-17 years of age.

4.4.3 Exposure and covariate definitions

Psychosocial stressors (exposure)

Self-reported: Youth self-reported whether people in their family fight a lot (yes vs. sometimes/no), whether they felt safe in their neighborhood (yes vs. sometimes/no) and whether they feel safe at school (yes vs. sometimes/no).

Caregiver-reported: The primary caregiver reported on the youth's behavioral/emotional health based on the Behavioral Problems Index (BPI), a measure of the frequency, type and range of behavior problems in children four years and older (83). The internalizing subscale (BPI-INT) is comprised of 11 questions and meant to measure 'over-control' of emotions, including withdrawn and sad behaviors. A summary score for internalizing behaviors subscale was created with lower scores signifying fewer internalizing behavioral problems. In 95.5% of the sample, the caregiver interviewed was the biological/adoptive mother. The other 4.5% either had a mother in the house that was not able to respond (1.5%) or did not live with their mother (3%) and thus had a non-maternal primary caregiver respond.

The primary caregiver also completed the Pearlin Self-Efficacy Scale (PSE) (84), a 7-question scale about their own beliefs and capabilities with questions such as "I often feel

helpless in dealing with the problems of life." Likert scale responses ranged from 1=strongly agree to 4=strongly disagree. We summed responses (reverse coding where necessary) to create a variable with low scores signifying low self-efficacy. Finally, the head of household reported whether the father of each child currently lives in the house.

Summary score: In an effort to measure the effects of multiple psychosocial stressors, we created a summary stress score by assigning one point for each of the six psychosocial stressors reported. Reports of family fighting, unsafe neighborhood, unsafe school, and absence of the father each received one point. Ordinal variables were assigned 1 point if they fell above the 75th percentile of the distribution. BPI-INT was scored one point if values were over 4, and caregiver PSE received one point if it was below 18. The final summary stress score ranged from 0-6.

Air pollution estimates

Our air pollution estimates have been described previously in detail (85). For this analysis, we adjusted models with inter-quartile range units of $PM_{2.5,}$, based upon its association with spirometry measures in both sexes (FEV males: -47.9ml, 95% CI -92.3, -3.6); (FEV females: -56.9ml, 95% CI-103.2, -10.6) adjusted for federal poverty level, household smoking, race, height, height-square, weight, weight-square , and maternal education. $PM_{2.5}$ estimates were generated by kriging available government monitoring data for the years 2002 and 2000, respectively. We used annual average measures of $PM_{2.5}$ at both residences and schools and weighted for time spent in each location in the past 12 months.

Child/household socio-demographic covariates

The following covariates were assessed in the survey and explored as covariates: youth's sex, age, race/ethnicity, and nativity were collected from the head of the household, as well as income used to calculate the household federal poverty level (FPL). Trained interviewers measured the youth's height and weight. Youth self- reported smoking behavior, and whether they like to read, walk to activities, or engage in sports. Finally, the primary caregiver reported maternal education, any reported smoking in the house, and the youth's asthma history and wheeze within the past 12 months.

4.4.4 Statistical analyses

FVC, FEV_1 and FEF_{25-75} were stratified by sex and confirmed to have normal distributions. In the sample of children aged 10-17, multiple linear regression was performed, creating individual models for each stressor (BPI-INT, family fighting, unsafe neighborhood, unsafe school, absence of father in the house, caregiver PSE and the summary stress score) and lung function measure (FVC, FEV_1, FEF_{25-75}), unadjusted and adjusted for potential confounders, including $PM_{2.5}$, child's age, FPL, smokers in the house, child's race/ethnicity, maternal education, height, height-square, weight, weight-square, and in models that included both sexes, sex and sex*age. Few youth (n=10) reported smoking, and inclusion in the models did not change estimates for air pollutants or stressors and we thus did not control for it in the final models. Robust standard errors were included to adjust for non-independence of sibling data. Models were stratified by age group (10-14, 15-17 years) and by sex to examine any potential effect modification. Finally, models were created with a stressor*sex interaction term.

Given the previous literature linking both air pollution and psychosocial stressors to childhood asthma (35,72,73,86), reduced lung function may be on the causal path to asthma and thus the child's previous asthma history should not be included in the models. Thus, in additional sensitivity analyses, we excluded those children who had a doctor's diagnosis of asthma with wheeze in the past 12 months (n=42).

The UCLA Office of the Human Research Protection Program and RAND approved this research; informed consent/assent was obtained from the subjects.

4.5 Results

Of the 584 youth with spirometry data from L.A.FANS-2, the mean age was 13.5 years, and the majority were US-born Hispanic with over 50% living at or below 200% of the federal poverty level. While only 10 individuals reported smoking, 22.3% lived in a house with a smoker. Boys were more likely to have doctor-diagnosed asthma with wheeze in the past 12 months. There was little difference by sex for BPI-INT, caregiver PSE, summary stress score, perceived school safety, family fighting or the absence of a father in the household. Males were more likely to feel that their neighborhood was safe (Table 4.1). $PM_{2.5}$ had a mean of 8.5μm/m3 with a range of 23.7 μm/m3 and inter-quartile range of 2.3 μm/m3.

Results were not consistent when stratified by age group as shown in Table 4.2. 10-14 year olds who reported an unsafe school had a reduced FEV_1 (-129.8ml, 95% CI -241.4, -18.2). While many coefficients were negative, all other psychosocial stressors and lung function estimates were imprecise and included the null values.

When stratified by sex (Table 4.3), there was a suggestion of a negative association between family fighting and both FVC and FEV_1 in males after adjusting for age, FPL, household smoking, race/ethnicity, maternal education, and height and weight variables, but confidence intervals crossed the null. Similarly, FVC and FEV were reduced by the reported absence of a father in males, while FEF_{25-75} increased in females. Males reporting more psychosocial stressors (summary stress score) had a reduced FEV_1, but confidence intervals included the null, only suggesting an association. There were no additional associations between selected psychosocial stressors and lung function observed in females or males.

In analyses (data not shown) that included both family fighting and absence of the father in models stratified by sex, the effect estimates observed in single stressor models were relatively unchanged.

