



## Asthma in Hispanics An 8-Year Update

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### Abstract

This review provides an update on asthma in Hispanics, a diverse group tracing their ancestry to countries previously under Spanish rule. A marked variability in the prevalence and morbidity from asthma remains among Hispanic subgroups in the United States and Hispanic America. In the United States, Puerto Ricans and Mexican Americans have high and low burdens of asthma, respectively (the "Hispanic Paradox"). This wide divergence in asthma morbidity among Hispanic subgroups is multifactorial, likely reflecting the effects of known (secondhand tobacco smoke, air pollution, psychosocial stress, obesity, inadequate treatment) and potential (genetic variants, urbanization, vitamin D insufficiency, and eradication of parasitic infections) risk factors. Barriers to adequate asthma management in Hispanics include economic and educational disadvantages, lack of health insurance,

and no access to or poor adherence with controller medications such as inhaled corticosteroids. Although considerable progress has been made in our understanding of asthma in Hispanic subgroups, many questions remain. Studies of asthma in Hispanic America should focus on environmental or lifestyle factors that are more relevant to asthma in this region (e.g., urbanization, air pollution, parasitism, and stress). In the United States, research studies should focus on risk factors that are known to or may diverge among Hispanic subgroups, including but not limited to epigenetic variation, prematurity, vitamin D level, diet, and stress. Clinical trials of culturally appropriate interventions that address multiple aspects of asthma management in Hispanic subgroups should be prioritized for funding. Ensuring high-quality healthcare for all remains a pillar of eliminating asthma disparities.

**Keywords:** asthma; Hispanics; genetics; risk factors

Eight years ago, we reviewed potential explanations for the marked variability in asthma morbidity among Hispanic subgroups, both in the United States and Latin America (1). Given limited knowledge, we advocated for research in well-defined Hispanic subgroups, while also emphasizing the need to broaden access to healthcare for Hispanics (1).

The purpose of this review is to provide an update on asthma in Hispanics. First, we show current demographics and indicators of asthma morbidity in Hispanics. Second, we assess recent findings on selected (known or potential)

risk factors for asthma in Hispanics. Third, we review new studies on the diagnosis and management of asthma in Hispanics. Finally, we discuss future directions in this field.

### The Hispanic Population

The term "Hispanic," as defined by the U.S. 2010 Census, refers to any peoples with roots in Spain or areas previously under Spanish rule, including Mexico, large parts of Central and South America, and some Caribbean Islands (2).

Hispanic America is geographically, racially, and economically diverse (Table 1) (3). Over the last decade, Hispanic America saw reductions in health and education inequalities yet continued to demonstrate substantial income inequalities (4). Most Hispanic American countries have achieved reductions in infant mortality rates in parallel with increments in their gross domestic product and human development index (3–5).

In 2010, there were 50.5 million Hispanics composing 16% of the U.S. population (2). Hispanics remain the largest growing minority in the United States (2).

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**Table 1:** Demographic and Healthcare Data for Selected Hispanic American Countries

| Country                                                             | Per Capita GDP*<br>(Δ from 2005) | HDI†  | IMR‡<br>(Δ from 2005) | Life<br>Expectancy§ | Health Spending  <br>(Δ from 2005) | Asthma<br>Mortality¶ | Urban<br>Population**<br>(%) |
|---------------------------------------------------------------------|----------------------------------|-------|-----------------------|---------------------|------------------------------------|----------------------|------------------------------|
| Argentina                                                           | \$17,900 (18.8%)                 | 0.811 | 10.2 (−5.0)           | 77.32               | \$892 (126%)                       | 14.7                 | 92                           |
| Chile                                                               | \$18,200 (39.9%)                 | 0.819 | 7.2 (−1.6)            | 78.27               | \$1,075 (118%)                     | 23.5                 | 89                           |
| Colombia                                                            | \$10,700 (33.4%)                 | 0.719 | 15.5 (−5.5)           | 75.02               | \$432 (111%)                       | 19.6                 | 75                           |
| Costa Rica                                                          | \$12,500 (7.1%)                  | 0.773 | 9.0 (−1.0)            | 78.06               | \$943 (159%)                       | 18.0                 | 64                           |
| Guatemala                                                           | \$5,200 (1.9%)                   | 0.581 | 24.3 (−11.6)          | 71.46               | \$214 (55%)                        | 33.0                 | 49                           |
| Mexico                                                              | \$15,400 (32.0%)                 | 0.775 | 16.3 (−4.7)           | 76.86               | \$620 (30%)                        | 27.1                 | 78                           |
| Nicaragua                                                           | \$4,400 (57.4%)                  | 0.599 | 21.1 (−8.0)           | 72.45               | \$125 (76%)                        | 41.8                 | 57                           |
| Peru                                                                | \$10,600 (55.7%)                 | 0.741 | 20.9 (−11.0)          | 72.98               | \$289 (125%)                       | 25.8                 | 77                           |
| Commonwealth of Puerto Rico<br>(possession of the United<br>States) | \$16,300 (−20.2%)                | —     | 8.0 (−0.2)            | 79.07               | —                                  | 33.0                 | 99                           |

*Definition of abbreviations:* GDP = gross domestic product; HDI = Human Development Index; IMR = infant mortality rate.

\*The GDP is total market value of all final goods and services produced in a country in a given year, equal to the total consumer investment, and government spending, plus the value of exports, minus the value of imports in 2012 U.S. dollars. Change corrected for inflation based on 2004 U.S. dollars. Source: CIA World Factbook, January 2014 (3).

†The HDI is calculated using various indicators for quality of life, while also accounting for GDP per capita in terms of Purchasing Power Parity and percentage of the population below the poverty line. Source: Human Development Report 2012 rankings, August 2013. Human development = very high (0.805–0.955); high (0.712–0.796); medium (0.536–0.710); low (0.304–0.534) (4).

‡The IMR is the number of children dying under a year of age divided by 1,000 live births. Source: CIA World Factbook, August 2013 (3).

§Average number of years to be lived by a group of people born in the same year, if mortality at each age remains constant in the future. Source: CIA World Factbook, August 2013 (3).

||Health care spending per capita in current U.S. dollars. Source: The World Bank, World Development Indicators, August 2013 (5).

¶Per 10,000 deaths based on International Classification of Diseases 10th revision codes. Most recent available data used: 2009 Argentina, Chile, Costa Rica, Nicaragua; 2008 Colombia, Guatemala; 2007 Peru, Puerto Rico. Source: Pan American Health Organization Regional Health Observatory, September 2013 (167).

\*\*Percentage of the population living in an urban environment. Information from 2010. Source: CIA World Factbook, August 2013 (3).

Persons of Mexican origin are the largest subgroup within the Hispanic population and increased by 54% since 2000 (Figure 1). The Hispanic population is diversely distributed, with persons of Mexican origin living mostly on the West Coast and the South; those of South American origin being more likely to reside in the South and the Northeast; and those of Puerto Rican, Dominican, and Cuban origin being more likely to reside in the Northeast (2).

Compared with non-Hispanic (NH) whites, Hispanics are more likely to be poor (25.4% vs. 13%) (6). Compared with other ethnic groups, Hispanics are least likely to have advanced degrees (6). Hispanics are less likely to have health insurance than NH whites or Blacks: ~29% of Hispanics are uninsured (6), with Mexican Americans least likely to be insured (7).

## Prevalence, Morbidity, and Mortality of Asthma in Hispanics

### Hispanic America

Phase III of the International Study of Asthma and Allergies in Childhood

(ISAAC) in Hispanic America showed continued marked variability in the prevalence of ever-asthma in school-aged children (Table 2) (8). An altitude over 2,000 m was correlated with lower asthma prevalence, a finding that could be explained by natural selection, environmental factors, or changes in trunk-to-limb ratio (8).

A study of 5,978 subjects aged 1 to 59 years in Colombia yielded nationwide estimates of the prevalence of ever-asthma and current asthma symptoms of ~23 and ~12%, respectively (9, 10). In one of few studies including rural areas of Hispanic America, a comparison of the prevalence of asthma in 6,821 Afro-Ecuadorian children living in urban and rural areas showed a strikingly similar prevalence of symptoms (10.1% vs. 9.4%, respectively) (11).

Even though assessing asthma mortality remains challenging for some Hispanic American countries, Table 1 lists such rates for selected countries. One study found that asthma mortality rates in Argentina decreased from the 1980s to the 1990s and speculated that this may be due to increased use of inhaled corticosteroids (ICS) (12).

### United States

In the United States, the prevalence of asthma remains more variable among Hispanic subgroups than across broadly defined racial/ethnic groups (Table 3). Among children and adults in the National Health Interview Survey (2001–2010), the prevalence of current asthma was highest in Puerto Ricans (16.1%) and lowest in Mexican Americans (5.4%), with intermediate values for NH whites (7.7%) and NH Blacks (11.2%) (18). Other studies have estimated that the prevalence of asthma (13–17, 19) or asthma morbidity (17) is highest in Puerto Ricans and lowest in Mexican Americans or Central Americans, with intermediate estimates in South Americans, Cubans, and Dominicans (13, 16).

