Racial/Ethnic Differences in Incidence and Persistence of Childhood Atopic Dermatitis

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Although previous studies have explored racial/ethnic differences in incident atopic dermatitis (AD) in childhood, few studies have examined risk factors associated with AD persistence. As such, we sought to examine differences in incidence and persistence of childhood AD by race/ethnicity accounting for sociodemographic characteristics and perinatal vitamin D levels. Using data from Project Viva, a prospective prebirth cohort in eastern Massachusetts, we studied 1,437 mother-child pairs with known AD status to examine the associations of race/ethnicity with maternally reported child AD. We used multivariable logistic regression, adjusting for sociodemographic factors and maternal plasma vitamin D, to estimate adjusted odds ratios (aORs) of AD incidence at early childhood and persistence at mid-childhood. Compared to non-Hispanic whites, non-Hispanic blacks (aOR = 2.71, 95% confidence interval = 1.75−4.19) and other non-Hispanics (aOR = 1.80, 95% confidence interval = 1.16−2.80) were more likely to have incident AD. Non-Hispanic blacks (aOR = 6.26, 95% confidence interval = 2.32−16.88) and Hispanics (aOR = 6.42, 95% CI = 1.93−21.41) with early childhood AD were more likely to have persistent AD. In conclusion, compared with non-Hispanic whites, AD incidence and persistence are higher among certain nonwhite racial/ethnic subgroups. Further research is warranted to identify environmental, socioeconomic, and genetic factors that may be responsible for the observed differences.

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INTRODUCTION

Atopic dermatitis (AD) is a highly prevalent chronic inflammatory skin disease that affects up to 20% of children worldwide (Odhiambo et al., 2009). The high prevalence and associated adverse health outcomes, including cutaneous symptoms, subsequent sleep disturbance, and mental health symptoms, impose a substantial burden to patients and the health care system, with economic costs estimated to be $252 million in the United States in 2013 (Lim et al., 2018).

Previous studies have shown racial/ethnic differences in the epidemiology of AD, with nonwhite children having higher incidence and prevalence compared with white children (Shaw et al., 2011; Williams et al., 1995). Given the episodic and relapsing nature of AD, persistent disease can be difficult to define and study. Most studies on racial/ethnic differences in AD have not examined persistent disease. Although approximately 40%−80% of early childhood AD resolves with time, AD in some cases can persist into mid-childhood and beyond (Abuabara et al., 2017b; Kim et al., 2016; Pyun, 2015). Our study (Blomberg et al., 2017) and other studies (Chiu et al., 2015; Peroni et al., 2011) showed that low maternal blood 25-hydroxyvitamin D (25[OH]D) levels were associated with higher incidence of AD in children and with AD severity (Baek et al., 2014; Pajno et al., 2003). Although these factors may influence persistence of AD, prior studies have not specifically accounted for effects of vitamin D levels on persistent AD. Individuals with darker skin tend to have lower levels of vitamin D and higher rates of vitamin D deficiency, because greater pigmentation reduces vitamin D production (Clemens et al., 1982), but the role of 25(OH)D has not been considered in earlier studies of racial/ethnic differences in AD incidence.

The purpose of this study was to examine associations of race/ethnicity with incident AD in early childhood and persistent AD in mid-childhood using data from Project Viva, a well-characterized prospective prebirth cohort. A better understanding of racial/ethnic differences in AD incidence and persistence may help clinicians monitor disease burden and elucidate the etiology of this very common disease including genetic, environmental, and socioeconomic causes.

RESULTS

Study population

Of 1,437 children included in the analysis of early childhood AD, 67.2% (n = 966) were non-Hispanic white, 13.3%

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AD, atopic dermatitis; CI, confidence interval; OR, odds ratio

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(n = 191) were non-Hispanic black, 9.7% (n = 139) were Hispanic, and 9.8% (n = 141) were other non-Hispanic races, including Asian (n = 50), combined white and Asian (n = 38), combined white and black (n = 30), and other multiracial combinations (n = 23). A total of 503 (35.0%) children had AD in early childhood (Table 1).