When sex*stressor interaction terms were included into models adjusted for FPL, household smoking, height and weight variables, sex and sex*age, the interactions terms were statistically significant between sex and absence of the father (p=0.009) as well as family fighting (0.06). The interaction was close to statistically significant between summary stress score and sex (p=0.13). When stratified by sex and age (Figure 4.1), each of the psychosocial stressors had the largest coefficients for reduction of FEV_1 in older males 15-17 years of age; FEV_1 estimates were largely null in younger males and females, and

older females had slightly higher FEV_1 estimates, although most confidence intervals crossed the null.

In sensitivity analyses excluding asthmatics with wheeze in the past 12 months from analyses, point estimates of the stressors remained within 10% of the original models' estimates i.e. they results generally did not change (data not shown).

4.6 Discussion

Our data suggests that in males but not females, and particularly those ages 15-17, there may be an association between reduced lung function and the absence of a father in the house, self-reported family fighting or from multiple psychosocial stressors. Additionally, we observed a negative influence on FEV_1 from feeling unsafe at school in youth 10-14 years of age, but these effects were not seen from feeling unsafe in neighborhood environments, negative internal emotions or low caregiver self-efficacy.

Our aim was to add to the literature on lung function and stress by examining a range of psychosocial stressors that may better characterize youth's stress than the measures previously examined. Stress theory informs us that external circumstances that challenge us are stressors, while stress is an internal arousal resulting from to the inability of the individual to achieve a balance when facing socio-environmental demands. The progression from stressor to an internal stress response varies by individual and their resources and skills (87). We therefore chose psychosocial stressors that have either

previously been associated with a stress response or have been associated with reduced lung function. From among the self-reported psychosocial stressors collected in LAFANS, we examined school and neighborhood safety based on both their face validity (e.g.- do you feel safe in your school/neighborhood: yes, no, sometimes) as well as literature that has found that a child's perceived neighborhood safety (88) and school safety (89) are associated with psychological distress and psychological trauma symptoms. Perceived school and neighborhood safety did not consistently predict lung function, however, since too few participants reported not feeling safe at all in their school or neighborhood, we combined the categories 'not at all' and 'sometimes' feeling safe (references was always feeling safe), possibly attenuating effects. However, while confidence intervals often crossed the null, we did find negative point estimates for unsafe school and all spirometry estimates in younger, but not older youth, suggesting that while not statistically significant in our sample, there may be a weak association between feeling unsafe at school and reduced lung function. This suggests the importance of perceived school safety, particularly in those aging towards adolescence.

We selected self-reported 'family fighting' based upon literature associating interparental conflict with increased cortisol levels in children (90,91), as well as findings that 6-7 year old girls had reduced FEV_1 and FVC when mothers reported high levels of interparental conflict (17). We found a weak reduction in FVC and FEV_1 among males who reported familial fighting but confidence intervals crossed the null. Previous research on interparental conflict and children's cortisol found that the child's involvement in the family fighting as well as externalizing behaviors mediated cortisol response, which we

were not able to assess. Additionally, children participating in previous research were much younger (ages 5-7)(90,91), limiting the relevance of these findings to our older sample.

Our examination of the absence of a father in the house was motivated by a large body of evidence that paternal absence has many negative consequences for children, including behavioral problems and psychological distress (review paper (92)). We found that FVC and FEV_1 were reduced in males from families in which the father was not present, and the association was stronger in older males 15-17. We were surprised by the finding that older females had increased FEF_{25-75}, but this might be a spurious finding driven by the large variability in the FEF_{25-75} measure. A previous study found father-absent male adolescents had higher cortisol levels compared with father-present adolescents, but there was no difference in cortisol levels between father-present/absent adolescent females (93). In LAFANS, we were not able to assess if a father-surrogate (stepfather, grandfather) was present in the house, which would be important in future work to disentangle what "father's absence" is truly measuring. The findings of an interaction between absence of the father and sex are interesting and may warrant further examination.

We examined negative emotions measured with BPI-INT based on studies in adults reporting that angry and hostile moods were associated with reduced lung function (94,95), and optimism was associated with higher levels of lung function (96). However, we did not find any association between internalizing behavior and lung function in our sample.

Finally, we examined caregiver PSE as an indicator of caregiver stress, as those with low self-efficacy are thought to have lower mediating resources towards stressors (87). We chose a caregiver stressor given the reliance on parental perceived stressor proxies (PSS) in a previous study examining lung function(77). Similar to the previous study, we did not find any association between caregiver PSE and lung function, which may be due to the older age of the participants in both of the studies' samples.

Effect estimates for our select psychosocial stressors on lung function may have been affected by the large variation in age of our sample, which in turn affects both the effects of psychosocial stressors and differential growth in lung function during this time period. In our sample, male and female FEV_1 increased with age fairly consistently until age 12, after which time FEV_1 continued to increase in males (change between mean FEV_1 at age 12 and mean FEV_1 at age 17) as much as 63% while it only increased by another 14% in females (Figure 4.2). This is consistent with the literature that shows that lung function increases linearly with age until the pre-pubescent growth spurt in girls at age 10 and boys at age 12, resulting in a tapering growth and plateau of pulmonary function for girls at age 16, with stronger growth maintained in boys until age 18 or later (97). This difference in growth rates may reduce our ability to observe any negative effects of stress on lung function growth in late childhood/adolescence, particularly in adolescent females who are already very close to pulmonary maturity. Another issue may be differences in the underlying stress mechanisms for adversity in youth. There is evidence that exposure to stress tests produces different cortisol responses based upon the timing of adversity in ones

childhood/adolescence; in a sample of adolescents that were administered social stress tests, those who had experienced higher adversities between ages 6-11 had increased cortisol levels from the social stress tests compared to those with lower adversities. However, those who experienced higher adversities between ages 12-13 and 14-15 had lower cortisol levels in response to social stress tests compared with those experiencing lower adversities, independent of previous adversities in childhood (98). Given the cross-sectional collection of our lung function and stressor data, we do not know if the stressors currently reported were also experienced earlier in childhood. However, the potential heterogeneity of cortisol response by timing of adversity observed in adolescents, combined with the decrease and plateau of pulmonary function in adolescent females may help to explain our largely null findings between the various psychosocial stressors and lung function in females. This hypothesis is further supported by the failure to find main effects from psychosocial stressors (measured as maternal PSS and racism) in either of the other two studies examining lung function in youth ages 11-13 (17,77).

