## Title
Gestational diabetes and childhood asthma in a racially diverse US pregnancy cohort



## Journal
Pediatric Allergy and Immunology, 32(6)

## ISSN
0905-6157

## Authors
Adgent, Margaret A
Gebretsadik, Tebeb
Reedus, Jada
et al.

## Publication Date
2021-08-01

## DOI
10.1111/pai.13523

Peer reviewed

HHS Public Access

Author manuscript

*Pediatr Allergy Immunol*. Author manuscript; available in PMC 2022 August 01.

Published in final edited form as:

*Pediatr Allergy Immunol*. 2021 August ; 32(6): 1190–1196. doi:10.1111/pai.13523.

# Gestational diabetes and childhood asthma in a racially diverse U.S. pregnancy cohort

**Margaret A. Adgent, PhD**[1,2], **Tebeb Gebretsadik, MPH**[3], **Jada Reedus, MS**[1,4], **Cornelia Graves, MD**[5], **Etoi Garrison, MD**[6], **Nicole Bush, PhD**[7,8], **Robert Davis, MD**[9], **Kaja Z. LeWinn, PhD**[7], **Frances Tylavsky, DrPH**[10], **Kecia N. Carroll, MD**[1]

[1]Division of General Pediatrics, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN USA

[2]Department of Health Policy, Vanderbilt University Medical Center, Nashville, TN USA

[3]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN USA

[4]Meharry Medical College, Nashville, TN USA

[5]University of Tennessee Health Sciences Center, College of Medicine, Nashville and Tennessee Maternal Fetal Medicine, Nashville, TN USA

[6]Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN USA

[7]Department of Psychiatry, University of California, San Francisco, San Francisco, CA USA

[8]Department of Pediatrics, University of California, San Francisco, San Francisco, CA USA

[9]Center for Biomedical Informatics, University of Tennessee Health Science Center, Memphis, TN, USA

[10]Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

## Abstract

**Background:** Childhood asthma is a common chronic disease that likely has prenatal origins. Gestational diabetes alters maternal physiology and may influence fetal risk for childhood onset disease. However, the association between gestational diabetes and child asthma is not well characterized.

**Objective:** To investigate the association between gestational diabetes and wheeze/asthma at approximately 4 years of age in a racially diverse U.S. cohort.

**Methods:** We studied mother-child dyads enrolled prenatally in the Conditions Affecting Neurocognitive Development and Learning in Early Childhood study. Gestational diabetes was determined by medical chart review. At approximately 4 years of age, we assessed child respiratory outcomes including parent report of physician-diagnosed asthma (ever), current

**Corresponding Author**: Kecia N. Carroll, MD, MPH. 2146 Belcourt Avenue, 2nd Floor Nashville, TN 37212; Telephone: 615-936-1139; kecia.carroll@vumc.org.

wheeze (symptoms within the past 12 months), and current asthma (physician diagnosis and/or medication or symptoms within the past 12 months). We used modified Poisson regression to assess associations of gestational diabetes and child respiratory outcomes, adjusting for maternal age, race, prenatal smoking, pre-pregnancy body mass index, parity, asthma history, socioeconomic status and infant sex.

**Results:** Among 1,107 women, 66% were African-American/Black. Six percent (n=62) had gestational diabetes documented during pregnancy. Gestational diabetes was associated with increased risk of physician-diagnosed asthma (adjusted risk ratio (RR) [95% Confidence Interval]: 2.13 [1.35, 3.38]; prevalence: 14%), current wheeze (RR: 1.85 [1.23, 2.78]; prevalence: 19%) and current asthma (RR: 2.01 [1.30, 3.10]; prevalence: 16%).

**Conclusions:** Gestational diabetes was associated with increased risk of asthma and wheeze outcomes. Additional studies are needed to elucidate modifiable pathways underlying this association.