Among 392 children who had early childhood AD and mid-childhood follow-up data, 60.7% (n = 238) were non-Hispanic white, 18.9% (n = 74) were non-Hispanic black, 8.9% (n = 35) were Hispanic, and 11.4% (n = 45) had other non-Hispanic race. In mid-childhood, 14.8% (n = 58) had persistent AD (Table 2). Characteristics of the participants by race/ethnicity were similar for the two analysis samples of incident AD in early childhood (n = 1,437) and persistent AD (n = 392). Compared with children of non-Hispanic black, Hispanic, and other non-Hispanic race, non-Hispanic white children had higher maternal plasma 25(OH)D levels and were more likely to have mothers with a college education, asthma diagnosis, and higher neighborhood household incomes.

Association of race/ethnicity with AD incidence and persistence

We found that non-Hispanic black race/ethnicity was associated with both AD incidence and persistence (Figure 1a and b). Compared with non-Hispanic white children, non-Hispanic black children had higher unadjusted odds of incident AD in early childhood (odds ratio [OR] = 2.12, 95% confidence interval [CI] = 1.55−2.90). The OR increased after adjusting for sociodemographic factors including child sex, maternal education, parental atopy, and neighborhood income (adjusted OR [aOR] = 2.67, 95% CI = 1.86−3.83) and maternal blood 25(OH)D level (aOR = 2.71, 95% CI = 1.75−4.19). Children with other non-Hispanic race also had higher unadjusted OR of early childhood AD compared with non-Hispanic white children (OR = 1.62, 95% CI = 1.13−2.32), with strengthening associations in adjusted analyses (aOR_{model2} = 1.67, 95% CI = 1.15−2.41; aOR_{model3} = 1.80, 95% CI = 1.16−2.80). There was no association between Hispanic ethnicity and incident AD (aOR_{model2} = 1.23, 95% CI = 0.82−1.86; aOR_{model3} = 1.10, 95% CI = 0.66−1.84) (Figure 1a).

A total of 58 (14.8%) children had persistent AD in mid-childhood. When we investigated persistent AD in mid-childhood among children with AD in early childhood, non-Hispanic black children (OR = 3.23, 95% CI = 1.64−6.35) and Hispanic ethnicity (OR = 3.24, 95% CI = 1.35−7.73) had higher odds of persistent disease in mid-childhood than non-Hispanic white children (Figure 1b). This positive association was strengthened after multivariable adjustment (non-Hispanic black vs. non-Hispanic white: aOR_{model2} = 6.07, 95% CI = 2.63−14.00; aOR_{model3} = 6.26, 95% CI = 2.32−16.88; Hispanic vs. non-Hispanic white: aOR_{model2} = 5.77, 95% CI = 2.14−15.57; aOR_{model3} = 6.42, 95% CI = 1.93−21.41). Although children with other non-Hispanic race showed increased odds of persistent AD compared with non-Hispanic white children, they did not reach the level of statistical significance, likely because of the small sample size and resulting wide confidence intervals (aOR_{model2} = 2.06, 95% CI = 0.81−5.25; aOR_{model3} = 1.19, 95% CI = 0.39−3.91). We also assessed the risk of persistent disease at any timepoint between 4 and 7 years and found similar results with non-Hispanic black children (aOR_{model3} = 3.44, 95% CI = 1.63−7.28) having greater odds of persistent AD compared with non-Hispanic whites.

Additional sensitivity analyses using plasma 25(OH)D as a dichotomous instead of a continuous variable showed similar results—that is, that non-Hispanic black children had higher odds of incident AD than non-Hispanic white children—as did analyses using 25(OH)D from cord blood instead of maternal second-trimester blood (see Supplementary Table S1 online). We also performed a sensitivity analysis based on a modified definition of incident AD in early childhood (using only the 3-year report of ever AD, independent of answers at the 6-month, 1-year, and 2-year assessments). This analysis reduced the number of children with AD from 503 to 331 but did not materially change the results (see Supplementary Table S2 online). When we excluded children with substituted maternal race/ethnicity values (n = 90), we found similar results with slight differences in magnitude (see Supplementary Table S3 online).

DISCUSSION

In this longitudinal, prospective cohort study of 1,437 children, non-Hispanic black children and children of other non-Hispanic race were more likely to have incident AD in early childhood, whereas Hispanic children had similar odds of developing AD, when compared with non-Hispanic white children. Non-Hispanic black children and Hispanic children had greater odds of persistent AD than non-Hispanic white children. The associations remained significant across different multivariable models adjusting for sociodemographic factors and maternal plasma vitamin D levels.