Mexican Americans have a relatively low prevalence of asthma, but those born in the United States have a higher risk of asthma than those born in Mexico (14, 20, 21). A higher degree of acculturation may also increase the risk of asthma in Mexican Americans (22). In contrast to these findings, Puerto Rican children living in Puerto Rico have higher odds of ever-asthma or hospitalizations for asthma

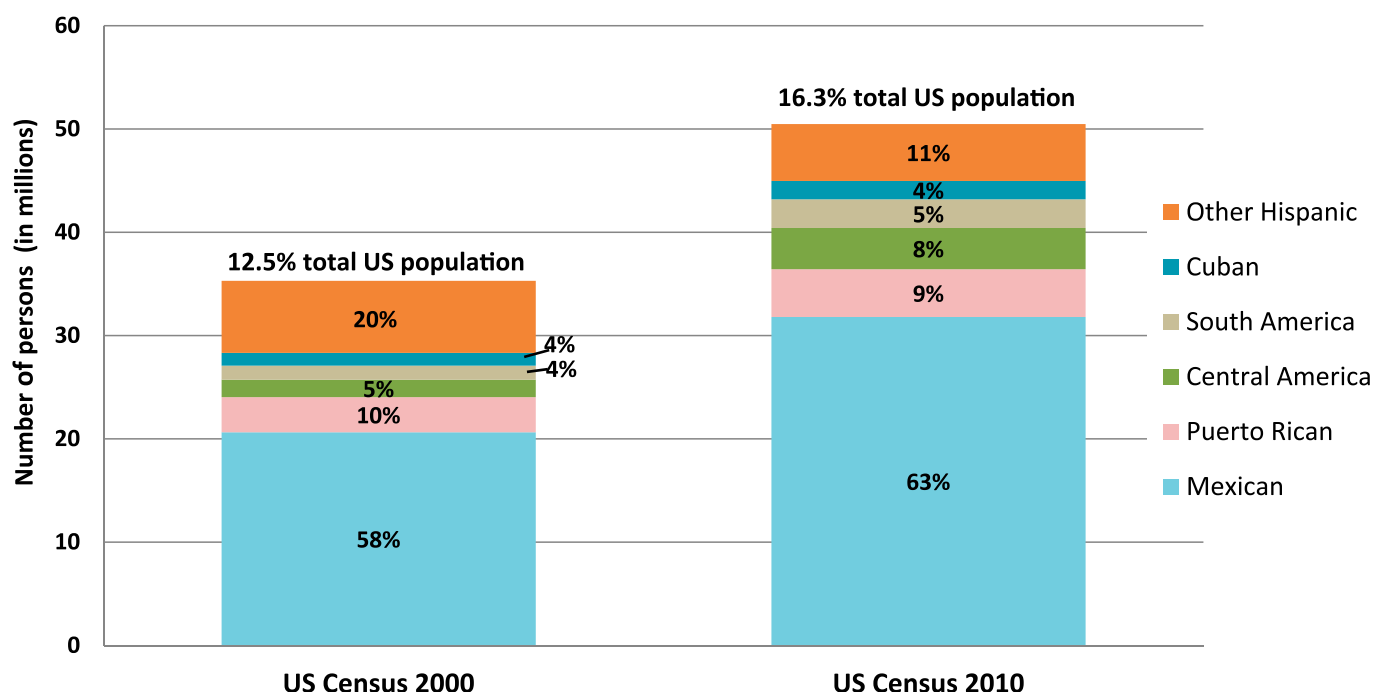


Figure 1. Hispanic population by origin in the U.S. Census, 2000 and 2010.

(by ~27–30%) than those living in the U.S. Northeast (23).

Puerto Ricans continue to share a disproportionate burden of asthma attacks in the United States (24). Among children with asthma in Rhode Island, Dominicans and Puerto Ricans were shown to have lower disease control but higher use of the emergency department (ED) for asthma than NH whites (25, 26). Puerto Ricans and Mexican Americans were previously reported to have the highest and lowest mortality rates from asthma, respectively, of any ethnic group in the U.S. mainland (27). Although overall asthma mortality rates have decreased in the United States (28),

ethnic minorities (including Hispanics) continued to have higher asthma mortality rates than whites in 2009 (29).

## Potential Risk Factors for Asthma in Hispanics

### Racial Ancestry and Genetics

Hispanic is an ethnicity and not a race: Hispanics can be of any race. Most Hispanics have variable proportions of European, Native American, and African ancestry (1). For example, Mexicans, Mexican Americans, and Costa Ricans living in the Central Valley of Costa Rica

have, on average, a higher proportion of Native American ancestry (ranging from 35–64%) but a lower proportion of African ancestry (ranging from 3–5%) than Puerto Ricans (in whom Native American ancestry ranges between 12 and 15% and African ancestry ranges between 18 and 25%) (30–32).

Recent results suggest that racial ancestry influences lung function in Hispanic subgroups (30, 31), with more inconsistent findings for asthma *per se* (33, 34). Variation in trunk-to-limb ratio is unlikely to fully account for ancestral effects on lung function (35).

Consistent with findings in African American adults without asthma (36), African ancestry was linearly and inversely associated with FEV<sub>1</sub> or FVC (but not with FEV<sub>1</sub>/FVC) in Puerto Rican children (with or without asthma) (31). On the other hand, Native American ancestry has been positively associated with FEV<sub>1</sub> and FVC (but inversely associated with chronic obstructive pulmonary disease) in adults in New Mexico (37) and Costa Rica (30). Taken together, these results may partly explain the “Hispanic Paradox”—the wide divergence in the burden from airway diseases (asthma or chronic obstructive pulmonary disease) between subjects of Mexican descent (predominantly of

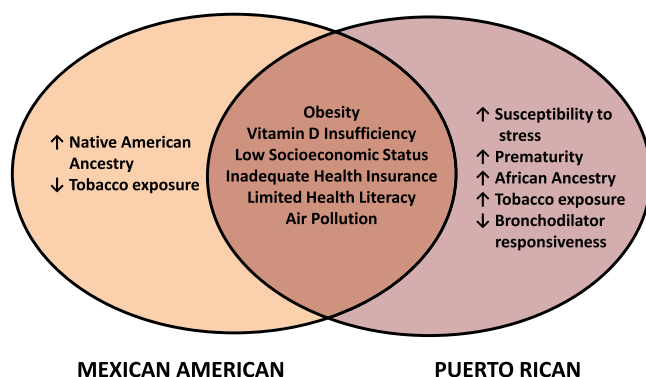


Figure 2. Potential explanations for the discrepancy in asthma or asthma morbidity between Mexican Americans and Puerto Ricans (the “Hispanic Paradox”).

**Table 2:** International Study of Asthma and Allergies in Childhood Phase Three: Estimated Prevalence of Asthma or Asthma Symptoms in 13- to 14-Year-Old Children in Selected Hispanic American Countries

| Country     | N      | Current Wheeze (%) | Asthma Ever (%) |
|-------------|--------|--------------------|-----------------|
| Argentina   | 12,716 | 12.5               | 9.3             |
| Bolivia     | 3,257  | 13.5               | 12.3            |
| Chile       | 13,793 | 15.3               | 15.1            |
| Costa Rica  | 2,436  | 27.3               | 23.2            |
| Cuba        | 3,026  | 17.8               | 30.9            |
| Ecuador     | 6,096  | 16.6               | 10.9            |
| El Salvador | 3,260  | 30.8               | 24.0            |
| Honduras    | 2,675  | 22.0               | 18.3            |
| Mexico      | 29,723 | 8.7                | 6.9             |
| Nicaragua   | 3,263  | 13.8               | 15.2            |
| Peru        | 3,022  | 19.6               | 33.1            |

Data from Reference 8.

European and Native American ancestry) and Puerto Ricans (predominantly of European and African ancestry). Whether genetic or environmental factors underlie ancestral effects on lung function is largely unknown.

Findings from genome-wide association studies (GWAS) and other studies suggest that a significant proportion of asthma-susceptibility variants are relevant to all ethnic groups, whereas others may be more relevant to particular ethnic groups (38–42). To date, no ethnic-specific asthma-susceptibility gene or variant has been confidently identified in Hispanic subgroups. A few asthma-susceptibility loci that were initially identified in subjects of European descent have been replicated at the single-nucleotide polymorphism (SNP) level in subjects of Puerto Rican and Mexican descent (e.g., the 17q21 locus [43, 44] and *IL33* [39]). Conversely, an asthma-susceptibility locus initially identified in Costa Ricans (*TLSP*) (40, 41) has been replicated in subjects of European and African descent (38, 45) as well as in a sample of combined Hispanic subgroups (38).

Insufficient statistical power and false-positive results may explain lack of replication of some GWAS findings or discovery of ethnic-specific loci for asthma in Hispanics. However, common variants identified by GWAS explain only part of the heritability of complex diseases such as asthma (46), with likely modest additional gains from studying rare variants (47). Thus, studies of gene-by-gene and gene-by-environment interactions, as well as epigenetics, are needed in Hispanic subgroups.

A few studies have focused on interactions between genetic variants and environmental or lifestyle (EL) factors (including sex [41, 48], SHS [49], allergens [50, 51], and air pollution [44]) on asthma in Hispanics. Using a candidate-gene approach, interactions between SNPs in *IL10* or *TGFB1* and dust mite allergen on asthma exacerbations or airway responsiveness were reported in Costa Ricans, with replication in NH whites (50, 51). Limited statistical power or insufficient replication has precluded confident identification of gene-by-environment interactions on asthma in Hispanic subgroups, in whom epigenetics has also been insufficiently studied.

#### Socioeconomic Status and Urbanization

Hispanic America faces unique challenges, as a high proportion of its population is now urban in the context of high rates of poverty, a polluted environment, and limited access to sanitation (4, 52). Consistent with worldwide literature (53), low socioeconomic status (SES) in/near urban areas, high levels of inequality, and urbanization are associated with childhood asthma in Hispanic America (54–57).

In the United States, Puerto Ricans and Mexican Americans are disproportionately represented among the poor but have widely divergent burdens from asthma (58, 59). SES was shown to be inversely associated with asthma in Mexican American children and young adults in San Francisco, California (60). In another report, Puerto Rican ethnicity was associated with asthma

in children in the U.S. mainland, even after adjustment for multiple indicators of SES (61). Together with previous results (1), these findings suggest that low SES is differentially correlated with unidentified factors affecting asthma risk in Puerto Ricans and Mexican Americans.

#### Stress

A growing body of literature strongly supports an association between stress and asthma (62–64) or asthma morbidity (62, 65–70).

Hispanics in the United States are disproportionately exposed to stressors such as poverty (6), unequal access to social benefits (71), discrimination (72), and physical or sexual abuse (73). Caregiver's stress or mental illness has been associated with asthma or asthma morbidity in Mexican American (74) and inner-city (~41% Puerto Rican and ~33% Mexican American) children in Chicago (75), minority children (~74% Hispanic) in New York (76), and Puerto Rican children in Puerto Rico or the Bronx (77, 78). Among school-aged children in Puerto Rico, physical or sexual abuse was associated with approximately twofold increased odds of asthma or asthma morbidity (70). The mechanisms underlying this association are unclear but may include dysfunction of the hypothalamic-pituitary-adrenal axis, cortisol insensitivity via down-regulation of receptors (79), abnormal production of inflammatory cytokines (80, 81), and increased susceptibility to environmental exposures (63, 82–84).

Signaling of the pituitary adenylate cyclase-activating polypeptide regulates physiologic stress responses and, together with corticotrophin-releasing hormone, modulates anxiety-related behavior (85). The gene for the PAC1 receptor (*ADCYAP1R1*) has been implicated in post-traumatic stress disorder (85) and childhood anxiety (86). Exposure to violence was associated with increased DNA methylation of *ADCYAP1R1* in Puerto Rican children, in whom such methylation changes were also associated with asthma (87). Moreover, an SNP in the promoter of *ADCYAP1R1* (rs2267735) was associated with asthma. Although these findings must be cautiously interpreted pending replication, they suggest that SNPs or DNA methylation in genes involved in stress regulation impacts asthma in Puerto Ricans.