This project has a number of strengths. Lung function estimates in our sample were sensitive to air pollutants ($PM_{2.5}$, NO_2 (data not shown)) as observed in many other studies (99,100), giving us confidence that the spirometry estimates were robust and appropriate for examination with psychosocial stressors. Additionally, we were able to examine a wide range of potential psychosocial stressors. By utilizing psychosocial stressor data self-reported by the youth, we attempted to reduce potential measurement error and add complexity to our stress measures rather than solely relying on parent reported stress.

Limitations include the cross-sectional report of stressors and spirometry assessments, making it more difficult to discern temporality as well as duration of the psychosocial stressor. Additionally, while we chose psychosocial stressors based upon empirical evidence of cortisol activity in other research, without our own bioanalytical observations, we do not know whether our psychosocial stressors actually caused a stress response in the youth. Between L.A.FANS 1-2, only 64% of the sample was retained. This degree of lost to follow-up may result in a sample not generalizable to the original L.A.FANS-1 enrollment. Finally, the limited sample size of youth ages 10-17 with a reproducible spirometry curve for analysis did not permit exploration by race/ethnicity or nativity in our majority Hispanic sample. Non-analyzable curves were interviewer dependent and more likely in young children not included in the analysis, and thus while these unavailable curves further limited our power, we expect bias from those with curves not analyzable to be non-differential in their impact on the reported estimate.

By studying a range of potential self-reported and perceived psychosocial stressors in a sample over-representing poor families, we attempted to elucidate the complex relationship of psychosocial stressors, environmental exposures and respiratory health in youth. Our data suggest that feeling unsafe at school may be associated with reduced lung function in youth ages 10-14. Additionally, in older males, the absence of a father, self-reported familial fighting or multiple psychosocial stressors may be associated with reduced lung function, warranting further investigation into these sex-stressor interactions and lung function in youth.

4.7 Tables and Figures

Table 4.1. Descriptive and demographic data for participants ages 10-17 in L.A.FANS-2, a neighborhood and household survey in Los Angeles, CA, 2006-8 (n=584).

	BOYS (n=316) n, %	GIRLS (n=268) n, %
Spirometry		
FVC (mL) mean (sd)	3559.9 (1112.4)	3091.82 (689.4)
FEV (mL) mean (sd)	2967.3 (953.1)	2625.6 (610.6)
FEF_{25-75} (mL/s) mean (sd)	3139.9 (1272.1)	3020.7 (987.6)
Psychosocial stressors		
BPI-INT[1] mean (sd)	2.7 (3.2)	3.1 (3.7)
Caregiver PSE[2] mean (sd)	20.7 (3.9)	20.1 (3.6)
Summary stress score[3] mean (sd)	1.5 (1.3)	1.7 (1.3)
Neighborhood feels safe	215 (68.0)	152 (56.7)
missing	2 (0.6)	3 (1.1)
School feels safe	244 (77.2)	199 (74.3)
missing	7 (2.2)	5 (1.8)
Family does not fight	280 (88.6)	239 (89.2)
missing	1 (0.3)	3 (1.1)
Dad lives in the house	202 (63.9)	181 (67.5)
Child covariates		
Age mean (sd)	13.4 (2.3)	13.6 (2.2)
10-14years	196 (62.0)	162 (60.5)
15-17years	120 (38.0)	106 (39.5)
Height (cm) mean (sd)	161.1 (13.4)	156.2 (8.9)
Weight (kg) mean (sd)	63.7 (20.8)	58.3 (16.9)
Race		
non-Hispanic white	44 (13.9)	40 (14.9)
Hispanic	203 (64.2)	189 (70.5)
Black	19 (6.0)	13 (4.9)
Asian/Pacific Islander	19 (6.0)	9 (3.4)
Other (multiple races)	31 (9.8)	17 (6.3)
Child's nativity		
US-born	289 (91.5)	243 (90.7)
Child smokes	8 (2.5)	2 (0.8)
missing	3 (0.9)	1 (0.4)
Asthma diagnosis with wheeze (12 months)	29 (9.2)	13 (4.9)
Child likes to read	227 (71.8)	232 (86.6)

missing	2 (0.6)	34 (12.7)
Family/household		
Maternal Education		
≤ 8th grade	75 (23.7)	62 (23.1)
9-12th grade	101 (32.0)	105 (39.2)
Vocational school	14 (4.4)	19 (7.1)
AA/some college	78 (24.7)	48 (17.9)
College+	45 (14.2)	33 (12.3)
missing	3 (0.9)	1 (0.3)
Federal poverty level		
<100%	94 (29.7)	76 (28.4)
101-200%	93 (29.4)	79 (29.5)
201-300%	49 (15.5)	45 (16.8)
301%+	80 (25.3)	68 (25.4)
Current house smoke	74 (23.4)	56 (20.9)

[1] BPI- higher numbers more internalizing negative behavior

[2] PSE- higher numbers signify better self-efficacy

[3] Summary stress score- higher numbers signify more stressors

Table 4.2. Adjusted*,beta, 95% confidence interval estimates for psychosocial stressors and lung function by age group in adolescents 10-17 in L.A.FANS (n=584).**

	FVC		FEV_1		FEF_{25-75}	
	10-14 years	15-17 years	10-14 years	15-17 years	10-14 years	15-17 years
Family fighting[a]	-55.9 (-220.2, 108.4)	29.7 (-191.8, 251.3)	-43.1 (-187.6, 101.5)	-48.1 (-265.8, 169.6)	11.8 (-264.1, 287.6)	-41.9 (-147.1, 63.3)
Unsafe school[b]	-84.9 (-219.3, 49.5)	72.1 (-124.8, 268.9)	-129.8 (-241.4, -18.2)	30.7 (-152.3, 213.9)	-165.2 (-386.5, 56.1)	-90.2 (-428.9, 248.6)
Unsafe neighborhood[c]	56.5 (-55.7, 168.8)	18.1 (-171.3, 207.5)	42.3 (-56.1, 140.8)	-24.7 (-186.1, 136.6)	112.9 (-76.0, 301.9)	-142.3 (-424.8, 140.2)
Absence of father[d]	-38.9 (-182.9, 104.9)	-76.2 (-269.2, 116.8)	-38.9 (-165.2, 87.3)	-42.4 (-214.6, 129.8)	-93.3 (-315.9, 129.3)	-28.2 (-316.3, 259.9)
BPI-INT[e]	-5.4 (-23.3, 12.6)	15.2 (-14.8, 45.1)	-6.3 (-20.6, 7.9)	3.8 (-24.8, 32.5)	-9.6 (-33.9, 14.7)	-18.9 (-65.8, 27.9)
Caregiver PSE[f]	1.9 (-13.3, 17.2)	-10.4 (-27.5, 6.8)	6.4 (-5.3, 18.1)	-15.5 (-32.6, 1.6)	15.5 (-6.1, 37.2)	-26.8 (-61.3, 7.7)
Summary stress score[g]	-11.7 (-55.3, 31.9)	-18.7 (-102.2, 64.8)	-10.5 (-49.2, 28.1)	-36.1 (-113.9, 41.7)	8.1 (-60.1, 76.4)	-80.4 (-214.8, 54.0)

*Adjusted for: PM 2.5, age, FPL, current house smoke, race/ethnicity, maternal education, height (cm), height-square, weight (kg) weight-square, sex, sex*age.