### Keywords

Diabetes; gestational; asthma; prenatal exposure delayed effects; pregnancy complications; pediatrics

## Introduction

Asthma is a prevalent chronic disease of childhood that, along with related wheezing conditions, disproportionately affects low-income children in the United States (U.S.), as well as certain racial or ethnic groups such as Blacks/African-Americans.(1) Asthma and wheeze likely have prenatal origins as immune system and lung development begin *in utero* and continue into childhood.(2) These conditions are commonly associated with a T helper 2 (Th2) dominant immune profile,(3) although other contributory mechanisms may be important. Fetal respiratory development is susceptible to prenatal exposures (e.g., tobacco smoke, air pollution and maternal obesity) that are linked to altered immune response, inflammation and oxidative stress.(4–6) Certain maternal complications during pregnancy, including diabetes mellitus, are also associated with these mechanisms.(7–9) As such, gestational diabetes may be a plausible modifiable risk factor for childhood asthma and related diseases.

Gestational diabetes mellitus (GDM) occurs with the onset of hyperglycemia in the second and third trimesters of pregnancy, commonly in the form of insulin resistance. In recent decades, the prevalence of GDM in the U.S. has increased from <1% (1979–1980) to 5.8% (2008–2010) among hospital deliveries.(10) Risk factors for GDM include obesity, hypertension, inactivity, polycystic ovarian syndrome, family history of diabetes, personal history of GDM, older age, and other lifestyle factors.(11) Maternal diabetes is associated with numerous perinatal complications, including prematurity and fetal distress, as well as offspring complications in childhood such as obesity and type 2 diabetes.(12)

Emerging evidence suggests that GDM can have lifelong effects on child health through changes that influence fetal development, including development of the lung and immune system.(13) Epidemiologic studies broadly support the association between maternal

diabetes and childhood respiratory outcomes (14), but are primarily focused on European/White populations, yielding limited generalizability. Further, few of these studies have distinguished GDM from existing type 2 diabetes. Among studies specific to GDM, a Danish registry-based study reported an association between GDM and early-onset persistent wheeze,(15) while a U.S. health-system based study estimated increased risks of asthma among GDM pregnancies requiring medication but not without.(16) In this analysis, we examined the relationship between GDM and the development of childhood asthma and wheeze in offspring using a well-characterized, racially diverse, prospective U.S. pregnancy cohort.

## Methods

### Study Population

We studied mother-child dyads enrolled in the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study, a prospective study based in Shelby County (Memphis), Tennessee. The study design and data collection methods for CANDLE have been previously described.(17, 18) In brief, CANDLE recruited women during the second trimester of pregnancy (16–28 gestational weeks) between 2006 and 2011. Eligible women were English-speaking Shelby County residents, age 16–40 years, with low medical risk, singleton pregnancies at enrollment and plans to deliver at a designated study hospital. Staff screened 5,228 women and 3,320 met eligibility; of these, 1,503 (45%) agreed to participate and enrolled in CANDLE.(17) All women were engaged in prenatal care at or prior to the time of enrollment. Low medical risk was defined as the absence of certain chronic medical conditions and pregnancy complications, including insulin-dependent (type 1) diabetes, although women with asthma remained eligible.(17) Within our analytic sample, we did not identify any women with active type 2 diabetes at enrollment. Fifteen multiparous women endorsed “ever” having diabetes at enrollment, but did not endorse having diabetes currently, with “ever” diabetes thus likely related to having GDM in a prior pregnancy.

CANDLE participants responded to questionnaires and provided biospecimens during the second and third trimesters and at delivery. In addition, study research nurses and assistants documented pregnancy complications and labor and delivery information through abstraction of birth records provided by study hospitals.(17) Postnatally, mother-child dyads participated in annual in-person clinic visits through age 3, and again at approximately age 4 years, with maximum age for this study capped at 6.5 years of age. For the current study, we included dyads with estimated gestational age ≥ 32 weeks, completion of a 4-year study visit, and documented GDM status. Each woman provided written informed consent for herself and her child at enrollment and at the 4-year visit. The study was approved by the Institutional Review Boards of Vanderbilt University and the University of Tennessee Health Science Center.

### Gestational diabetes

For all participants included in this analysis, GDM was determined by study nurses and staff through medical record review.