**Table 3:** Estimates of the Prevalence (as Percentages) of Asthma or Asthma Outcomes in Hispanic and Hispanic Populations in the United States

| Study                     | Age Range of Participants | Outcome                       | Non-Hispanic White | Non-Hispanic Black | Hispanic (A/I) | Puerto Rican | Mexican | Dominican | Cuban | Other Hispanic | South American | Central American |
|---------------------------|---------------------------|-------------------------------|--------------------|--------------------|----------------|--------------|---------|-----------|-------|----------------|----------------|------------------|
| Leong et al. (13)         | NHIS (2006–2008) all ages | Lifetime asthma               | 12.2               | 13.7               | 9.9            | 21.8         | 8       |           |       |                |                |                  |
|                           |                           | Current asthma                | 7.8                | 9.5                | 6.3            | 14.2         | 4.9     |           |       |                |                |                  |
|                           |                           | Asthma attacks                | 4.2                | 4.9                | 3.6            | 8.4          | 2.8     |           |       |                |                |                  |
|                           | CHIS (2007) all ages      | Lifetime asthma               | 14.8               | 20.1               | 11.2           | 23.5         | 10.3    |           |       | 18.0*          | 16.6           | 9.2              |
| Lara et al. (16)          | Ages 2–17 yr, n = 46,511  | Lifetime asthma               | 12.7               | 15.8               | 12.4           | 25.8         | 10.1    | 14.9      | 14.9  | 11.6           |                |                  |
|                           | Ages ≥ 18 yr, n = 19,400  | Asthma attacks                | 5.8                | 7.5                | 5.13           | 11.8         | 4.0     | 5.3       | 5.9   | 4.7            |                |                  |
| Dumanovsky and Matte (17) | All ages                  | Asthma attacks                | 3.3                | 5.9                | 6.6            | 11.8         |         | 5.4†      |       | 10.4†          |                |                  |
| Akinbami et al. (18)      | All ages                  | Current asthma                | 7.7                | 11.2               | ~6.5           | 16.1         | 5.4     | 3.8‡      |       | 2.2‡           |                |                  |
| Rose et al. (19)          | Ages ≥ 18 yr              | Lifetime asthma               | 9.2                | 9.6                |                | 17.0         | 7.5     |           |       | 7.3            |                |                  |
| Eldeirawi et al. (21)     | Ages 2 mo–16 yr           | Current asthma                | 3.5                | 3.6                |                | 9.2          | 3.0     |           |       | 2.4            |                |                  |
|                           |                           | Lifetime asthma               |                    |                    |                |              | 8.5†    |           |       |                |                |                  |
|                           |                           | Wheezing (last 12 mo)         |                    |                    |                |              | 2.8‡    |           |       |                |                |                  |
|                           |                           | Lifetime asthma               |                    |                    |                |              | 21.4†   |           |       |                |                |                  |
|                           |                           | Hospitalized for asthma, ever |                    |                    |                |              | 12.6‡   |           |       |                |                |                  |
| Cohen et al. (23)         | Ages 5–13 yr              |                               |                    |                    |                | 35.3§        |         |           |       |                |                |                  |
|                           |                           |                               |                    |                    |                | 41.3         |         |           |       |                |                |                  |
|                           |                           |                               |                    |                    |                | 36.5§        |         |           |       |                |                |                  |
|                           |                           |                               |                    |                    |                | 48.7         |         |           |       |                |                |                  |

Definition of abbreviations: CHIS = California Health Interview Survey; NHIS = National Health Interview Survey.

\*Two or more Hispanic subgroups.

†Born in the United States.

‡Born in home country.

§Puerto Ricans living in the Bronx, NY.

||Puerto Ricans living in Puerto Rico.

### Tobacco Smoke and Air Pollution

Consistent with findings in NHs (88–91), those in Hispanics support a causal association between smoking (including environmental tobacco smoke) or air pollution and asthma morbidity.

**Hispanic America.** The prevalence of current smoking varies among Hispanic countries and the United States (see Table E1 in the online supplement). A study in Argentina showed that ~33% of the population (and ~13% of adolescents) currently smokes and that ~60% of the population is exposed to secondhand smoke (SHS) at home (92). In that study, current smoking was associated with current asthma (odds ratio [OR] = 1.8; 95% CI, 1.4–2.4). A study of Mexican adolescents found an equally high prevalence of current smoking in subjects with and without asthma (~34%) (93).

Residential proximity to a major road (a proxy for traffic-related pollution) has been associated with asthma (94), asthma symptoms, and atopy (95) among children in Lima, where particulate matter (PM) levels are higher than in rural areas of Peru (55). Exposure to aggregate or individual components of traffic exhaust (NO<sub>2</sub>, ozone, and PM) is common and associated with wheezing (96) and reduced lung function (97) in children in Mexico City, where a sound emissions control policy could prevent as many as 2.99 million asthma attacks (98). In contrast to the prominent role of traffic-related pollution in Mexico City, exposure to volatile organic compounds had a relatively greater estimated effect on asthma morbidity in a study of urban Argentinean children (99).

**United States.** Hispanic children are more than 2.5 times more likely to live near heavy traffic than white children in California (100). In a study of a combined sample of Hispanic (n = 3,343) and African American (n = 977) children in five cities in the U.S. mainland and in Puerto Rico, exposure to NO<sub>2</sub> (estimated from residential history and prior air monitoring data) in the first year of life was associated with asthma (OR = 1.17; 95% CI, 1.04–1.31) (101). In Puerto Rico, exposure to PM less than 2.5 µm in diameter (PM<sub>2.5</sub>) or SO<sub>2</sub> during the first 3 years of life was also associated with asthma. In another study, yearly mean PM<sub>2.5</sub> exposure was not significantly

associated with asthma or asthma attacks among Hispanic adults (not differentiated into subgroups) (102).

Few studies have examined interactions between genetic variants or environmental exposures and air pollution on asthma. In a study of 3,023 children (including ~30% Hispanics, without differentiation among subgroups), homozygosity for the *TGFB1*-509T allele was associated with asthma in subjects exposed to traffic-related emissions or maternal smoking in early life (103). In another study including 349 Dominican and African American children without asthma, prenatal or early postnatal exposure to cockroach allergen was associated with atopy, particularly among children exposed to polyaromatic hydrocarbons. In a subgroup analysis, this association was stronger in children who were null for a mutation in the gene for glutathione-S-transferase (*GSTM1*) (104). In another study of urban children (~50% Hispanic), traffic-related pollution was associated with asthma only in those exposed to violence (63).

Although tobacco use is lower in Mexican Americans than in African Americans or whites, SHS is associated with asthma and nocturnal awakenings from asthma in Mexican American children (105, 106). In a study including African American, Mexican, and Puerto Rican children, *in utero* SHS was associated with persistent asthma (107) and poor asthma control (108).

### Vitamin D

Findings in Hispanic and NH populations have motivated ongoing clinical trials of vitamin D supplementation to prevent asthma or asthma morbidity (109, 110).

Vitamin D insufficiency (a serum 25[OH]D < 30 ng/ml) is common among Hispanic Americans in Argentina, Mexico, and Costa Rica (111–114). In a study of 1,025 Mexican children, 28% of subjects aged 6 to 12 years had vitamin D insufficiency (113), which was more common in urban (43%) than rural (25%) areas. Vitamin D insufficiency was common and associated with asthma morbidity in a study of 616 Costa Rican children (114).

In two studies, vitamin D insufficiency was found in ~90% of Mexican Americans aged 12 years and older (110) and in

more than 44% of school-aged children in Puerto Rico (115). Among 273 children with asthma in Puerto Rico, vitamin D insufficiency was associated with severe exacerbations, with a greater effect estimate in nonatopic children (OR = 6.2; 95% CI, 2–21.6) than in atopic children (OR = 2.0; 95% CI, 1–4.1) (115). Although preliminary, these findings suggest that vitamin D partly impacts asthma exacerbations through nonatopic mechanisms (e.g., steroid responsiveness or immune modulation of viral infections).

### Obesity

Obesity is associated with asthma (116, 117), asthma morbidity (118–121), and reduced response to ICS (122, 123) in children and adults, with most—but not all—studies showing a stronger link in female than in male subjects. The explanation for these observations is the subject of intense research (124, 125).

Obesity is becoming increasingly more common in Hispanic America (126–129). In the United States, overweight or obesity is common and associated with asthma in Mexican Americans and Puerto Ricans (130–134). A study of 681,122 children in California found that body mass index was more strongly associated with asthma in Hispanics (predominantly Mexican Americans) than in other ethnic groups (135). Of relevance to Mexican Americans and other Hispanic subgroups with substantial Native American ancestry, a recent systematic review found obesity rates in the United States to be highest in American Indians (136).

Few reports have examined obesity and asthma morbidity in U.S. Hispanics. Among African American and Hispanic (~29% Mexican and ~40% Puerto Rican) children, obesity was associated with poor asthma control in boys, regardless of ethnicity. Among girls, however, obesity was more strongly associated with poor asthma control in Mexican Americans (OR = 1.91; 95% CI, 1.12–3.28) (137). Of note, only 17.6% of participants in that study had well-controlled asthma. In a study of Puerto Rican children, adiposity measures other than body mass index (percent body fat, waist circumference, and waist-to-hip ratio) provided a better assessment of obesity and asthma in Puerto Ricans, in whom atopy may mediate the effect of obesity on asthma morbidity (132).

### Parasitic Infections

Few studies have examined the complex relation between parasitic infection and asthma in Hispanics (138–141). Data from Hispanic America indicate that chronic parasitic (11, 138, 142) and other infections (142) of childhood are associated with lower risk of atopy, but the effects on asthma are less clear. Allergic sensitization to *Ascaris*, but not active infections *per se*, appears to be a risk factor for asthma symptoms (140, 143), an observation that could be explained by migration of *Ascaris* larvae to the lungs with periodic exposures (140). Sensitization to *Ascaris* has been associated with asthma morbidity or airway responsiveness among children in Costa Rica (where parasitism is rare) (139) and rural Venezuela (144). A study of Ecuadorean schoolchildren provided some evidence that active parasitic infections might attenuate the association between atopy and wheeze (140) and is supported by the observation of a lower prevalence of atopic wheeze among children with heavy parasite burdens with *Trichuris trichiura* (145).