** Adjusted n's: younger adolescents=322, older adolescents=204

[a] Family fighting (ref=no/sometimes family fighting)

[b] Unsafe school (ref=safe all of the time)

[c] Unsafe neighborhood (ref=safe all of the time)

[d] Father present in the house is reference

[e] BPI-INT (higher numbers worse behavior)

[f] Caregiver Pearlin self efficacy (reverse code- higher numbers worse self efficacy)

[g] Count of 6 psychosocial stressors (unweighted)

Table 4.3.Beta, 95% confidence interval estimates for psychosocial stressors and lung function by sex in youth 10-17 in L.A.FANS (n=584).

	FVC		FEV_1		FEF_{25-75}	
	Males	Females	Males	Females	Males	Females
Family fighting[a]	-174.1 (-362.5, 14.3)	90.7 (-89.7, 271.1)	-156.2 (-327.8, 15.5)	41.5 (-101.4, 184.4)	-68.4 (-400.1, 263.4)	-74.6 (-369.2, 220.0)
Unsafe school[b]	-56.6 (-230.7, 117.5)	3.0 (-134.2, 140.3)	-85.2 (-229.5, 59.1)	-50.0 (-184.1, 84.1)	-138.4 (-416.6, 139.9)	-119.1 (-384.4, 146.2)
Unsafe neighborhood[c]	68.8 (-87.0, 224.8)	13.4 (-114.1, 140.9)	13.0 (-121.3, 147.4)	29.3 (-89.5, 148.1)	-89.4 (-328.3, 149.5)	143.1 (-79.5, 365.8)
Absence of father[d]	-156.9 (-329.9, 16.0)	35.5 (-107.5, 178.5)	-176.2 (-322.7, -29.7)	76.7 (-52.8, 206.2)	-371.8 (-607.8, -135.8)	253.0 (12.3, 493.8)
BPI-INT[e]	8.1 (-13.7, 29.9)	-2.1 (-24.0, 19.9)	1.5 (-16.7, 19.7)	-6.1 (-26.3, 14.2)	-9.6 (-40.2, 20.9)	-16.0 (-49.2, 17.3)
Caregiver PSE[f]	-8.9 (-24.6, 6.7)	8.7 (-7.9, 25.3)	-9.1 (-23.6, 5.3)	11.7 (-1.2, 24.5)	-11.5 (-40.1, 17.1)	15.1 (-10.6, 40.8)
Summary stress score[g]	-33.7 (-92.8, 25.4)	8.2 (-43.0, 59.4)	-45.6 (-97.6, 6.3)	12.1 (-37.0, 61.2)	-74.1 (-166.1, 17.9)	41.7 (-46.0, 129.4)

*Adjusted for: PM 2.5, age, FPL, current house smoke, race, maternal education, height (cm), height-square, weight (kg) weight-square.

** Adjusted males n=281, female n=245

[a] Family fighting (ref=no/sometimes family fighting)

[b] Unsafe school (ref=safe all of the time)

[c] Unsafe neighborhood (ref=safe all of the time)

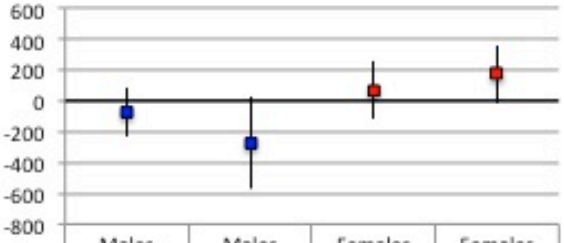
[d] Father present in the house is reference

[e] BPIINT (higher numbers worse behavior)

[f] Caregiver Pearlin self efficacy (reverse code- higher numbers worse self efficacy)

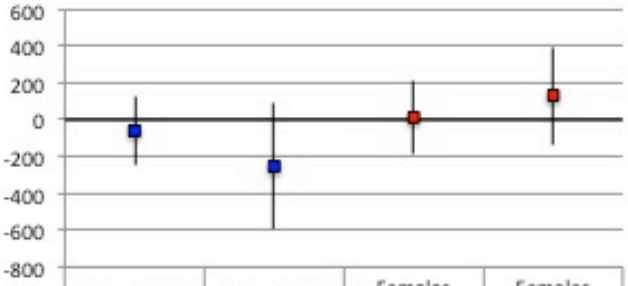
[g] Count of 6 psychosocial stressors (unweighted)

Absence of father in house and FEV_1 (a)



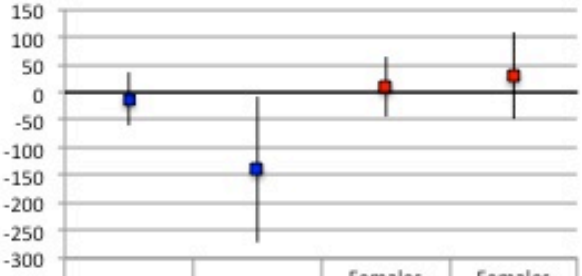
	Males 10-14	Males 15-17	Females 10-14	Females 15-17
Upper CI	83.1	31.8	258.6	365.3
Lower CI	-226	-570.2	-121.2	-16.0
Point estimate	-71.5	-269.2	68.7	174.6

Family fighting and FEV_1(b)



	Males 10-14	Males 15-17	Females 10-14	Females 15-17
Upper CI	121.6	84.3	214.2	393.2
Lower CI	-243.8	-592.5	-187.6	-133.7
Point estimate	-61.1	-254.1	13.2	129.8

Summary stress score and FEV_1 (c)



	Males 10-14	Males 15-17	Females 10-14	Females 15-17
Upper CI	34.6	-7.7	63.8	106.7
Lower CI	-60.9	-271.2	-43.6	-48.8
Point estimate	-13.2	-139.4	10	28.9

Figure 1. Select psychosocial stressors and FEV_1 estimates stratified by sex and age group. P for interaction in (a) 0.009, (b) 0.06, (c) 0.13.