### Childhood respiratory assessment

Research assistants assessed child's history of wheeze and asthma by parent-report at the 4-year visit using questionnaires based on the International Study of Asthma and Allergies in Children (19) and report of asthma-specific medication and healthcare use.(20) We defined current wheeze as experiencing wheezing or whistling in the chest in the past 12 months and current asthma as meeting at least two of the following criteria: (1) current wheeze; (2) parent report of provider diagnosis of asthma (or reactive airway disease); or (3) asthma-specific medication use in past 12 months. Parent report of provider diagnosis of asthma was analyzed as a separate outcome ("diagnosed asthma").

### Statistical Analysis

For descriptive purposes, we compared characteristics for dyads with and without GDM using Pearson $X^2$ and Wilcoxon rank sum tests for categorical and continuous variables, respectively (ascertainment of covariates described in Supplemental Methods). We also compared characteristics between eligible dyads who were included in the study and those who were not. We determined the association between maternal GDM and child respiratory outcomes using modified Poisson regression with robust sandwich errors to estimate risk ratios (RR) and corresponding 95% confidence intervals (95% CI). We developed a directed acyclic graph (DAG) based on published literature and clinical expertise to identify confounders for the primary models, assuming a similar confounding structure for asthma and wheeze outcomes (e-Figure 1). Primary models were adjusted a priori for child sex (male; female), as well as the following minimal adjustment set identified by the DAG: maternal age (years), race (African-American/Black; White or Other), prenatal smoking (yes; no), pre-pregnancy BMI (continuous kg/m$^2$), parity (0; ≥ 1), asthma history (yes; no), and SES composite score (continuous). Birth outcomes and postnatal factors were considered to potentially be on the causal pathway between GDM and childhood asthma/wheeze and therefore were not included in our adjustment set. Pregnancy-related factors, including gestational hypertension and total weight gain during pregnancy, were added to the adjustment set in sensitivity analyses. We used SAS version 9.4 (Cary, North Carolina) for data management and R version 3.4.0 (The R Foundation, Vienna, Austria) for analyses, and a two-sided type 1 error rate of 0.05 for statistical significance.

## Results

Of 1503 enrolled pregnancies, 1435 live births occurred at or after 32 weeks gestation and remained active in the study up to delivery. Of these, 1110 (77%) children participated in 4-year follow-up visit between ages 3.7 and 6.5 years of age. The final analytic sample included 1107 dyads (n=3 excluded due to missing GDM status). Dyads included in the analysis were more likely to be parous, and had older maternal age and higher maternal education, pre-pregnancy BMI, and SES than eligible CANDLE live births that were not included (e-Table 1). Among included dyads, 66% of women identified as Black/African-American, 33% identified as White, and 1% identified as another race; 57% reported a high school education or less and 43% reported a history of atopic disease. Women had a median age of 26 years (interquartile range [IQR]: 22, 30) at enrollment, a median pre-pregnancy

BMI of 26 kg/m$^2$ (IQR: 22, 32), and a median weight gain during pregnancy of 14 kg (IQR: 10, 18) (Table 1).

Gestational diabetes was documented for 5.6% of pregnancies (n=62) (Table 1). Women with GDM were older than women without GDM (median 31 vs. 26 years), had higher socioeconomic status (SES composite score, median: 0.20 vs. −0.10) and higher pre-pregnancy BMI (median 30 vs. 26 kg/m$^2$). Women with GDM gained less weight during pregnancy than women without GDM (median 11 vs. 14 kg) and were more likely to experience pre-eclampsia/gestational hypertension (17.7% vs. 9.0%). Maternal history of asthma did not differ by GDM status. Among children, those born to mothers with GDM were larger at birth (median birth weight: 3362 vs. 3250 g) compared to those who were not.