A study comparing schoolchildren living in Ecuadorean communities who were and were not treated with antihelminthics over 15 to 17 years found that treatment was associated with a higher prevalence of atopy but did not appear to affect asthma symptoms (138). Ongoing longitudinal studies (146) and clinical trials should help advance this field.

## Diagnosis and Management of Asthma in Hispanics

### Hispanic America

Recent studies continue to suggest that barriers to diagnosis and management of asthma in Hispanic America include inadequate disease-specific education and healthcare access (e.g., spirometric testing or use of controller medications), both of which can lead to poor asthma control (147). Only 8% of participants in a study of adults and adolescents with current asthma in four Latin American countries and Puerto Rico could be objectively classified as having well-controlled disease, even though ~60% believed that their asthma was completely or well controlled (147).

Over the last few years, implementation of nationwide programs that focused on

improving education, diagnosis, and (particularly) treatment has been correlated with reduced use of specialty care (148), increased use of controller medications (149), and decreased morbidity/mortality from asthma (148, 149) among children and adults in El Salvador, Chile, and Costa Rica.

### United States

Recent studies suggest that language barriers (150), lack of health insurance (151, 152), inadequate health literacy (153), and cultural beliefs continue to contribute to asthma morbidity among U.S. Hispanics.

Hispanics continue to be less likely to be prescribed or adhere to controller medications such as ICS (154–156). A nationwide study of 2,499 children showed that although the use of preventive asthma medications increased in all ethnic groups from 1988 through 2004 to 2005 through 2008, Mexican Americans were 40% less likely to use preventive asthma medications than whites at the end of follow-up (95% CI for OR, 0.4–0.9), even after accounting for health insurance and other covariates (154). In a study of 277 children who were prescribed controller medications for asthma, Puerto Ricans or Dominicans in Rhode Island and Puerto Ricans in Puerto Rico were less likely to adhere to treatment than NH whites in Rhode Island (156). Among all children, family organization and parental beliefs were associated with medication adherence after accounting for SES (156). Nonadherence with controller medications may also be due to concerns about side effects, medication costs, language barriers, and low expectations for asthma control (157, 158).

Inadequate literacy or numeracy (understanding of basic mathematics) may be a barrier to asthma management in children of Mexican (159) and Puerto Rican (153) descent. Among Puerto Rican children (153), low parental numeracy was associated with visits to the ED or urgent care for asthma. Among participants not using ICS, low parental numeracy was associated with nearly threefold increased odds of one or more hospitalizations for asthma (95% CI, 1.4–5.6;  $P < 0.01$ ) (153).

Subjective perception of lung function may differ by ethnicity (160). In a study of school-aged children, NH whites in Rhode Island had a more accurate

perception of their peak flow measurement than either Puerto Ricans in Puerto Rico or Hispanics in Rhode Island. More accurate perception of lung function was in turn associated with decreased healthcare use for asthma (160).

The efficacy of asthma medications may vary across Hispanic subgroups. Puerto Ricans have lower bronchodilator responsiveness than subjects of Mexican descent (161). Genetic variants may explain this finding, but confirmatory studies are needed (162).

A home-based study in Puerto Rico assessed an intervention consisting of educating families of low-income children on culturally appropriate asthma management (163). Such intervention was associated with decreased ED use, hospitalizations, and nighttime symptoms. Findings from this and another study (164) support further assessment of culturally tailored interventions to improve asthma management in Puerto Ricans and other Hispanic subgroups.

## Future Directions

Considerable progress has been made in identifying or better understanding potential protective or risk factors for asthma in Hispanic subgroups (Table E2), but many questions remain unanswered.

Studies of asthma in Hispanic America should focus on EL factors that are more relevant to asthma in this region, including urbanization, parasitism, SHS, air pollution, obesity, and stress.

In the United States, studies of asthma in Hispanic subgroups other than Puerto Ricans or Mexican Americans are needed. Further understanding of the “Hispanic Paradox” can be gained by identifying genetic, epigenetic, and EL factors that predispose Puerto Ricans or protect Mexican Americans against asthma (Figure 2). Such factors may include but are not limited to rare genetic variants, DNA methylation, prematurity (165), SHS, diet, and stress. In parallel with this effort, studies of factors that are common in both Puerto Ricans and Mexican Americans and may affect asthma (obesity or vitamin D insufficiency) are needed. Regarding clinical trials, culturally appropriate interventions that address multiple aspects of asthma management should be prioritized for funding.

The Affordable Care Act (ACA) should improve healthcare access and asthma management in previously uninsured Hispanics (166). However, several barriers may preclude optimal asthma care for those

newly insured or those not covered by the ACA (e.g., migrants without legal residency status, children in states not approving Medicaid expansion). Removing residual barriers to care for the insured, coupled with advocacy for

broader healthcare access, are essential to optimize asthma care in Hispanics. ■

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## **Asthma in Hispanics: An 8-year Update**

Franziska J. Rosser, Erick Forno, Philip J. Cooper, Juan C. Celedón

**ONLINE REPOSITORY**

### Search Strategy and Selection Criteria:

We searched PubMed for articles published from January 1<sup>st</sup>, 2006 to December 31<sup>st</sup>, 2013. For sections new to the review (Vitamin D and Stress), relevant articles from prior to 2006 were included. All sections were searched with terms “asthma” (Mesh term “asthma” or “exercise-induced asthma” or “respiratory sounds” (to include wheezing)) and “Hispanics” (Mesh term “Hispanic American” [includes Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture living in the United States] or “Latin America”[includes Central America, Caribbean, Mexico] or “Central America” or “South America”). Countries not defined as Hispanic by the US Census were excluded (e.g. Brazil).

For specific sections, additional terms of “prevalence”, “morbidity”, “mortality”, “genetics”, “epigenetics”, mesh term “poverty”, mesh term “social class” [including “socioeconomic status”], mesh term “stress disorders” [includes “traumatic acute” and “post traumatic”], mesh term “violence” [including “domestic” and “family”], mesh term “tobacco smoke pollution”, mesh term “air pollution” [includes “indoor air pollution” and “tobacco smoke pollution”, mesh term “Vitamin D” [includes “ergocalciferols” and “25-Hydroxyvitamin D2”], mesh term “obesity” and mesh term “pediatric obesity”, “parasites”, “diagnosis” and “management”. Articles were selected based on relevance. Additionally, if few articles (per section) were available, sections were searched with above mentioned terms for asthma and section topic. Articles containing a significant portion of Hispanic participants were included even if initially the article was not categorized as Hispanic by PubMed.

Lastly, articles germane to the topic from the authors' personal collection were also added.

**Table E1. Prevalence of current smoking among  
persons  $\geq 15$  years in selected Hispanic  
American countries and the United States**

| Country            | Smoking Prevalence<br>among $\geq 15$ years, 2009 |      |
|--------------------|---------------------------------------------------|------|
|                    | Female                                            | Male |
| Argentina          | 22%                                               | 32%  |
| Bolivia            | 18%                                               | 42%  |
| Chile              | 33%                                               | 38%  |
| Costa Rica         | 8%                                                | 24%  |
| Dominican Republic | 13%                                               | 17%  |
| Guatemala          | 4%                                                | 22%  |
| Mexico             | 8%                                                | 24%  |
| Paraguay           | 14%                                               | 30%  |
| Peru               | 9%                                                | ---  |
| United States      | 25%                                               | 33%  |
| Uruguay            | 22%                                               | 31%  |

Data from the World Health Organization. Available at

<http://www.who.int/gho/tobacco/use/en/> Accessed February 22, 2014

**Table E2. Summary of studies of asthma or asthma-related outcomes in Hispanics (published since 2006 and included in this review)**

| First author, year published (reference in the main manuscript) | Study Design                                                                                                                                                                    | Main Findings                                                                                                                                                                                                                                                                                        | Study Limitations                                                                                                            |
|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| <b>Prevalence, Morbidity and Mortality</b>                      |                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                      |                                                                                                                              |
| Mallol et al, 2010 (8)                                          | Cross-sectional study of the prevalence and severity of asthma in 165,917 school-aged children from 56 centers in 17 Latin American countries                                   | Estimates of the prevalence of asthma and asthma symptoms varied among countries. This variability was not correlated with gross national income, latitude, or tropical setting. Asthma was common in children living in low SES areas.                                                              | Inadequate assessment of the prevalence of asthma in rural areas of Hispanic America                                         |
| Dennis et al 2012 (10)                                          | Cross-sectional study of the prevalence of asthma, allergic rhinitis and eczema among 5,978 subjects ages 1 to 59 yrs. in six Colombian cities                                  | Current asthma (12%) and hospitalizations or emergency department visits for asthma in the prior year were common among study participants                                                                                                                                                           | Asthma outcomes are not directly comparable to those reported in ISAAC<br><br>Non-assessment of asthma in rural areas        |
| Cooper et al, 2013 (11)                                         | Cross-sectional study of environmental or lifestyle factors, atopy and current wheeze among school-aged Ecuadorean children living in rural (n=4,295) and urban (n=2,526) areas | Current wheeze was more common in urban areas than in rural areas. Lack of potable drinking water was associated with current wheeze (adjusted [a] odds ratio [OR]=1.44, 95% CI=1.16 to 1.78, P <0.01). A small proportion of current wheeze was attributable to atopy, particularly in rural areas. | Potential recall bias and misclassification bias.<br><br>Cross-sectional design limits assessment of temporal relationships. |
| Neffen et al, 2006 (12)                                         | Ecological study of trends in mortality rates from asthma and sales of asthma medications (1980-1989 to 1990-1999) in Argentina                                                 | Increased sale of inhaled corticosteroids (ICS) was correlated with decreased asthma mortality (r= -0.84, p=0.003).                                                                                                                                                                                  | No information about individual exposures or treatment<br><br>Potential ecological fallacy                                   |
| Leong, Ramsey and Celedón, 2012 (13)                            | Review of studies of asthma in minorities, including the National Health Interview Survey (2006-2008), the National Hospital Ambulatory Medical Care Survey (2005-              | Minorities are disproportionately affected by asthma. There is marked variation in the prevalence of current or lifetime asthma between Mexican Americans and Puerto                                                                                                                                 | NHIS data on Hispanics referred predominantly to Mexican Americans.<br><br>Some data were only available for all             |