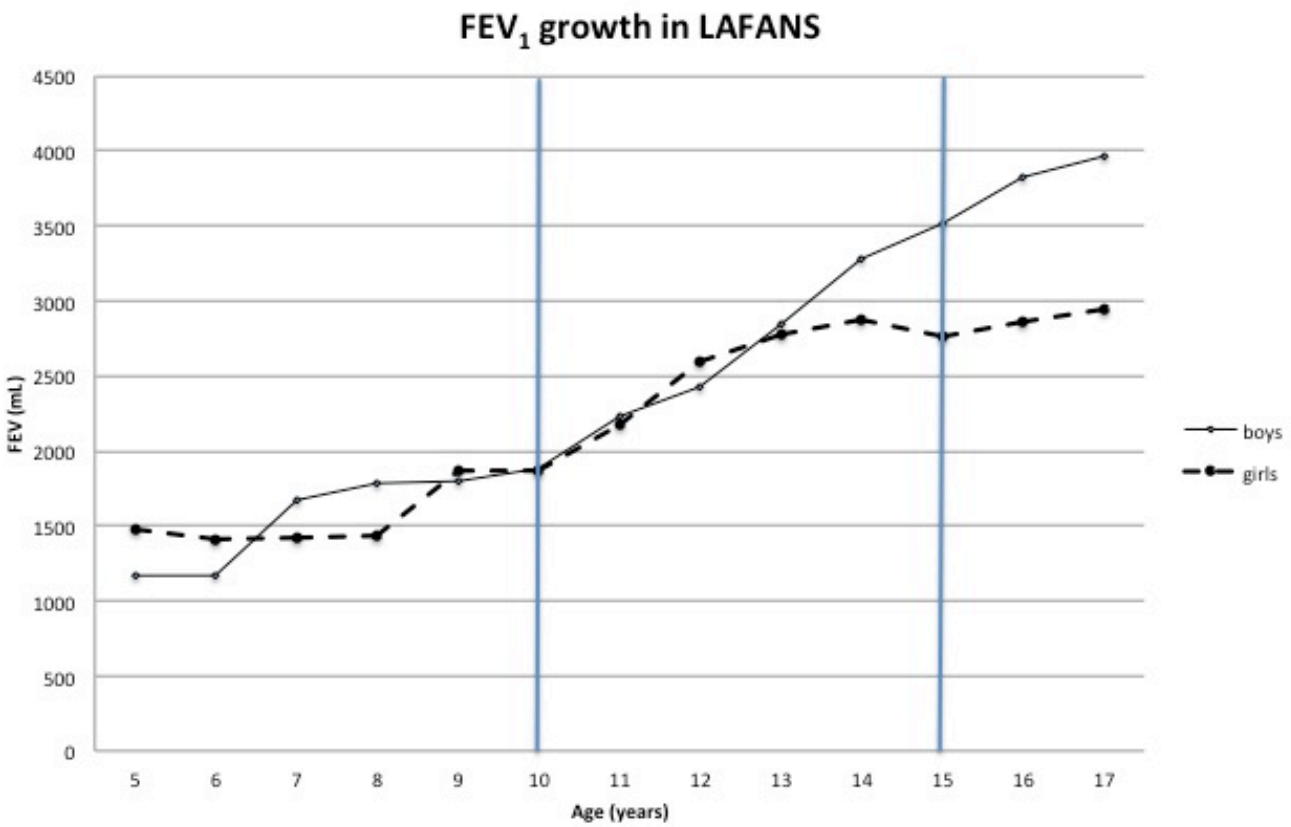


Figure 2. FEV1 growth by sex in LAFANS, ages 5-17. Vertical blue bars represent age groups for analysis (10-14, 15-17 years).

Chapter V. Public health importance

Childhood asthma and wheeze present an enormous burden to the individual, the families and to the healthcare system (9). Importantly, they disproportionately affect minorities and the poor, and these disparities are not fully explained by increased exposures to air pollutants (101). These persisting disparities may be partially accounted for by increased vulnerabilities to disease, including respiratory illnesses, resulting from the individual's perceived stress. Psychosocial stressors may be exacerbated in low-income neighborhoods, and residents may face additional challenges in the built environment and have fewer coping mechanisms at hand. Further, racial and ethnic minorities and immigrants may experience additional stressors resulting from perceived discrimination.

Two of our studies focus on prenatal and postnatal psychosocial stressors in attempts to better elucidate the complicated construct of perceived stress and provide tailored messages about psychosocial stressors and their effects on respiratory health. Our third paper examining breastfeeding and asthmatic symptoms in Latinas identifies a protective factor that should continue to be promoted in the US-born Latina population.

Ultimately, all of these factors are potentially modifiable and are being proposed with the intention of providing public health information that is more applicable and accessible to specific populations, with the hopes of gaining the most effective strategies as possible in preventing or managing these important childhood and adolescent diseases.

Chapter VI. References

1. NHLBI [Internet]. [cited 2014 Jan 11]. Available from: http://www.nhlbi.nih.gov/health/health-topics/topics/asthma/

2. Granell R, Sterne J a C, Henderson J. Associations of different phenotypes of wheezing illness in early childhood with environmental variables implicated in the aetiology of asthma. PLoS One. 2012 Jan;7(10):e48359.

3. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson C a, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief. 2012 May;(94):1–8.

4. Akinbami L. The state of childhood asthma, United States, 1980-2005. Adv Data. 2006 Dec 12;(381):1–24.

5. Frieden TR. Forward: CDC Health Disparities and Inequalities Report - United States, 2011. MMWR Surveill Summ. 2011 Jan 14;60 Suppl:1–2.

6. Lara M, Akinbami L, Flores G, Morgenstern H. Heterogeneity of Childhood Asthma Among Hispanic Children: Puerto Rican Children Bear a Disproportionate Burden. Pediatrics. 2006;117(1):43–53.