Previous studies have explored racial/ethnic differences in AD prevalence and severity in childhood and have shown that AD is more common and severe in nonwhite children than in white children (Shaw et al., 2011; Silverberg and Simpson, 2014; Sun and Sundell, 2011; Wegienka et al., 2012a). However, racial/ethnic differences in AD persistence in children have not been extensively studied, with only two published articles, which have shown conflicting results. A US-based cohort study reported that white children showed greater odds of persistent AD than nonwhite children (Margolis et al., 2014), and another US-based study showed higher odds of persistent AD among nonwhite compared with white children (Abuabara et al., 2017a). Although both studies used the same nationwide registry of children with AD, the results may be different because of the different outcome measures and covariates used in the analyses. However, these studies used relatively short symptom-free intervals (i.e., 6 months) to assess persistent AD and did not adjust for maternal or cord vitamin D levels; in our analysis, this adjustment strengthened associations. This study adds to the limited existing literature on the association between race/ethnicity and persistent AD.

Understanding risk factors for persistent AD is important because persistent AD is more likely to have greater disease severity, as shown by a meta-analysis of 45 studies on persistent AD that found that disease severity at the diagnosis is associated with AD persistence (Kim et al., 2016). Our

Table 1. Characteristics of study participants according to race/ethnicity

Characteristics	Early Childhood AD		Total (N = 1,437)	Non-Hispanic White (n = 966)	Non-Hispanic Black (n = 191)	Hispanic (n = 139)	Other Non-Hispanic (n = 141)
	Yes (n = 503)	No (n = 934)					
Child sex, n (%)							
Male	266 (52.9)	472 (50.5)	738 (51.4)	489 (50.6)	100 (52.4)	78 (56.1)	71 (50.4)
Female	237 (47.1)	462 (49.5)	699 (48.6)	477 (49.4)	91 (47.6)	61 (43.9)	70 (49.6)
Mother college graduate, n (%)							
No	141 (28.1)	284 (30.5)	425 (29.7)	197 (20.4)	110 (57.9)	83 (60.6)	35 (25.2)
Yes	360 (71.9)	647 (69.5)	1007 (70.3)	769 (79.6)	80 (42.1)	54 (39.4)	104 (74.8)
Parental history of atopy (n = 1,432), n (%)							
No	164 (32.7)	419 (45.0)	583 (40.7)	391 (40.5)	86 (45.3)	54 (39.4)	52 (37.4)
Yes	337 (67.3)	512 (55.0)	849 (59.3)	575 (59.5)	104 (54.7)	83 (60.6)	87 (62.6)
Ever asthma early childhood, n (%)							
No	414 (82.3)	855 (91.7)	1269 (88.4)	883 (91.6)	152 (79.6)	113 (81.3)	121 (85.8)
Yes	89 (17.7)	77 (8.3)	166 (11.6)	81 (8.4)	39 (20.4)	26 (18.7)	20 (14.2)
Ever allergic rhinitis early childhood, n (%)							
No	418 (83.3)	889 (95.2)	1307 (91.0)	888 (92.0)	161 (84.3)	127 (91.4)	131 (92.9)
Yes	84 (16.7)	45 (4.8)	129 (9.0)	77 (8.0)	30 (15.7)	12 (8.6)	10 (7.1)
Any pets birth to early childhood, n (%)							
No	267 (53.1)	474 (50.7)	741 (51.6)	455 (47.1)	129 (67.5)	64 (46.0)	93 (66.0)
Yes	236 (46.9)	460 (49.3)	696 (48.4)	511 (52.9)	62 (32.5)	75 (54.0)	48 (34.0)
Pregnancy smoking status (n = 1,431), n (%)							
Never	338 (67.6)	645 (69.3)	983 (68.7)	633 (65.8)	150 (79.4)	93 (66.9)	107 (75.9)
Former	106 (21.2)	184 (19.8)	290 (20.3)	235 (24.4)	15 (7.9)	21 (15.1)	19 (13.5)
During pregnancy	56 (11.2)	102 (11.0)	158 (11.0)	94 (9.8)	24 (12.7)	25 (18.0)	15 (10.6)
Median neighborhood income at birth in $1,000/y, mean (SD)	58.4 (20.6)	58.9 (21.8)	58.7 (21.4)	64.4 (20.2)	40.4 (15.4)	46.3 (18.1)	56.5 (19.6)
Maternal second-trimester blood 25(OH)D level in nmol/L, mean (SD)	58.8 (21.0)	59.8 (21.1)	59.5 (21.1)	63.3 (20.2)	48.5 (22.1)	50.1 (18.3)	52.1 (19.8)
Breastfeeding duration in months, mean (SD)	6.6 (4.5)	6.2 (4.6)	6.3 (4.6)	6.6 (4.6)	5.0 (4.4)	5.5 (4.5)	6.9 (4.3)