At follow-up, children had a median age of 4.2 years (IQR: 4.1, 4.5). The reported prevalence of current wheeze and current asthma was 19.0% (n=209) and 15.7% (n=173), respectively. Parent-reported diagnosed asthma was documented for 14.1% of children (n=155) (Table 1). All outcomes were more common among children of women with GDM than among children of women without (current wheeze: 30.6% vs. 18.3%; current asthma: 27.4% vs. 15.0%; diagnosed asthma: 25.8% vs. 13.4%) (Table 1), corresponding to unadjusted RRs (95% CI) of 1.67 (95%CI: 1.13, 2.49) for current wheeze, 1.83 (95%CI: 1.19, 2.81) for current asthma and 1.93 (95%CI: 1.23, 3.02) for diagnosed asthma. Following adjustment for our primary set of covariates, RR estimates remained consistent at 1.85 (95%CI: 1.23, 2.78) for current wheeze, 2.01 (95%CI: 1.30, 3.10) for current asthma and 2.13 (95%CI: 1.35, 3.38) for diagnosed asthma (Table 2). Sensitivity analyses additionally adjusting for gestational hypertension or total weight gain did not substantially change these results (e-Table 2).

## Discussion

In this large and racially diverse prospective cohort study, we investigated the association between GDM and childhood asthma and wheeze at approximately 4 years of age. We observed that GDM was associated with increased risk of both current wheeze and asthma, as well as parent-reported diagnosed asthma. Findings were robust to adjustment for multiple confounding factors.

While noting some inconsistencies (14), several prior studies have reported positive associations between maternal diabetes and childhood respiratory outcomes.(15, 16, 21–26) For example, several large European cohort studies have examined maternal diabetes and childhood wheeze (21, 22) and asthma (23–25). In general, these studies did not distinguish between pre-existing and gestational onset diabetes. In a large Italian cohort, Rusconi et al. reported an odds ratio of 1.84 (95% CI 1.06, 3.20) for persistent wheezing at age 6–7, based on parental questionnaire, with a maternal diabetes prevalence of approximately 2%. Zugna et al. conducted a pooled analysis of multiple European cohorts and observed a borderline association between maternal diabetes and recurrent wheeze (RR 1.24, 95% CI, 0.86, 1.79) but not ever wheeze (RR 1.04 95% CI 0.97, 1.13) up to age 2, noting high variability in GDM definitions and screening practices across countries/cohorts.(22) In a series of Swedish register-based studies, Aspberg reported elevated odds of asthma, defined as asthma

medication prescription fills (OR: 1.19 95% CI 1.12, 1.28) (24) or as asthma hospitalization (OR: 1.20 95% CI: 1.02, 1.42) (23) in children older than 2 years. In contrast, Haajata et al. observed a significant positive association with maternal diabetes and child asthma among those born moderately preterm, but not among those born at term, also relying on asthma medication prescription fills to define asthma cases.(25)

Of the few studies that distinguished maternal diabetes type, a large Danish registry-based study demonstrated an association between GDM (defined as diabetes first diagnosed during pregnancy) and early-onset persistent wheeze (wheezing at 0–3 years and 4–6 years of age) (OR: 1.15 95% CI: 1.05, 1.26).(15) Similar to other European studies, the prevalence of GDM was low in this study at 1.5%. In a racially diverse Boston-based cohort, Kumar et al. observed increased odds of allergic sensitization at age 3 in association with GDM (prevalence: 5.3%); however, childhood asthma and wheeze were not specifically assessed. (27) Finally, a health system-based study in California reported increased risk of childhood asthma after age 5 for pregnancies with GDM requiring medication (adjusted Hazard Ratio [aHR]: 1.17 [95% CI 1.06, 1.30]); associations were stronger for pregnancies with existing type 2 diabetes (aHR: 1.32 [95% CI 1.19, 1.46]), but null for pregnancies with GDM not requiring medication (aHR: 1.00 [95% CI 0.92, 1.08]).(16) While this study does support some association between GDM and child asthma, there appear to be differences in the magnitude of the point estimates when compared to ours. These differences may be due, in part, to differences in study design and study sample demographics.