|                                 |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                         |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                 | 2007), and the California Health Survey (2007).                                                                                                                                                                             | Ricans.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Hispanics, without differentiation into subgroups                                                                                                       |
| Subramanian et al, 2009 (14)    | Multilevel, multi-method longitudinal accelerated cohort study of nativity and asthma in 2,209 participants (ages 0 to 18 yrs.) from the Project on Human Development in Chicago Neighborhoods (2000-2001)                  | Substantial heterogeneity in lifetime asthma prevalence among Hispanic subgroups, with nativity being a stronger predictor of lifetime asthma prevalence than race or Hispanic ethnicity.                                                                                                                                                                                                                                                                                                                                                                                                                      | Uncertain generalizability (Hispanics were predominantly of Mexican descent)<br><br>Cross sectional design limits assessment of temporal relationships. |
| Moorman et al, 2011 (15)        | Cross-sectional study of asthma prevalence among subjects of all ages who participated in the National Health Interview Survey (2006-2008)                                                                                  | Puerto Ricans had higher prevalence of current asthma than non-Hispanic Whites, non-Hispanic Blacks and multiracial individuals. Among Puerto Ricans, poverty was correlated with current asthma                                                                                                                                                                                                                                                                                                                                                                                                               | Potential recall bias and misclassification bias.<br><br>Cross sectional design limits assessment of temporal relationships.                            |
| Lara et al, 2006 (16)           | Cross-sectional study of lifetime asthma and asthma attacks in 46,511 participants (ages 2 to 17 years) from the National Health Interview Survey (1997-2001)                                                               | Puerto Ricans had the highest prevalence of lifetime asthma and recent asthma attacks. Compared with U.S.-born non-Hispanic white children with U. S.-born parents, the aORs were 1.95 (95% CI: 1.48-2.57) for Puerto Rican children in families with the child and parent(s) born in the 50 states/District of Columbia and 2.50 (95% CI: 1.51-4.13) for island-born Puerto Rican children with island-born parents. The corresponding aORs for Mexican children were 1.05 (95% CI: 0.90-1.22) for families born in the 50 states/District of Columbia and 0.43 (95% CI: 0.29-0.64) for those born in Mexico. | Cross sectional design limits assessment of temporal relationships<br><br>Potential recall bias and misclassification bias                              |
| Dumanovsky and Matte, 2007 (17) | Cross-sectional study of the prevalence of asthma attacks (defined as an asthma diagnosis and symptoms in the prior year) among 19,400 subjects (aged 18 years and older) in the New York City Telephone survey (2003-2004) | Puerto Ricans had the highest prevalence of asthma attacks. Dominicans and other Hispanics not born in the U.S. had a lower prevalence of asthma attacks than their U.S. born counterparts.                                                                                                                                                                                                                                                                                                                                                                                                                    | Potential selection bias and recall bias<br><br>Uncertain generalizability to Hispanics living in other states or territories of the U.S.               |
| Akinbami et al, 2012 (18)       | NCHS Data Brief and NHIS data used to estimate asthma prevalence.                                                                                                                                                           | Puerto Ricans had the highest asthma prevalence of all ethnic groups.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Potential recall bias and misclassification bias                                                                                                        |

|                                       |                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                             |                                                                                                                                               |
|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Rose, Mannino and Leaderer, 2006 (19) | Cross-sectional study of the prevalence of asthma in 95,615 participants (aged $\geq 18$ years) from the National Health Interview Survey (1998-2000)                                                             | The prevalence of asthma was highest in Puerto Ricans and lowest in Mexican Americans, with geographic variations in asthma prevalence.                                                                                                                     | Potential recall bias and misclassification bias                                                                                              |
| Eldeirawi and Persky, 2006 (22)       | Cross-sectional study of lifetime asthma and current wheezing among 1,770 Mexican Americans (aged 12 to 19 years) in the National Health and Nutrition Examination Survey (NHANES) (1999-2000 and 2001-2002)      | Among Mexican Americans, birth place in the US and high acculturation were associated with greater odds of asthma and current wheezing                                                                                                                      | Relatively small sample size precluded adequate adjustment for potential confounders<br><br>Potential recall bias and misclassification bias  |
| Cohen et al, 2007 (23)                | Cross-sectional study of birth place and lifetime asthma and hospitalizations for asthma in a randomly selected cohort of 2,491 Puerto Rican children (ages 5-13 years) living in the Bronx (NY) and Puerto Rico  | Among Puerto Rican children, birth in Puerto Rico was associated with increased odds of asthma (aOR=1.7 [1.03-1.57]) and hospitalizations for asthma (aOR=1.47 [1.04-2.07]).                                                                                | Potential recall bias and misclassification bias<br><br>Lack of data on potential confounders (e.g. quality and access to health care).       |
| Moorman et al, 2013 (24)              | Cross-sectional study of the prevalence of asthma attacks among 14,230 participants (all ages) in the National Health Interview Survey (2001-2010)                                                                | Female sex, childhood, poverty, and Puerto Rican or multiracial ethnicity were all associated with more asthma attacks. Asthma attacks were more common in the South and West                                                                               | Potential recall bias and selection bias<br><br>Lack of data on environmental or lifestyle factors                                            |
| Everhart et al, 2012 (25)             | Cross-sectional study of caregiver quality of life in a convenience sample of 972 children with asthma (ages 7-16 years) living in Rhode Island (Puerto Rican, Dominican and non-Hispanic White) and Puerto Rico. | Hispanic caregivers at both study sites reported worse quality of life (QOL) scores, with Puerto Rican caregivers in the island of Puerto Rico reporting the worst scores. Caregiver QOL was inversely associated with asthma morbidity at both study sites | Potential selection bias, recall bias and misclassification bias<br><br>Cross-sectional design precludes assessment of temporal relationships |
| Canino et al 2012 (26)                | Cross-sectional study of emergency department (ED) utilization in a convenience sample of 804 children (ages 7 to 15 years) with asthma in Puerto Rico and Rhode Island                                           | Hispanic children at both sites had significantly higher ED utilization rates than non-Hispanic whites. Poor asthma or greater asthma severity (per parental report) and type of health insurance were also associated with increased ED utilization.       | Cross sectional study limits assessment of temporal relationships.<br><br>Potential selection bias and misclassification bias                 |
| Sly, 2006 (28)                        | Cross-sectional study of asthma mortality using data from the National Center for                                                                                                                                 | Although asthma mortality decreased in Hispanics from 1999 to 2001, Hispanics still                                                                                                                                                                         | Lack of data for Hispanic subgroups                                                                                                           |

|                                 |                                                                                                                                                                                  |                                                                                                                                                                                                                    |                                                                                                                                                                                                                             |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                 | Health Statistics (1999-2001) identifying asthma (ICD-10) as the underlying cause of death among residents in the US mainland and D.C.                                           | had higher asthma mortality rates than non-Hispanic whites in 2001                                                                                                                                                 | Potential misclassification bias                                                                                                                                                                                            |
| <b>Racial Ancestry/Genetics</b> |                                                                                                                                                                                  |                                                                                                                                                                                                                    |                                                                                                                                                                                                                             |
| Chen et. al., 2013 (30)         | Hybrid case-control/family-based study of Native American ancestry and COPD or lung function in 578 Costa Rican adolescents and adults with and without COPD                     | Native American ancestry was associated with decreased odds of COPD but positively associated with lung function in Costa Ricans.                                                                                  | Cross sectional study limits assessment of temporal relationships<br><br>Limited statistical power due to relatively small sample size                                                                                      |
| Brehm et al., 2012 (31)         | Cross-sectional study of African ancestry and lung function in 943 Puerto Rican children (ages 6-14 years) with and without asthma                                               | African ancestry was significantly associated with lower FEV1 and FVC among children with and without asthma. However, the observed association was stronger in children with asthma.                              | Cross-sectional design precludes assessment of temporal relationships<br><br>Non-assessment of trunk to limb ratio                                                                                                          |
| Choudhry et al, 2006 (33)       | Case-control study of interactions between racial ancestry and socioeconomic status (SES) on asthma in Puerto Ricans with (n=135) and without (n=156) asthma (ages 8-40 years)   | Among subjects of low SES, European ancestry was associated with increased odds of asthma but African ancestry was associated with decreased odds of asthma. Among subjects of high SES, the converse was observed | Small sample size<br><br>Potential selection bias<br><br>Non-replication of the reported interaction in another cohort                                                                                                      |
| Vergara et al, 2009 (34)        | Case-control study of African ancestry and asthma or total IgE in subjects with (n=368) and without (n=365) asthma (aged $\geq 8$ years)                                         | African ancestry was significantly associated with asthma (aOR=2.97, 95% CI=1.08-8.08) and an elevated total IgE (aOR=1.9, 95% CI=1.2-3.1).                                                                        | Racial ancestry assessed with small number of markers<br><br>Potential misclassification of asthma<br><br>Possible residual confounding by SES                                                                              |
| Bruse et al, 2011 (37)          | Longitudinal study of Hispanic ethnicity and COPD or lung function among 1,949 former and current smokers (Hispanic and non-Hispanic white) from New Mexico, aged 40 to 75 years | Hispanic ethnicity (which was highly correlated with greater Native American ancestry) was associated with reduced lung function decline and decreased odds of chronic obstructive pulmonary disease (COPD).       | Inability to conduct an analysis of Native American ancestry and COPD or lung function in Hispanics only (due to small sample size)<br><br>Racial ancestry assessed with relatively few ancestry informative markers (AIMs) |