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AD, atopic dermatitis; SD, standard deviation.

study (Blomberg et al., 2017) and other studies (Chiu et al., 2015, Peroni et al., 2011) found that low maternal prenatal 25(OH)D levels are associated with childhood AD and with AD severity in infants (Baek et al., 2014). Previous studies reported that individuals with darker skin tend to have lower levels of vitamin D and higher rates of vitamin D deficiency, at least in part because greater pigmentation reduces vitamin D production. As expected, maternal plasma 25(OH)D levels were lower among mothers of non-Hispanic black, Hispanic, and other non-Hispanic children than among non-Hispanic white children in this study. Also, the proportions of college graduates and those with high neighborhood income were lower among mothers of non-Hispanic black and Hispanic children. These sociodemographic factors may have an impact on prevalent AD given early life exposures with allergic inflammatory response to allergens. Our finding that non-Hispanic black children were more likely to develop incident AD in early childhood and persistent AD at mid-childhood even after adjustment of maternal plasma 25(OH)D levels and sociodemographic factors might reflect additional environmental, cultural, and physical factors that are heterogeneous across racial and ethnic categories (Flohr and Mann, 2014; Sun and Sundell, 2011).

Factors that may not be fully captured in cohort studies, including access to medical care, trust in the medical system, adherence to therapy, and pattern of health care-seeking behavior, might affect racial/ethnic disparities in AD persistence. A recent article reported that non-Hispanic black children showed low rates of health care use for AD (Fischer et al., 2017). Despite this lower rate of health care use overall, those non-Hispanic black children who accessed medical care for AD had more ambulatory visits and prescriptions for AD, suggesting a greater disease severity (Fischer et al., 2017). In addition, a growing body of evidence suggests racial differences in genetic and immune-related factors that are associated with increased incidence and prevalence of AD. Filaggrin is a structural protein that is involved in skin barrier function (Elias et al., 2017; Kelleher

Table 2. Characteristics of study participants with incident AD in early childhood with known AD status in mid-childhood by race/ethnicity (n = 392)