7. Strina A, Barreto ML, Cooper PJ, Rodrigues LC. Risk factors for non-atopic asthma/wheeze in children and adolescents: a systematic review. Emerg Themes Epidemiol. 2014 Jan;11(1):5.

8. Von Mutius E, Hartert T. Update in asthma 2012. Am J Respir Crit Care Med. 2013 Jul 15;188(2):150–6.

9. Connell EJO. The burden of atopy and asthma in children. Allergy. 2004;59(3):7–11.

10. Barnett S, Nurmagambetov T. Costs of asthma in the United States: 2002-2007. J Allergy Clin Immunol. 2011;127(1):145–52.

11. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, et al. Economic burden of asthma: a systematic review. BMC Pulm Med. 2009 Jan;9:24.

12. Henderson J, Granell R, Heron J, Sherriff a, Simpson a, Woodcock a, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. Thorax. 2008 Nov;63(11):974–80.

13. Morgan WJ, Stern D a, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med. 2005 Nov 15;172(10):1253–8.

14. Götschi T, Heinrich J, Sunyer J, Künzli N. Long-term effects of ambient air pollution on lung function: a review. Epidemiology. 2008 Sep;19(5):690–701.

15. Schünemann HJ, Dorn J, Grant BJ, Winkelstein W, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest. 2000 Sep;118(3):656–64.

16. Bisgaard H, Jensen SM, Bønnelykke K. Interaction between asthma and lung function growth in early life. Am J Respir Crit Care Med. 2012 Jun 1;185(11):1183–9.

17. Suglia SF, Ryan L, Laden F, Wright RJ. Violence exposure, a chronic psychosocial stressor, and childhood lung function. Psychosom Med. 2008;70(2):160–9.

18. Rovers MM. The burden of otitis media. Vaccine. 2008 Dec 23;26 Suppl 7:G2–4.

19. Klein JO. The burden of otitis media. Vaccine. 2000 Dec 8;19 Suppl 1:S2–8.

20. Godfrey KM, Barker DJ. Fetal programming and adult health. Public Health Nutr. 2007 Sep 27;4(2b).

21. Wright RJ. Perinatal stress and early life programming of lung structure and function. Biol Psychol. Elsevier B.V.; 2010 Apr;84(1):46–56.

22. Wright RJ. Epidemiology of stress and asthma: from constricting communities and fragile families to epigenetics. Immunol Allergy Clin North Am. 2011 Mar;31(1):19–39.

23. Provençal N, Binder E. The effects of early life stress on the epigenome: From the womb to adulthood and even before. Exp Neurol. Elsevier B.V.; 2014 Sep 9;1–10.

24. Dunkel-Schetter C, Glynn L. Stress in Pregnancy: Empirical Evidence and the Theoretical Issues to Guide Interdisciplinary Research. The Handbook of Stress Science. 2010. p. Ch 24.

25. Ghosh JKC, Wilhelm MH, Dunkel-Schetter C, Lombardi C a, Ritz BR. Paternal support and preterm birth, and the moderation of effects of chronic stress: a study in Los Angeles county mothers. Arch Womens Ment Health. 2010 Aug;13(4):327–38.

26. Fang F, Höglund CO, Arck P, Lundholm C, Långström N, Lichtenstein P, et al. Maternal bereavement and childhood asthma-analyses in two large samples of Swedish children. PLoS One. 2011 Jan;6(11):e27202.

27. Mathilda Chiu Y-H, Coull B a, Cohen S, Wooley A, Wright RJ. Prenatal and postnatal maternal stress and wheeze in urban children: effect of maternal sensitization. Am J Respir Crit Care Med. 2012 Jul 15;186(2):147–54.

28. Reyes M, Perzanowski MS, Whyatt RM, Kelvin E a., Rundle AG, Diaz DM, et al. Relationship between maternal demoralization, wheeze, and immunoglobulin E among inner-city children. Ann Allergy, Asthma Immunol. Ann. Allergy Asthma Immunol.; 2011 Jul;107(1):42–9.e1.

29. Cookson H, Granell R, Joinson C, Ben-Shlomo Y, Henderson a J. Mothers' anxiety during pregnancy is associated with asthma in their children. J Allergy Clin Immunol. 2009 Apr;123(4):847–53.e11.

30. Guxens M, Sonnenschein-van der Voort AMM, Tiemeier H, Hofman A, Sunyer J, de Jongste JC, et al. Parental psychological distress during pregnancy and wheezing in preschool children: the Generation R Study. J Allergy Clin Immunol. 2014 Jan;133(1):59–67.e1–12.

31. Wood R a, Bloomberg GR, Kattan M, Conroy K, Sandel MT, Dresen A, et al. Relationships among environmental exposures, cord blood cytokine responses, allergy, and wheeze at 1 year of age in an inner-city birth cohort (Urban Environment and Childhood Asthma study). J Allergy Clin Immunol. Elsevier Ltd; 2011 Apr;127(4):913–9.e1–6.

32. Chiu Y-HM, Coull B a, Sternthal MJ, Kloog I, Schwartz J, Cohen S, et al. Effects of prenatal community violence and ambient air pollution on childhood wheeze in an urban population. J Allergy Clin Immunol. Elsevier Ltd; 2014 Mar;133(3):713–22.e4.

33. Braveman P, Marchi K, Egerter S, Kim S, Metzler M, Stancil T, et al. Poverty, near-poverty, and hardship around the time of pregnancy. Matern Child Health J. 2010 Jan;14(1):20–35.

34. Lauderdale DS, Wen M, Jacobs E a, Kandula NR. Immigrant perceptions of discrimination in health care: the California Health Interview Survey 2003. Med Care. 2006 Oct;44(10):914–20.

35. Wright RJ, Rodriguez M, Cohen S. Occasional reviews Review of psychosocial stress and asthma : an integrated biopsychosocial approach. Thorax. 1998;53:1066–74.

36. Dunkel Schetter C, Schafer P, Lanzi RG, Clark-Kauffman E, Raju TNK, Hillemeier MM. Shedding Light on the Mechanisms Underlying Health Disparities Through Community Participatory Methods: The Stress Pathway. Perspect Psychol Sci. 2013 Nov 4;8(6):613–33.

37. Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JKC. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. Am J Epidemiol. 2007 Nov 1;166(9):1045–52.

38. Hoggatt KJ, Flores M, Solorio R, Wilhelm M, Ritz B. The "Latina epidemiologic paradox" revisited: the role of birthplace and acculturation in predicting infant low birth weight for Latinas in Los Angeles, CA. J Immigr Minor Health. 2012 Oct;14(5):875–84.

39. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. Eur Respir J. 1995 Mar 1;8(3):483–91.

40. Dunkel Schetter C. Psychological science on pregnancy: stress processes, biopsychosocial models, and emerging research issues. Annu Rev Psychol. 2011 Jan;62(November 2010):531–58.

41. Rini CK, Dunkel-Schetter C, Wadhwa PD, Sandman C a. Psychological adaptation and birth outcomes: the role of personal resources, stress, and sociocultural context in pregnancy. Health Psychol. 1999 Jul;18(4):333–45.

42. Cohen S, Kamarck T MR. A global measure of perceived stress. J Heal Soc Behav. 1983;24(4):385–96.

43. Fang J. Using SAS ® Procedures FREQ , GENMOD , LOGISTIC , and PHREG to Estimate Adjusted Relative Risks – A Case Study. SAS Global Forum 2011. 2011. p. 345.

44. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol. 1989 Jan;129(1):125–37.

45. Miller AH. Reviews and Overviews When Not Enough Is Too Much : The Role of Insufficient Glucocorticoid Signaling in the Pathophysiology of Stress-Related Disorders. Am J Psychiatry. 2003;160(September):1554–65.

46. Nielsen NM, Hansen AV, Simonsen J, Hviid A. Prenatal stress and risk of infectious diseases in offspring. Am J Epidemiol. 2011 May 1;173(9):990–7.

47. Merlot E, Couret D, Otten W. Prenatal stress, fetal imprinting and immunity. Brain Behav Immun. 2008 Jan;22(1):42–51.

48. Veru F, Laplante DP, Luheshi G, King S. Prenatal maternal stress exposure and immune function in the offspring. Stress. 2014;17(2):133–48.

49. Wright RJ, Visness CM, Calatroni A, Grayson MH, Gold DR, Sandel MT, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. Am J Respir Crit Care Med. 2010 Jul 1;182(1):25–33.

50. Gelfand EW. THE IMPACT OF ASTHMA ON THE PATIENT. Johns Hopkins Adv Stud Med. 2008;8(3):57–63.

51. Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, et al. Breastfeeding and maternal and infant health outcomes in developed countries. Evid Rep Technol Assess (Full Rep). 2007 Apr;(153):1–186.

52. Heine RG. Preventing atopy and allergic disease. Nestle Nutr Inst Workshop Ser. 2014 Jan;78:141–53.

53. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. J Pediatr. 2001 Aug;139(2):261–6.

54. Kramer MS. Breastfeeding and allergy: the evidence. Ann Nutr Metab. 2011 Jan;59 Suppl 1(suppl 1):20–6.

55. Björkstén B, Aït-Khaled N, Innes Asher M, Clayton TO, Robertson C. Global analysis of breast feeding and risk of symptoms of asthma, rhinoconjunctivitis and eczema in 6-7 year old children: ISAAC Phase Three. Allergol Immunopathol (Madr). 2011;39(6):318–25.

56. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. Lancet. 2002 Sep 21;360(9337):901–7.

57. Dogaru CM, Nyffenegger D, Pescatore AM, Spycher BD, Kuehni CE. Dogaru et al. Respond to "Does Breastfeeding Protect Against 'Asthma'?" Am J Epidemiol. 2014 Apr 11;179(10):1171–2.

58. Dogaru CM, Nyffenegger D, Pescatore AM, Spycher BD, Kuehni CE. Breastfeeding and Childhood Asthma: Systematic Review and Meta-Analysis. Am J Epidemiol. 2014 Apr 11;179(10):1153–67.

59. Kramer MS. Invited Commentary: Does Breastfeeding Protect Against "Asthma"? Am J Epidemiol. 2014 Apr 11;179(10):1168–70.

60. Centers for Disease Control. Progress in Increasing Breastfeeding and Reducing Racial/Ethnic Differences — United States, 2000–2008 Births. 2008.

61. Gibson-Davis CM, Brooks-Gunn J. Couples' immigration status and ethnicity as determinants of breastfeeding. Am J Public Health. 2006 Apr;96(4):641–6.

62. Gill SL. Breastfeeding by Hispanic women. J Obstet Gynecol Neonatal Nurs. 2009;38(2):244–52.

63. Camacho-Rivera M, Kawachi I, Bennett GG, Subramanian S V. Revisiting the Hispanic Health Paradox: The Relative Contributions of Nativity, Country of Origin, and Race/Ethnicity to Childhood Asthma. J Immigr Minor Health. 2014 Jan 1;

64. Lee HJ, Elo IT, Culhane JF. Racial/Ethnic Differences in Breastfeeding Initiation and Duration Among Low-income, Inner-city Mothers. Soc Sci Q. 2010;90(5):1251–71.

65. Harley K, Stamm N, Eskenazi B. The Effect of Time in the U.S. on the Duration of Breastfeeding in Women of Mexican Descent. Matern Child Heal J. 2007;11(2):119–25.

66. Silvers KM, Frampton CM, Wickens K, Pattemore PK, Ingham T, Fishwick D, et al. Breastfeeding protects against current asthma up to 6 years of age. J Pediatr. 2012 Jun;160(6):991–6.e1.

67. Brew BK, Allen CW, Toelle BG, Marks GB. Systematic review and meta-analysis investigating breast feeding and childhood wheezing illness. Paediatr Perinat Epidemiol. 2011 Nov;25(6):507–18.

68. Matheson MC, Erbas B, Balasuriya A, Jenkins MA, Wharton CL, Tang ML-K, et al. Breast-feeding and atopic disease: a cohort study from childhood to middle age. J Allergy Clin Immunol. 2007 Nov;120(5):1051–7.

69. Kramer MS, Matush L, Vanilovich I, Platt R, Bogdanovich N, Sevkovskaya Z, et al. Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial. BMJ. 2007 Oct 20;335(7624):815.

70. Natland ST, Andersen LF, Nilsen TIL, Forsmo S, Jacobsen GW. Maternal recall of breastfeeding duration twenty years after delivery. BMC Med Res Methodol. BMC Medical Research Methodology; 2012 Jan;12(1):179.

71. Camacho-Rivera M, Kawachi I, Bennett GG, Subramanian S V. Perceptions of neighborhood safety and asthma among children and adolescents in Los Angeles: a multilevel analysis. PLoS One. 2014 Jan;9(1):e87524.