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| Torgerson et. al. (38)      | Meta-analysis of genome-wide association studies (GWASs) of asthma in 5,416 ethnically diverse individuals, with replication studies in an additional 12,649 individuals.                     | Five asthma-susceptibility loci were identified, including four previously reported and a new locus at <i>PYHIN1</i> in persons of African descent.                                                                                                                                       | Limited sample size precluded adequate replication studies in specific Hispanic subgroups                                                            |
| Galanter et al, 2011 (39)   | Candidate-gene family-based association study of 124 genes (previously implicated on asthma) and asthma in subjects of Mexican and Puerto Rican descent                                       | Only a small number of genetic association findings were replicated in Mexicans and Puerto Ricans; those that were replicated were “cosmopolitan” (i.e. not specific to any particular ethnic group).                                                                                     | Limited statistical power due to small sample size<br><br>Lack of replication in other cohorts including subjects of Puerto Rican or Mexican descent |
| Hunninghake et al 2008 (40) | Genome-wide linkage analysis of 653 members of eight large families in Costa Rica with children with asthma, ages 6-14 years                                                                  | In a sex-stratified analysis chromosome 5q23 was linked to IgE to cockroach in females. A strong candidate gene in the linked region ( <i>TSLP</i> ) was associated with cockroach IgE in Costa Rican girls, and with total IgE in Costa Rican girls and non-Hispanic white girls in CAMP | Limited replication of association findings<br><br>Non-exclusion of other relevant candidate genes in the linked region                              |
| Hunninghake et al 2010 (41) | Genetic association study of <i>TSLP</i> and asthma in 439 Costa Rican parent-child trios, with replication studies in four cohorts.                                                          | Two SNPs in <i>TSLP</i> were significantly associated with asthma in the combined analysis of all cohorts. In this analysis, sex-specific findings were noted for each SNP                                                                                                                | Limited statistical power to exclude weak effects in the sex-stratified analysis                                                                     |
| Forno et al, 2012 (42)      | GWAS of age of onset of asthma among participants in the Childhood Asthma Management Program, with replication studies in three cohorts of children in North America, Sweden, and Costa Rica. | Two SNPs were associated with earlier onset of childhood asthma in the combined analysis of all cohorts                                                                                                                                                                                   | Inadequate sample size to detect modest genetic effects.<br><br>Retrospective assessment of asthma onset in three of the study cohorts               |
| Galanter et al, 2008 (43)   | Genetic association study of <i>ORMDL3</i> and asthma in parent-child trios of Puerto Rican, Mexican, and African American descent                                                            | Two SNPs in <i>ORMDL3</i> were significantly associated with asthma in both Mexicans and African Americans, with a non-statistically significant trend for an association in Puerto Ricans.                                                                                               | Limited statistical power due to small sample size                                                                                                   |
| Wu. et al, 2009 (44)        | Case-parent triad study of 615 nuclear families of children with asthma in Mexico, ages 4-17 years, attempting to                                                                             | Two alleles were significantly associated with asthma, suggesting that <i>ORMDL3</i> and <i>GSDML</i> contribute to asthma in Mexican children.                                                                                                                                           | Small proportion of non-atopic children with asthma (8%).                                                                                            |

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|                                                         | replicate the association of <i>ORMDL3</i> and <i>GSDML</i> with asthma and atopy.                                                                                                            |                                                                                                                                                                                                                                  | Limited statistical power to detect modest genetic effects                                                                |
| Raby et al, 2007 (48)                                   | Genome-wide linkage analysis of total IgE in families of 655 Costa Rican children (ages 6-14 years) with asthma                                                                               | Sex-stratified analysis showed linkage of a locus on chr. 20p12 to total IgE in boys but not in girls.                                                                                                                           | Lack of replication in independent cohorts<br><br>Non-mapping of the linked region                                        |
| Wu et al, 2007 (49)                                     | Case-parent triad study of 596 nuclear families of children with asthma (ages 4-17 years) in Mexico, evaluating the association between TNF $\alpha$ or TNF $\beta$ with asthma and atopy.    | Two SNPs in <i>TNF-<math>\alpha</math></i> were associated with asthma, particularly among children of non-smoking parents (relative risk [RR]=2.06, 95% CI=1.19-3.55 for TNF-308/A and RR=2.21, 95% CI=1.14-4.30 for TNF-238/A) | Lack of replication in independent cohorts                                                                                |
| Hunninghake et al, 2008 (50)                            | Study of gene ( <i>IL10</i> ) by dust mite allergen interactions on allergy and asthma in 417 Costa Rican parent-child trios and 503 nuclear families of North American children with asthma. | Dust mite allergen level significantly modified the effect of some <i>IL10</i> SNPs on total IgE and asthma exacerbations.                                                                                                       | Limited power to detect interactions with modest effects                                                                  |
| Sharma et al, 2009 (51)                                 | Study of gene ( <i>TGFB1</i> ) by dust mite allergen interactions on asthma severity in 416 Costa Rican parent-child trios and 465 North American nuclear families of children with asthma    | Certain SNPs in <i>TGFB1</i> were associated with asthma exacerbations and airway responsiveness. Some of these SNPs interacted with dust mite allergen on asthma exacerbations and airway responsiveness                        | Lack of replication of some findings may be due to underlying differences between study populations.                      |
| <b>Socio-Economic Status (SES)/Urbanization Studies</b> |                                                                                                                                                                                               |                                                                                                                                                                                                                                  |                                                                                                                           |
| Rodriguez et al, 2011 (54)                              | Ecological study of asthma in children (5 to 17 years) in 59 communities in Esmeraldas, Ecuador (2005-2008)                                                                                   | The prevalence of childhood asthma increased with increasing levels of urbanization.                                                                                                                                             | Potential ecologic fallacy<br><br>Lack of data at the individual level                                                    |
| Robinson et al, 2011 (55)                               | Cross-sectional study of urbanization and asthma or atopy in 1,851 participants from Pampas (peri-urban town) and Tumbes (rural village) in Peru                                              | Adolescents from peri-urban environments, with increased air pollution exposure, had a higher prevalence of asthma and atopy than those in rural environments.                                                                   | Cross sectional design limits assessment of temporal relationships.<br><br>Limited age range may affect generalizability. |
| Valdivia et al, 2009 (56)                               | Cross-sectional study of SES and asthma in 4,561 children (ages 6-7 and 13-14 years) in Santiago (Chile)                                                                                      | Low SES was associated with increased prevalence of childhood asthma                                                                                                                                                             | Cross sectional design limits assessment of temporal relationships<br><br>Potential misclassification of asthma           |

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| Fattore, Santos and Barreto, 2013 (57) | Ecological study of SES and asthma in 29 Latin American urban centers that participated in ISAAC III (2002-2003)                                                                                     | Crowding, sanitation, variation in infant mortality rates and homicide rates explained a significant proportion of the variance in asthma prevalence between centers ( $r^2=0.75$ ).            | Potential ecological fallacy<br><br>Lack of data at the individual level                                                                                                                                                   |
| Thakur et al, 2013 (60)                | Case-control study of SES and asthma in 1,843 participants from the GALA II and SAGE II studies                                                                                                      | SES was associated with asthma, but the direction of the association differed by ethnic and racial group.                                                                                       | Cross sectional design limits assessment of temporal relationships.<br><br>Ethnic groups consisted of Mexican Americans and “other Hispanics” only.<br><br>Lack of adjustment for confounders such as violence or obesity. |
| Holt, Theall & Rabito, 2013 (61)       | Longitudinal cohort of the incidence of asthma in 1,784 children from Fragile Families and Child Well-being Study, In-Home longitudinal Study of Pre-Schooled Age Children, followed to age 5 years, | Among SES indicators, lack of health insurance was significantly associated with asthma. The only neighborhood factor that was significantly associated with asthma was educational attainment. | Potential misclassification of asthma<br><br>Non-assessment of temporal changes in neighborhood characteristics                                                                                                            |
| <b>Stress</b>                          |                                                                                                                                                                                                      |                                                                                                                                                                                                 |                                                                                                                                                                                                                            |
| Cohen et al, 2008 (70)                 | Cross-sectional study of physical or sexual abuse in 1,213 children (ages 5 to 13 years) in Puerto Rico                                                                                              | Physical or sexual abuse in the prior year was associated with current asthma, health care use for asthma, and medication use for asthma (aOR=2.35, 95% CI= 1.05-5.26, P <0.05).                | Cross sectional design limits assessment of temporal relationships<br><br>Limited phenotypic assessment of asthma                                                                                                          |
| Martin et al, 2007 (74)                | Cross-sectional study of acculturation and asthma in 455 Mexican American caregivers of children ages 5-12 years in Chicago                                                                          | Caregiver life stress and insurance type were associated with childhood asthma                                                                                                                  | Cross sectional design limits assessment of temporal relationships.<br><br>Potential selection bias                                                                                                                        |
| Gupta et al, 2010 (75)                 | Cross-sectional study of stress and asthma or asthma morbidity in 874 students in Chicago’s Humboldt Park, a primarily minority community                                                            | Report of caregiver stress, stress due to community crime, and inability to cope with everyday life were positively associated with asthma morbidity and poor asthma control.                   | Cross sectional design limits assessment of temporal relationships.<br><br>Potential selection bias                                                                                                                        |
| Vangeepuram et al, 2012 (76)           | Cross-sectional study of parental perception of neighborhood safety and                                                                                                                              | Feeling unsafe walking in the neighborhood was associated with asthma (aOR = 1.89, 95%                                                                                                          | Cross sectional design limits assessment of temporal relationships                                                                                                                                                         |

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|                                        | asthma in 504 urban children (ages 6 to 8 years)                                                                                                                                                         | CI= 1.13-3.14, P<0.05).                                                                                                                                                                                                                                                                                            | Potential misclassification of asthma in young children                                                                      |
| Feldman et al, 2010 (77)               | Cross-sectional study evaluating children's physical health problems, psychological factors, and acculturative stress in child-parent dyads from the South Bronx, NY (n=1,138) and Puerto Rico (n=1,353) | Children's physical health problems (including asthma) were associated with children's anxiety, parental psychopathology, and acculturation stress.                                                                                                                                                                | Cross sectional design limits assessment of temporal relationships<br><br>Potential recall bias and misclassification bias   |
| Lange et al, 2011 (78)                 | Birth cohort study of parental psychosocial stress and asthma morbidity in 339 pairs of Puerto Rican twins followed for 3 years                                                                          | Parental psychosocial stress was associated with asthma or asthma morbidity (e.g. aOR for asthma = 1.08 per 1-point increase in parental post-traumatic stress disorder [PTSD] score, 95% CI=1.03-1.14])                                                                                                           | Potential misclassification of asthma<br><br>Limited phenotypic assessment of asthma                                         |
| Chen et al, 2013 (87)                  | Case-control study of exposure to violence, epigenetic/genetic variation in <i>ADCYP1R1</i> and asthma in 516 Puerto Rican children (ages 6-14 years)                                                    | Exposure to violence was associated with increased methylation of a CpG site in <i>ADCYP1R1</i> , and this increased methylation was associated with asthma (aOR per each 1% increment=1.3, 95% CI=1.0-1.6, P <0.05). A SNP in the promoter of <i>ADCYP1R1</i> was associated with asthma in Puerto Rican children | Cross sectional design limits assessment of temporal relationships.<br><br>Lack of replication in independent cohorts        |
| <b>Tobacco Smoke and Air Pollution</b> |                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                    |                                                                                                                              |
| Gomez et al, 2009 (92)                 | Cross-sectional study of current smoking and asthma in 3,000 children (ages 13 to 14 years in Salta (Argentina)                                                                                          | Current smoking was associated with asthma and rhinitis.                                                                                                                                                                                                                                                           | Cross sectional design limits assessment of temporal relationships.<br><br>Potential recall bias and misclassification bias. |
| Vazquez-Rodriguez et al, 2012 (93)     | Cross-sectional study of smoking habits or parental smoking and asthma in 4,778 non-student children (ages 13 to 18 years) in Mexico                                                                     | Active smoking was similar in children with (33.9%) and without (34.2%) asthma. Risk factors for smoking include parental approval of smoking and friends who smoke.                                                                                                                                               | Cross sectional design limits assessment of temporal relationships.<br><br>Potential recall bias and misclassification bias. |
| Carbajal-Arroyo et al, 2007 (94)       | Cross-sectional study of traffic density, PM2.5 level and asthma in 6,287 children                                                                                                                       | Increased traffic flow was significantly associated with asthma, current wheezing, and                                                                                                                                                                                                                             | Cross sectional design limits assessment of temporal relationships.                                                          |