Characteristics	Persistent AD in Mid-childhood		Total (n = 392)	Non-Hispanic White (n = 238)	Non-Hispanic Black (n = 74)	Hispanic (n = 35)	Other Non-Hispanic (n = 45)
	Yes (n = 58)	No (n = 334)					
Child sex, n (%)							
Male	30 (51.7)	171 (51.2)	201 (51.3)	116 (48.7)	42 (56.8)	17 (48.6)	26 (57.8)
Female	28 (48.3)	163 (48.8)	191 (48.7)	122 (51.3)	32 (43.2)	18 (51.4)	19 (42.2)
Mother college graduate, n (%)							
No	17 (29.3)	87 (26.1)	104 (26.6)	38 (16.0)	36 (48.6)	22 (64.7)	8 (17.8)
Yes	41 (70.7)	246 (73.9)	287 (73.4)	200 (84.0)	38 (51.4)	12 (35.3)	37 (82.2)
Parental history of atopy (n = 391), n (%)							
No	20 (34.5)	113 (33.9)	133 (34.0)	75 (31.5)	30 (40.5)	11 (32.4)	17 (37.8)
Yes	38 (65.5)	220 (66.1)	258 (66.0)	163 (68.5)	44 (59.5)	23 (67.6)	28 (62.2)
Ever asthma mid-childhood, n (%)							
No	34 (58.6)	253 (76.9)	287 (74.2)	188 (80.3)	47 (63.5)	21 (60.0)	31 (70.5)
Yes	24 (41.4)	76 (23.1)	100 (25.8)	46 (19.7)	27 (36.5)	14 (40.0)	13 (29.5)
Ever allergic rhinitis mid-childhood, n (%)							
No	21 (36.2)	230 (70.1)	251 (65.0)	161 (69.1)	38 (51.4)	21 (60.0)	31 (70.5)
Yes	37 (63.8)	98 (29.9)	135 (35.0)	72 (30.9)	36 (48.6)	14 (40.0)	13 (29.5)
Any pets birth to early childhood, n (%)							
No	36 (62.1)	183 (54.8)	219 (55.9)	121 (50.8)	52 (70.3)	17 (48.6)	29 (64.4)
Yes	22 (37.9)	151 (45.2)	173 (44.1)	117 (49.2)	22 (29.7)	18 (51.4)	16 (35.6)
Pregnancy smoking status (n = 391), n (%)							
Never	43 (74.1)	233 (70.0)	276 (70.6)	160 (67.5)	60 (81.1)	21 (60.0)	35 (77.8)
Former	9 (15.5)	74 (22.2)	83 (21.2)	62 (26.2)	7 (9.5)	7 (20.0)	7 (15.6)
During pregnancy	6 (10.3)	26 (7.8)	32 (8.2)	15 (6.3)	7 (9.5)	7 (20.0)	3 (6.7)
Median neighborhood income at birth in $1,000/year, mean (SD)	58.6 (22.6)	57.6 (19.5)	57.8 (20.0)	64.6 (18.5)	40.7 (14.7)	46.7 (16.8)	57.5 (16.9)
Maternal second-trimester blood 25(OH)D level in nmol/L, mean (SD)	55.9 (24.8)	59.4 (21.3)	59.5 (21.1)	63.3 (20.2)	48.5 (22.1)	50.1 (18.3)	52.1 (19.8)
Breastfeeding duration in months, mean (SD)	7.1 (4.5)	6.8 (4.5)	6.3 (4.6)	6.6 (4.6)	5.0 (4.4)	5.5 (4.5)	6.9 (4.3)

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AD, atopic dermatitis; SD, standard deviation.

et al., 2015; Thyssen and Kezic, 2014), and loss-of-function *FLG* mutation and reduced filaggrin levels have been associated with increased odds of AD (Brown et al., 2012; Kelleher et al., 2015; Margolis et al., 2012; Rupnik et al., 2015; Thyssen and Kezic, 2014). *FLG* mutations show population specificity (Brown and McLean, 2012; Margolis et al., 2012; Thawer-Esmail et al., 2014; Winge et al., 2011), and Margolis et al. reported that *FLG2* mutations were associated with the persistence of AD in African Americans (Margolis et al., 2012). In addition, dysfunctions of innate and adaptive immunity have been relevant factors in AD development, which are different among different races (Dowd et al., 2014; Ungar et al., 2017; Wegienka et al., 2012a, 2012b). A recent study reported phenotypic differences of AD between Asian, white, and African American children that may reflect different immune responses (Leung, 2015). In sum, there may be correlations between genetic, physical, and environmental factors in the pathogenesis of AD, and these may contribute to racial/ethnic differences in the development and persistence of AD.

Strengths of our study include the longitudinal design of the large cohort and accounting for maternal plasma 25(OH)D levels, which is a confounder in AD development. Also, participants were not selected based on increased risk of AD, nor were they aware of the aim of this study while filling out questionnaires. Our study has some limitations. First, AD was defined by maternal report of provider-diagnosed AD and relevant symptoms. Validation studies, however, have shown very high reliability for self-reported diagnosis of AD compared with caregiver reports or clinical examinations (Laughter et al., 2000; Silverberg et al., 2015). Second, there was no information on health care use, therapeutics, or insurance type, which could affect outcomes, such as persistent disease. However, we recruited all participants from a single health care system, reducing the risk of disparities in access to care and treatment. Defining persistent AD can be