Immune and lung system development begins prenatally, so it is plausible that asthma development might be influenced by pregnancy complications such as GDM. However, the mechanisms by which GDM might influence asthma risks in offspring are unclear, particularly since diabetes is associated with multiple pathological factors. During a healthy pregnancy, maternal insulin sensitivity adapts to the needs of the developing fetus, progressing from increased insulin sensitivity in early pregnancy to a modest state of insulin resistance later in pregnancy, designed to increase glucose transport across the placenta and promote fetal growth.(28, 29) This insulin resistance is exaggerated in women with GDM, leading to multiple metabolic disruptions including increased glucose and downstream effects such as fetal hyperinsulinemia and hypoxia (30) which may influence lung development. Diabetes is also associated with processes such as inflammation, oxidative stress, and altered T-cell immune profiles (7–9) which have been hypothesized to influence the development of asthma.(2)

Our study has many strengths. Relative to the published literature, our study is among few to prospectively assess associations between GDM and allergic/respiratory outcomes in a predominantly Black/African-American cohort, addressing an important data gap by extending generalizability outside European and predominantly White populations. While CANDLE is not designed as a truly representative cohort, it shares many characteristics with births in the underlying population of Shelby County, TN. For example, both include majority Black populations and both have a majority of high school or less for maternal educational attainment.(17) We note some loss to follow up between birth and age 4, however this attrition did not substantially alter the demographics of our analytic sample. In addition, both exposure and outcome characterizations were well captured, as cases of GDM

were confirmed through medical record review, and childhood respiratory outcomes were assessed prospectively using a widely validated questionnaire.(19) Similarly, our rich covariate data allowed for adequate adjustment for many confounding factors and for co-occurring pregnancy complications such as gestational hypertension. This attribute is useful in demonstrating that gestational diabetes, not pregnancy complications more generally, are associated with respiratory outcomes. Finally, our follow-up extended to 4 years of age, which allows for characterization of asthma outcomes (as opposed to early, transient wheeze).

Our study also has limitations. It is possible that a woman may have had unreported or undiagnosed type 2 diabetes at study entry that was subsequently captured as GDM. Additionally, despite a thorough approach to confounding adjustment, we acknowledge the possibility for unmeasured confounding. We relied on self-report for pre-pregnancy BMI which may contribute to misclassification of maternal BMI, an important confounder. Our study had no information on diabetes management or medication use during pregnancy. Our data show that women with GDM gained less weight than women without GDM, suggesting some effective clinical management of disease. However, this was not examined directly. Understanding the relationship between diabetes, diabetes management (including diet, medications, and glycemic control) and child respiratory outcomes will be an important next step in elucidating mechanism related to the associations we observed here. Lastly, larger studies will be needed to assess potentially informative effect modifiers, such as maternal atopy.

In conclusion, we observed a strong association between GDM and childhood asthma and wheeze, suggesting GDM may be a childhood asthma risk factor. This relationship was robust to adjustment for multiple possible confounding factors. We have characterized this association in an urban, racially diverse, understudied population of the southern U.S., but our findings may be generalizable to other populations. Our findings warrant replication in other racially diverse cohorts, with further characterization of childhood asthma phenotypes and exploration of possible underlying mechanisms.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

We acknowledge the contributions of the study research staff and families who enrolled in the Conditions Affecting Neurocognitive Development and Learning in Early Childhood study. This work was funded by the Urban Child Institute, NIH R01 HL109977, K24 HL150312, and the Vanderbilt Institute for Clinical and Translational Research Grant Number: UL1RR024975.

**Funding support:** This work was funded by the Urban Child Institute, NIH R01 HL109977, K24 HL150312, and the Vanderbilt Institute for Clinical and Translational Research Grant Number: UL1RR024975.