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|                                     | (ages 6-7 years) in Lima, Peru                                                                                                                                                                                                | asthma attacks in the last year.                                                                                                                                                                     |                                                                                                                                                             |
| Baumann et al, 2011, (95)           | Cross-sectional study of distance from a heavily transited road and asthma in 725 children (ages 13-15 years) in Peru                                                                                                         | Increased proximity to a heavily transited roadway was associated with asthma symptoms (aOR=2.0, P <0.05) and atopy                                                                                  | Cross sectional design limits assessment of temporal relationships<br><br>Limited phenotypic assessment of asthma                                           |
| Escamilla-Núñez et al, 2008 (96)    | Cohort study air pollution and incident asthma symptoms in 197 children (ages 6 to 14 years) in Mexico City (147 asthmatics and 50 controls).                                                                                 | Increased PM2.5, NO2, and O3 levels were associated with wheezing.                                                                                                                                   | Lack of individual data on air pollution<br><br>Small sample size                                                                                           |
| Barraza-Villarreal et al, 2008 (97) | Cohort study of air pollution, airway inflammation and lung function in 208 children (ages 6-14 years) in Mexico City (158 asthmatics, 50 controls).                                                                          | Exposure to PM2.5 was associated with higher FeNO and lower FEV1/FVC in children with asthma. Among control subjects, PM2.5 exposure was associated with higher IL-8 and lower FVC.                  | Individual pollution exposures assumed to follow variations of central monitoring stations.<br><br>Most children with asthma had mild intermittent disease. |
| Bell et al, 2006 (98)               | Modeling studies of the effects of ozone and particulate matter emissions on asthma attacks in 3 Latin American cities (Santiago, Sao Paulo and Mexico City) for 2000-2020.                                                   | Adopting a control policy was estimated to potentially prevent 2.9 million asthma attacks in Mexico City, 0.48 million in Santiago, and 0.8 million in Sao Paulo.                                    | Models included only a subset of air pollutants and health outcomes, and are dependent on several assumptions                                               |
| Meng et al, 2006 (100)              | UCLA Health Policy Research Brief examining the relationship between traffic related air pollution and asthma severity in Los Angeles and San Diego counties using California Health Information Survey 2001 (ages 1+ years). | Hispanic children were two and a half times more likely to live near heavy traffic than white children. Increased traffic density was associated with ED visits and symptoms in subjects with asthma | Cross sectional design limits assessment of temporal relationships<br><br>Non-assessment of individual pollutants                                           |
| Nishimura et al, 2013 (101)         | Cross-sectional study of air pollution and asthma in 3,343 Latino and 977 African American subjects (ages 8 to 21 years)                                                                                                      | Increased exposure to NO2 in the first year of life was associated with asthma (aOR per 5-ppb NO increase =1.17, 95% CI=1.04-1.31)                                                                   | Lack of individual-level data on air pollution exposure<br><br>Cross sectional design limits assessment of temporal relationships                           |

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| Nachman and Parker, 2012 (102)     | Cross-sectional study of exposure to PM2.5 and asthma morbidity in 109,485 adults participating in the National Health Information Survey                                                                | Exposure to PM2.5 was significantly associated with current asthma or asthma attacks in non-Hispanic Blacks, but not in Hispanics or non-Hispanic Whites.                                                                                                                                     | Cross sectional design limits assessment of temporal relationships<br><br>Hispanics evaluated only as a whole group                        |
| Salam et al, 2007 (103)            | Cross-sectional study of oxidant stress exposures, <i>TGFB1</i> , and asthma in 3,023 Hispanic and non-Hispanic white children from the Children's Health Study                                          | <i>TGFB1</i> -509TT genotype was associated with early-onset asthma, particularly among children exposed to oxidant stress.                                                                                                                                                                   | Cross sectional design limits assessment of temporal relationships<br><br>Lack of categorization of Hispanic participants into subgroups   |
| Perzanowski et al, 2013 (104)      | Longitudinal study of early-life exposure to cockroach allergen and polycyclic aromatic hydrocarbons (PAH), and cockroach sensitization in 727 nonsmoking pregnant women (African American or Dominican) | Prenatal cockroach allergen exposure was associated with cockroach sensitization at age 5-7 years, but only in children with greater than the median sum of 8 non-volatile PAH levels. Furthermore, the association was of greater magnitude in children null for <i>GSTM1</i> polymorphisms. | Potential selection bias due to differential loss of follow-up<br><br>Lack of replication of interaction findings                          |
| Quinto et al, 2013 (105)           | NCHS Data Brief on findings from NHANES (1999-2010)                                                                                                                                                      | Second-hand smoke (SHS) decreased during the study period in non-asthmatic children, but did not change in children with asthma                                                                                                                                                               | Subject to recall bias and misclassification bias                                                                                          |
| Akinbami, Kit, & Simon, 2013 (106) | Cross-sectional study of SHS and disease symptoms in 925 non-smoking subjects with asthma (ages 6-19 years) from NHANES (2003-2010)                                                                      | Half of the participants were exposed to SHS. SHS was associated with more adverse outcomes in children ages 6-11 years. SHS was significantly associated with nocturnal asthma symptoms in Mexican children                                                                                  | Cross sectional design limits assessment of temporal relationships.<br><br>Potential recall bias and misclassification bias                |
| Akuete et al, 2011 (107)           | Cross-sectional study of in utero exposure to tobacco smoke and persistent asthma in 295 Mexican, Puerto Rican and black children (ages 8-16 years)                                                      | Exposure to in utero (but not current SHS) tobacco smoke was associated with persistent asthma (adjusted OR=3.6, P=0.03). Exposure to in utero tobacco smoke was also associated with nocturnal asthma symptoms and ED visits for asthma in the prior year                                    | Potential selection bias, recall bias and misclassification bias<br><br>Cross-sectional design limits assessment of temporal relationships |

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|                         |                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                            | Small sample size                                                                                                                                                                                 |
| Oh et al, 2012 (108)    | Cross-sectional study of SHS (in utero and current) and disease control in 2,481 Black and Hispanic (Puerto Rican and Mexican) children (ages 8-17 years)                        | In utero SHS was associated with poor asthma control, early-onset asthma, daytime symptoms, and activity limitations                                                                                                                                                                                                                                                                       | <p>Potential recall bias and misclassification bias</p> <p>Cross-sectional design limits assessment of temporal relationships</p> <p>Lack of objective markers of SHS (e.g. urinary cotinine)</p> |
| <b>Vitamin D</b>        |                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                   |
| Brehm et al, 2009 (114) | Cross-sectional study of serum vitamin D level and markers of asthma severity or control in 616 Costa Rican children with asthma (ages 6 – 14 years)                             | Vitamin D insufficiency or deficiency was found in 28% of study participants. Vitamin D level was inversely associated with several markers of asthma severity or control.                                                                                                                                                                                                                 | <p>Cross sectional design limits assessment of temporal relationships.</p> <p>Potential “reverse causation”</p>                                                                                   |
| Brehm et al, 2012 (115) | Cross-sectional study of vitamin D insufficiency (a serum 25(OH)D level <30 ng/ml) and asthma or severe asthma exacerbations in 560 children (ages 6 to 14 years) in Puerto Rico | Vitamin D insufficiency, found in over 40% of participants, was not associated with asthma. Among children with asthma, vitamin D insufficiency was associated with severe exacerbations. However, this association was stronger in non-atopic children (adjusted [a]OR=6.2, 95% CI, 2–21.6; P=0.002) than in atopic children (aOR=2.0; 95% CI=1.0–4.1, P=0.04).                           | <p>Cross sectional design limits assessment of temporal relationships.</p> <p>Potential residual confounding by unmeasured covariates (e.g. ICS adherence) and “reverse causation”</p>            |
| <b>Obesity</b>          |                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                   |
| Forno et al, 2013 (132) | Case-control study of adiposity indicators, atopy and asthma in 678 children (ages 6 to 14 years) in Puerto Rico                                                                 | All adiposity indicators (body mass index [BMI], percent body fat, waist to hip ratio and waist circumference) were associated with asthma. However, the association between adiposity and some indicators of asthma severity or control differed across measurements. Atopy mediated a significant proportion of the association between adiposity and asthma or asthma-related outcomes. | <p>Cross-sectional study limits assessment of temporal relationships</p> <p>Limited statistical power for mediation analysis</p>                                                                  |

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| Vangeepuram et al, 2011 (134) | Cross-sectional study of obesity and asthma in 505 children (ages 6 to 8 years) who belonged to ethnic minority groups (Mexican, Dominican, Puerto Rican, Other/Mixed Hispanic, and Non-Hispanic Black) and lived in New York City | BMI, percent body fat, and waist circumference were all associated with increased prevalence ratios of asthma.                                                                                                                                     | Potential selection bias and misclassification bias<br><br>Cross-sectional design limits assessment of temporal relationships<br><br>Limited phenotypic assessment of asthma                                   |
| Black et al, 2012 (135)       | Cross-sectional study of overweight or obesity and asthma in 681,122 members of an integrated health plan (ages 6-19 years)                                                                                                        | Overweight, moderate and extreme obesity were all associated with asthma in study subjects. The association between overweight or obesity and asthma was strongest among Hispanics.                                                                | Limited phenotypic assessment of asthma<br><br>Cross sectional design limits assessment of temporal relationships.                                                                                             |
| Borrell et al, 2013 (137)     | Cross-sectional study of overweight or obesity and asthma control in 2,174 subjects (ages 8 to 19 years) who belong to ethnic minorities (Puerto Rican, Mexican and African American)                                              | Overweigh or obesity was significantly associated with poor asthma control in males, regardless of ethnicity. Among female participants, obesity was only significantly associated with poor asthma control in Mexicans (aOR=1.9, 95% CI=1.1–3.3). | Assessment of asthma control limited to a 1–week period<br><br>Cross sectional design limits assessment of temporal relationships<br><br>Limited statistical power for analyses stratified by age or ethnicity |
| <b>Parasites</b>              |                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                |
| Endara et al, 2010 (138)      | Cross-sectional study of prior community-level treatment for onchocerciasis (with Ivermectin) and atopy (skin test reactivity to at least one allergen) or allergic symptoms in 3,901 Ecuadorean children (aged 15-17 years)       | Community-level treatment with Ivermectin was associated with atopy and recent eczema symptoms (adjusted OR= 2.24, 95% CI= 1.1–4.8, P = 0.04) but not with recent symptoms of asthma or rhinitis                                                   | Lack of data for Ivermectin treatment at the individual level<br><br>Potential selection bias and misclassification bias<br><br>Cross-sectional design limits assessment of temporal relationships.            |
| Hunninghake et al, 2007 (139) | Cross-sectional study of a positive IgE (sensitization) to Ascaris and asthma severity or control in 439 Costa Rican children (aged 6-14 years old)                                                                                | Sensitization to Ascaris was associated with atopy, increased total IgE level and airway responsiveness, and hospitalizations for asthma (adjusted OR=3.1, 95% CI= 1.2-7.7; P=0.02).                                                               | Stool exams were only conducted in a subset of study participants<br><br>Potential selection bias<br><br>Cross-sectional design limits assessment of temporal relationships                                    |