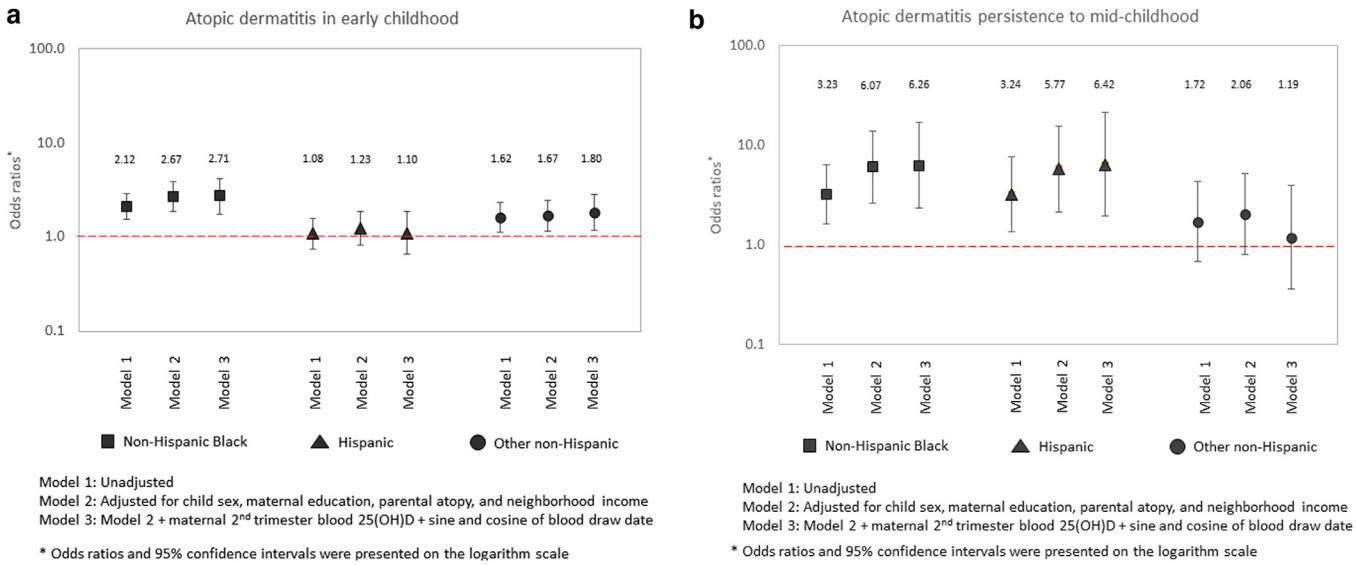

Figure 1. Unadjusted and adjusted odds ratios of incident and persistent atopic dermatitis. (a) Unadjusted and adjusted odds ratios of incident atopic dermatitis. **(b)** Unadjusted and adjusted odds ratios of persistent atopic dermatitis. 25(OH)D, 25-hydroxyvitamin D. Whiskers represent 95% confidence intervals that are presented on the logarithm scale.

challenging without treatment data, given that the disease can be quiescent with appropriate treatment. However, completely quiescent disease is more likely to be mild, and as such, our findings regarding persistence may reflect more severe disease. In addition, although severity of AD may affect disease courses and patterns (including persistent AD), disease severity data were not available in this study. Third, those participants who were included in the study without missing data were more likely to be non-Hispanic white, which is a part of the reference group in this study. Finally, although we tried to control for any plausible confounding factors using multivariable analytic models, there might be residual unmeasured confounding factors, especially for socioeconomic status, and some variables may be correlated.

In this prospective longitudinal cohort, compared with non-Hispanic white children, non-Hispanic black children and children with other non-Hispanic race were at higher risk for incident AD, and non-Hispanic black children and Hispanic children had an increased risk of persistent AD, even after accounting for differences in sociodemographic characteristics and vitamin D levels. However, because race/ethnicity and exposures related to socioeconomic status are tightly linked in the United States, unmeasured confounders could explain these results. Further research may be warranted to elucidate environmental, socioeconomic, and genetic factors that may be responsible for the observed differences for better understanding of disease progress, and approaches to management, disease control, and prevention. Specifically, future studies that incorporate genetic markers of ancestry may shed light on biologic risk factors associated with AD incidence and persistence.

MATERIALS AND METHODS

Study population

Study participants included children enrolled in Project Viva, an ongoing, prospective, prebirth cohort study that recruited pregnant mothers at the first prenatal visit between 1999 and 2002 from one of eight urban and suburban obstetric offices of Atrius Harvard Vanguard Medical Associates, a multispecialty group practice in eastern Massachusetts. The purpose of Project Viva is to study the effect of environmental exposures on maternal and child health. Detailed information about recruitment and retention procedures has been reported previously (Oken et al., 2015). Eligible mothers were those who had singleton pregnancies of less than 22 weeks' gestation and could answer questions in English. We followed up with health-related questionnaires and in-person interviews with mothers during pregnancy and after birth and had in-person visits in early childhood at approximately age 3 years (median = 3.3 years, range = 2.8–6.2 years) and in mid-childhood at approximately age 7 years (median = 7.7 years, range = 6.6–10.6 years). Questionnaires were also mailed at ages 4, 5, and 6 years. We obtained written informed consent from all mothers at recruitment and each visit and verbal assent from the children in mid-childhood. The institutional review board of Harvard Pilgrim Health Care approved the study protocols.