72. Shankardass K, McConnell R, Jerrett M, Milam J, Richardson J, Berhane K. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. Proc Natl Acad Sci U S A. 2009 Jul 28;106(30):12406–11.

73. Turyk ME, Hernandez E, Wright RJ, Freels S, Slezak J, Contraras A, et al. Stressful life events and asthma in adolescents. Pediatr Allergy Immunol. 2008 May;19(3):255–63.

74. Wolf JM, Miller GE, Chen E. Parent psychological states predict changes in inflammatory markers in children with asthma and healthy children. Brain Behav Immun. 2008 May;22(4):433–41.

75. Wright RJ, Cohen S, Carey V, Weiss ST, Gold DR. Parental Stress as a Predictor of Wheezing in Infancy A Prospective Birth-Cohort Study. Am J Respir Crit Care Med. 2002;165:358–65.

76. Milam J, McConnell R, Yao L, Berhane K, Jerrett M, Richardson J. Parental stress and childhood wheeze in a prospective cohort study. J Asthma. 2008 May;45(4):319–23.

77. Islam T, Urman R, Gauderman WJ, Milam J, Lurmann F, Shankardass K, et al. Parental stress increases the detrimental effect of traffic exposure on children's lung function. Am J Respir Crit Care Med. 2011 Oct 1;184(7):822–7.

78. Astell-Burt T, Maynard MJ, Lenguerrand E, Whitrow MJ, Molaodi OR, Harding S. Effect of air pollution and racism on ethnic differences in respiratory health among adolescents living in an urban environment. Health Place. 2013;23(100):171–8.

79. Hänsel A, Hong S, Cámara RJ a, von Känel R. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neurosci Biobehav Rev. 2010;35:115–21.

80. Sastry N, Ghosh-Dastidar B, Adams J, Pebley AR. The design of a multilevel survey of children, families, and communities: The Los Angeles Family and Neighborhood Survey. Soc Sci Res. 2006 Dec;35(4):1000–24.

81. Peterson CE, Pebley AR, Sastry N, Yuhas K, Ghosh-dastidar B, Haas ANNC, et al. The Los Angeles Family and Neighborhood Survey , Wave 2 User ' s Guide and Codebook. 2011.

82. Recommenhations E, Validation E, Control Q, Recommendations MP, Qualifications P, Performance T, et al. Standardization of Spirometry. Time. 1994;(6).

83. Peterson JL, Zill N. Marital Disruption, Parent-Child Relationships, and Behavior Problems in Children. J Marriage Fam. 1986;295–307.

84. Pearlin LI, Lieberman MA, Menaghan EG, Mullan JT. The Stress Process. J Health Soc Behav. 1981;22:337–56.

85. Ritz BR, Ghosh JKC, Tuner MW, Qiu J, Jerrett M, Su J, et al. Traffic-Related Air Pollution and Asthma in Economically Disadvantaged and High Traffic Density Neighborhoods in Los Angeles County, California [Internet]. 2009. p. 1–113. Available from: http://www.arb.ca.gov/research/single-project.php?row_id=64715

86. McConnell R, Islam T, Shankardass K, Jerrett M, Lurmann F, Gilliland F, et al. Childhood incident asthma and traffic-related air pollution at home and school. Environ Health Perspect. 2010 Jul;118(7):1021–6.

87. Aneshensel CS. Social stress: Theory and research. Annual Review of Sociology. 1992. p. 15–38.

88. Booth, J., Ayers, S. L., & Marsiglia FF. Perceived neighborhood safety and psychologival distress: Exploring protective factors. J Sociol Soc Welf. 2012;39(4):137–56.

89. Flannery DJ, Wester KL, Singer MI. Impact of Exposure To Violence in School on Child and Adolescent Mental. J Community Psychol. 2004;32:559–73.

90. Davies PT, Sturge-apple ML, Cicchetti D, Cummings EM. The Role of Child Adrenocortical Functioning in Pathways Between Interparental Conflict and Child Maladjustment. Dev Psychol. 2007;43(4):918–30.

91. Davies PT, Sturge-Apple ML, Cicchetti D, Cummings EM. Adrenocortical Underpinnings of Children's Psychological Reactivity to Interparental Conflict Patrick. Child Dev. 2008;79(6):1693–706.

92. McLanahan S, Tach L, Schneider D. The Causal Effects of Father Absence. Annu Rev Sociol. 2013;399(June):399–427.

93. Flinn M V., Quinlan RJ, Decker S a., Turner MT, England BG. Male-female differences in effects of parental absence on glucocorticoid stress response. Hum Nat. 1996;7(2):125–62.

94. Affleck G, Apter A, Tennen H, Reisine S, Barrows E, Willard A, et al. Mood States Associated With Transitory Changes in Asthma Symptoms and Peak Expiratory FlowSciences, Behavioral. Pyschosomatic Med. 2000;62:61–8.

95. Kubzansky LD, Sparrow D, Jackson B, Cohen S, Weiss ST, Wright RJ. Angry breathing: A prospective study of hostility and lung function in the Normative Aging Study. Thorax. 2006 Oct;61(10):863–8.

96. Kubzansky LD, Wright R, Cohen S, Weiss ST, Sparrow D. Breathing Easy : A Prospective Study of Optimism and Pulmonary Function in the Normative Aging Study. Ann Behav Med. 2002;24(4):345–53.

97. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol. 1993;15(2):75–88.

98. Bosch NM, Riese H, Reijneveld S a., Bakker MP, Verhulst FC, Ormel J, et al. Timing matters: Long term effects of adversities from prenatal period up to adolescence on adolescents' cortisol stress response. The TRAILS study. Psychoneuroendocrinology. 2012;37(9):1439–47.

99. Chen Z, Salam MT, Eckel SP, Breton C V, Gilliland FD. Chronic effects of air pollution on respiratory health in Southern California children: findings from the Southern California Children's Health Study. J Thorac Dis. 2015;7(17):46–58.

100. Anderson JO, Thundiyil JG, Stolbach A. Clearing the Air: A Review of the Effects of Particulate Matter Air Pollution on Human Health. J Med Toxicol. 2012;8:166–75.

101. O'Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, Gouveia N, et al. Health, wealth, and air pollution: Advancing theory and methods. Environ Health Perspect. 2003;111(16):1861–70.