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| Moncayo et al, 2013 (140)       | Case-control study of geohelminth infection and current wheeze in 376 subjects (ages 7-19 years) living in rural Ecuador                                                                                                       | Geohelminth infection was not significantly associated with wheeze. Anti-Ascaris IgE was significantly associated with current wheeze, independently of atopy. The fraction of current wheeze attributable to anti-Ascaris IgE was ~46%          | Limited statistical power<br><br>Atopy defined as sensitization to one of only two allergens (cockroach/dust mite)<br><br>Potential selection bias<br><br>Cross-sectional design limits assessment of temporal relationships. |
| Walsh, 2011 (141)               | Cross-sectional study of Toxocara infection (assessed by an antibody) and FEV1 in 12,174 adults (aged 18-65 years) using NHANES III data (1988-1994)                                                                           | 12% of Mexican Americans had evidence of Toxocara infection. Among all subjects, Toxocara infection was associated with decreased FEV1.                                                                                                          | Cross-sectional design limits assessment of temporal relationships<br><br>Potential residual confounding by socioeconomic status                                                                                              |
| Hagel et al, 2007 (144)         | Cross-sectional study of infection or sensitization to <i>Ascaris lumbricoides</i> and airway hyper-responsiveness (AHR) in 470 school-aged Venezuelan children living in rural and urban areas                                | In rural children, sensitization to <i>Ascaris</i> was associated with AHR and decreased % predicted FEV1. In urban children, sensitization to dust mite (but not to <i>Ascaris</i> ) was associated with BHR                                    | Cross-sectional design limits assessment of temporal relationships<br><br>Potential selection bias                                                                                                                            |
| Moncayo et al, 2010 (145)       | Cross-sectional study of atopic and non-atopic wheeze in 3960 children, (ages 6-16 years) living in rural Ecuador                                                                                                              | Most current wheeze (85.6%) was non-atopic. Heavy infection with <i>Trichuris trichiura</i> was inversely associated with atopic wheeze. Maternal allergic symptoms and a sedentary lifestyle were positively associated with non-atopic wheeze. | Cross-sectional design limits assessment of temporal relationships<br><br>Potential misclassification of asthma symptoms and selection bias<br><br>Helminthiasis assessed in a single stool exam                              |
| <b>Diagnosis and Management</b> |                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                               |
| Maspero et al, 2013 (147)       | Cross-sectional study of perception, knowledge and attitudes about asthma in 2,169 subjects (12 years and older) from four Latin American countries (Brazil, Mexico, Venezuela, Argentina) and the Commonwealth of Puerto Rico | Latin Americans overestimated control of their asthma (60% reported well or completely controlled asthma, while only 8% met criteria for well-controlled asthma) and a large percentage (44%) had sought acute care for asthma symptoms.         | Lack of measures of lung function or allergy                                                                                                                                                                                  |

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| Soto-Martinez et al 2013 (149)  | Ecological study of temporal trends in hospitalizations and number of deaths due to asthma in Costa Rica over a 12- to 15-year period, before and after implementation of a national asthma program (NAP)                   | Whereas the percentage decrement in the rates of hospitalization for asthma in subjects <20 years old was similar before and after the NAP, the reduction in both deaths due to asthma and rates of asthma hospitalizations in older subjects were more pronounced after the NAP, when prescriptions for beclomethasone were also increased by approximately 129% | Potential ecological fallacy<br><br>Findings may not be generalizable to countries with low literacy or lacking universal health care                                     |
| Claudio & Stingone, 2009 (150)  | Cross-sectional study of language barriers and asthma management in 1,847 Hispanic children from 26 public elementary schools (located in the highest, median and lowest asthma hospitalization zip codes) in New York City | Compared to children from English-speaking households, those from Spanish-speaking households were less likely to report symptoms but more likely to have public health insurance, to be hospitalized and to have decreased access to care on the weekends                                                                                                        | Potential misclassification of English proficiency<br><br>Potential recall bias                                                                                           |
| Rosas-Salazar et al, 2013 (153) | Cross-sectional study of parental numeracy and asthma exacerbations in 351 children (ages 6-14 years) in Puerto Rico                                                                                                        | Low parental numeracy was associated with ED/urgent care visits for asthma (aOR=1.7, 95% CI=1.03-2.7, P=.04) in all children. Among children not receiving inhaled corticosteroids (ICS), low parental numeracy was associated with hospitalizations for asthma                                                                                                   | Cross sectional design limits assessment of temporal relationships.<br><br>No data on ICS adherence                                                                       |
| Kit et al, 2012 (154)           | Longitudinal analysis of trends in preventative asthma medication (PAM) use in 2,499 participants (ages 1 to 19 years) from NHANES (1988-1994, 1999-2002, 2005-2008)                                                        | Overall, rates of PAM use increased in all children. At the end of the study, however, PAM use remained lower in non-Hispanic black or Mexican American children than in white children                                                                                                                                                                           | Lack of data on asthma severity<br><br>Potential confounding by quality of healthcare                                                                                     |
| Crocker et al, 2009 (155)       | Cross-sectional study of ethnicity and healthcare utilization in 1,485 participants from the National Asthma Survey (2003-2004), ages ≤ 18 years                                                                            | Compared to non-Hispanic white children, minority children (non-Hispanic blacks and Hispanics) had increased ED visits, increased use of rescue medications and lower use of inhaled corticosteroids                                                                                                                                                              | No delineation of Hispanic subgroups<br><br>Hispanic likely represents Mexican Americans given study sites<br><br>Potential misclassification of asthma in young children |

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| McQuaid et al, 2012 (156)        | Cross-sectional study of ethnicity and adherence to treatment in 277 children (ages 7-16 years) with asthma                                                                             | Non-Hispanic white children had higher levels of medication adherence than Hispanic children.                                                                                                                                                                                                            | Potential selection bias<br><br>Lack of categorization of Hispanics into subgroups for data analysis                                                                 |
| Wisnivesky et al, 2009 (157)     | Prospective cohort of language proficiency and disease morbidity in 318 urban adults with persistent asthma                                                                             | Limited English proficiency was significantly associated with poorer asthma control, increased resource utilization and lower quality of life , concerns about medication side effects, and reduced adherence                                                                                            | Hispanics not categorized into subgroups<br><br>Potential confounding by variables correlated with English proficiency                                               |
| Wu et al, 2008 (158)             | Cross-sectional study of perception of asthma in parents of 739 children with persistent asthma                                                                                         | Compared to parents of white children, minority parents had lower expectations for functioning with asthma. Parents of Hispanic children were more likely to have concerns about asthma medications.                                                                                                     | Findings may not be generalizable to Spanish-speaking or less acculturated Hispanic parents<br><br>Lack of categorization of Hispanics into subgroups                |
| Bialostozky & Barkin, 2012 (159) | Cross-sectional qualitative study of comprehension of questions related to asthma in 40 Mexican American Spanish-speaking parents of children with and without asthma (ages 2-18 years) | The majority of parents, in either group, demonstrated limited comprehension of common clinical words used to describe asthma and relied more on sounds and physical symptoms                                                                                                                            | Small sample size<br><br>Findings may not be generalizable to more acculturated Mexican Americans                                                                    |
| Fritz et al, 2010 (160)          | Cross-sectional study of ethnicity and perception of lung function in 512 children (ages 7-16 years) with asthma                                                                        | Hispanic children perceived lung function less accurately than non-Hispanic white children. Children living in the island of Puerto Rico had the lowest perceptual accuracy of their lung function. Overall, accurate perception was associated with less morbidity and reduced health care utilization. | Potential selection bias<br><br>Results may not be generalizable to other Hispanic populations                                                                       |
| Drake et al, 2013 (162)          | GWAS of bronchodilator response (BDR) in 1,782 Hispanic children with asthma, ages 8-21, and replication in additional 531 Hispanics.                                                   | Rare genetic variants contribute to differences in BDR among Hispanic children with asthma.                                                                                                                                                                                                              | Effects in replication cohort were in the same direction but not statistically significant.<br><br>Requires replication efforts in different and larger populations. |

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| Canino et al, 2008 (163)        | Randomized controlled intervention trial of a culturally sensitive family asthma management intervention (CALMA) in 221 children (ages 5 to 12 years) from low income households in Puerto Rico.  | Children in the CALMA group were less likely to seek ED care or to be hospitalized, and were more likely to have better controlled asthma.                                                                            | Results may not be generalizable to wealthier Hispanic groups or to other Hispanic subgroups.               |
| Lara et al, 2013 (164)          | Observational case study of evidence-based interventions and disease morbidity in 117 children (ages 0 to 17 years) with moderate to severe asthma in 2 public housing communities in Puerto Rico | The study intervention reduced asthma symptoms, ED use, and hospitalizations over a 1-year period                                                                                                                     | Lack of a control group<br><br>Potential misclassification of asthma<br><br>Small sample size               |
| Rosas-Salazar et al, 2013 (165) | Case-control study of prematurity and asthma in 678 children in Puerto Rico, ages 6-14 years                                                                                                      | Prematurity was significantly associated with asthma in atopic children (aOR=4.7, 95% CI, 1.5-14.3, P = .007) In contrast, there was no significant association between prematurity and asthma in non-atopic children | Cross sectional design limits assessment of temporal relationships.<br><br>Potential misclassification bias |