Of the 2,128 live singleton births in the cohort, we excluded 675 who did not provide any early childhood data and an additional 16 children missing early childhood AD status (Figure 2). We compared characteristics of the 1,437 included in our current analyses with the 691 excluded pairs and found that included children were more often non-Hispanic white (67.2% vs. 56.0%), more likely to have parenteral history of atopy (59.3% vs. 55.5%), and had older mothers (mean maternal age = 32.3 vs. 30.8 years) with a college education (70.3% vs. 52.5%) and an annual neighborhood household income exceeding $70,000 at birth (26.4% vs. 19.4%).

Definition of race/ethnicity

Mothers reported their child's race/ethnicity at the early childhood visit in categories including (i) Hispanic or Latina/o, (ii) white or Caucasian, (iii) black or African American, (iv) Asian or Pacific Islander, (v) American Indian or Alaskan Native, and (vi) other, specify. If a mother chose the category

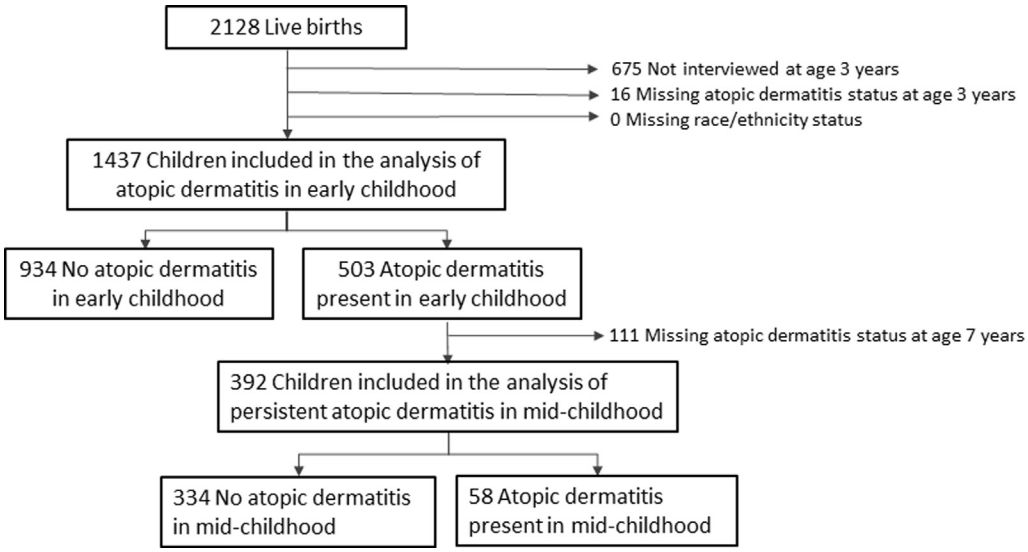

Figure 2. Study population flowchart.

other and wrote in a specific answer, we compared the written answer with the US census definitions and reclassified when appropriate. If a mother selected more than one race, we categorized the child's race as *more than one race*. We substituted maternal race/ethnicity value if a child's race/ethnicity was missing (n = 90 of 1,437). The distribution of children race/ethnicity did not differ before and after substituting the missing values (see Supplementary Table S4 online). For this analysis, we grouped the children into four race/ethnicity categories: non-Hispanic white, non-Hispanic black, Hispanic, and other non-Hispanic race (see Supplementary Figure S1 online). We did not further refine the other non-Hispanic race category because of small sample size within each of the subcategories.

Measurement of atopic dermatitis

We had two outcomes, incident AD in early childhood and persistent AD at mid-childhood. We defined persistent disease at approximately age 7 years because it was ascertained with both questionnaire and in-person interviews and allowed us to have more time elapsed since the incident AD diagnosis at approximately age 3 years. Mothers reported provider's diagnoses of AD and AD symptoms of their children via questionnaires. We defined incident AD in early childhood as an affirmative response at the 6-month, or 1-, 2-, or 3-year assessment to the question *Have you ever been told by a healthcare professional that your child has eczema (atopic dermatitis)?* among participants with a nonmissing response. Among those with incident AD in early childhood, we defined persistent AD as affirmative responses in mid-childhood to all of the following questions from the International Study of Asthma and Allergies in Childhood questionnaire (Deckers et al., 2012; Williams et al., 1999):

1. Have you ever been told by a health care professional that your child has eczema (atopic dermatitis)?
2. Has your child had this itchy rash at any time in the past 12 months?
3. In the past 12 months, has this itchy rash been in any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?

Covariate assessment

We obtained information on potential confounding variables from questionnaires and interviews, including maternal age at enrollment, maternal education, and parental atopy (defined as a mother or father with asthma, AD, or allergic rhinitis). We used median household income in the census tract at birth, based on 2000 US census data, as an estimate of neighborhood income. We obtained child sex from maternal inverviews at birth. We defined asthma and allergic rhinitis in early and mid-childhood as an affirmative response at the early childhood and mid-childhood interviews to the question *Have you ever been told by a health care professional, such as a doctor, physician assistant or nurse practitioner, that your child has asthma (or hay fever, seasonal allergies or allergic rhinitis, respectively)?* We defined *any pet exposure in early-childhood* as an affirmative response at the 6-month, 1-year, 2-year, and early childhood questionnaires to the question *At any time since your child was born (6 months, 1 year, or 2 years old, respectively), have you owned a dog, a cat, or another furry pet, for example, gerbil, hamster, guinea pig, or rabbit)?* We collected venous blood from mothers at 16–26 weeks' gestation and from the umbilical cord at birth. The blood was centrifuged to separate plasma and frozen to −80 °C within 24 hours. To determine 25(OH)D concentrations, we used both an automated chemiluminescence immunoassay and a manual radioimmunoassay (Ersfeld et al., 2004; Hollis et al., 1993). The results of these analyses were not identical (maternal $r = 0.81$, cord plasma $r = 0.88$), and we therefore used the average of the two values to get more stable values.

Statistical analysis

First, we examined bivariate relationships of child race/ethnicity with potential confounding variables based on a priori assumptions and knowledge. We then ran unadjusted and multivariable logistic regression models to examine associations of race/ethnicity with incident and persistent AD.

We explored all clinically relevant covariates defined a priori as potential confounders in the relationship between race/ethnicity and incident/persistent AD. We then removed covariates that did not substantially change the relationship between race/ethnicity and AD, including pregnancy smoking status, early-childhood pet exposure, and breastfeeding duration. Model 1 is unadjusted; model 2 is adjusted for child sex, maternal education, parental atopy, and neighborhood income; and model 3 is further adjusted for maternal second-trimester blood 25(OH)D levels and seasonal trends (modeled as sine and cosine functions of the data from blood draws) (Harris et al., 2015; Sordillo et al., 2018). We included median neighborhood income and maternal second-trimester blood 25(OH)D levels as continuous covariates to avoid any convergence issues. We performed an additional analysis with persistent AD at any timepoint between 4 years and 7 years using generalized estimating equations among those with incident AD in early childhood to account for AD outcomes at ages 4, 5, 6, and approximately 7 years. Additionally, we performed sensitivity analyses adjusted for maternal second-trimester blood 25(OH)D as a dichotomous variable using the cutoff value of 25 nmol/L because of its clinical relevance (Blomberg et al., 2017), as well as cord blood 25(OH)D level as a continuous variable instead of maternal plasma 25(OH)D level in model 3. Also, we performed a sensitivity analysis with incident AD in early childhood among participants with a nonmissing response at early childhood and an additional analysis among those children with nonmissing children's race/ethnicity information. Also, we examined whether associations of race/ethnicity with persistent AD differed among those with versus without other early childhood atopy (i.e., ever asthma or allergic rhinitis by approximately 3 years). We did not find evidence of an interaction of race/ethnicity with other early childhood atopy on persistent AD (P for interaction = 0.25), so we do not present stratified results. We performed all statistical analyses with SAS 9.4 (SAS Institute, Cary, NC).

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2018.10.029.

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