**Conflict of Interest Statement:** KN Carroll and T Gebretsadik report funding from NIH NHLBI grants R01 HL109977 and K24 HL150312. No other authors report funding sources or other conflicts of interest related to this work. Funding sources were not involved in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

## Abbreviations:

| | |
|---|---|
| **GDM** | gestational diabetes mellitus |
| **CANDLE** | Conditions Affecting Neurocognitive Development and Learning in Early Childhood cohort |
| **SES** | socioeconomic status |
| **BMI** | body mass index |
| **IQR** | interquartile range |
| **RR** | risk ratio |
| **95% CI** | 95% Confidence Interval |

## References:


1. Akinbami LJ, Simon AE, Rossen LM. Changing Trends in Asthma Prevalence Among Children. Pediatrics. 2016;137(1) 10.1542/peds.2015-2354.
2. Henderson AJ, Warner JO. Fetal origins of asthma. Semin Fetal Neonatal Med. 2012;17(2):82–91 10.1016/j.siny.2012.01.006. [PubMed: 22265927]
3. van Aalderen WM, Sprikkelman AB, Hoekstra MO. Is childhood asthma an inflammatory disease? Allergy. 1999;54 Suppl 49:62–7 10.1111/j.1398-9995.1999.tb04390.x. [PubMed: 10422750]
4. Segovia SA, Vickers MH, Gray C, Reynolds CM. Maternal obesity, inflammation, and developmental programming. Biomed Res Int. 2014;2014:418975 10.1155/2014/418975. [PubMed: 24967364]
5. Wang P, You D, Saravia J, Shen H, Cormier SA. Maternal exposure to combustion generated PM inhibits pulmonary Th1 maturation and concomitantly enhances postnatal asthma development in offspring. Part Fibre Toxicol. 2013;10:29 10.1186/1743-8977-10-29. [PubMed: 23856009]
6. Noakes PS, Thomas R, Lane C, Mori TA, Barden AE, Devadason SG, et al. Association of maternal smoking with increased infant oxidative stress at 3 months of age. Thorax. 2007;62(8):714–7 10.1136/thx.2006.061630. [PubMed: 17356057]
7. Wedekind L, Belkacemi L. Altered cytokine network in gestational diabetes mellitus affects maternal insulin and placental-fetal development. J Diabetes Complications. 2016;30(7):1393–400 10.1016/j.jdiacomp.2016.05.011. [PubMed: 27230834]
8. Newsholme P, Cruzat VF, Keane KN, Carlessi R, de Bittencourt PI Jr. Molecular mechanisms of ROS production and oxidative stress in diabetes. Biochem J. 2016;473(24):4527–50 10.1042/BCJ20160503C. [PubMed: 27941030]
9. Sifnaios E, Mastorakos G, Psarra K, Panagopoulos ND, Panoulis K, Vitoratos N, et al. Gestational Diabetes and T-cell (Th1/Th2/Th17/Treg) Immune Profile. In Vivo. 2019;33(1):31–40 10.21873/invivo.11435.
10. Lavery JA, Friedman AM, Keyes KM, Wright JD, Ananth CV. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. BJOG. 2017;124(5):804–13 10.1111/1471-0528.14236. [PubMed: 27510598]
11. Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018;131(2):e49–e64 10.1097/AOG.0000000000002501. [PubMed: 29370047]
12. Burlina S, Dalfra MG, Lapolla A. Short- and long-term consequences for offspring exposed to maternal diabetes: a review. J Matern Fetal Neonatal Med. 2017:1–171 10.1080/14767058.2017.1387893.

13. Lock M, McGillick EV, Orgeig S, McMillen IC, Morrison JL. Regulation of fetal lung development in response to maternal overnutrition. Clin Exp Pharmacol Physiol. 2013;40(11):803–16 10.1111/1440-1681.12166. [PubMed: 24033542]
14. Azad MB, Moyce BL, Guillemette L, Pascoe CD, Wicklow B, McGavock JM, et al. Diabetes in pregnancy and lung health in offspring: developmental origins of respiratory disease. Paediatr Respir Rev. 2017;21:19–26 10.1016/j.prrv.2016.08.007. [PubMed: 27665512]
15. Liu X, Agerbo E, Li J, Dharmage SC, Thomsen RW, Olsen J, et al. Maternal pregestational or gestational diabetes and childhood wheezing: A population-based cohort study. Allergy. 2018;73(11):2247–50 10.1111/all.13551. [PubMed: 29987908]
16. Martinez MP, Lin J, Chow T, Chung J, Wang X, Xiang AH. Maternal Gestational Diabetes and Type 2 Diabetes During Pregnancy and Risk of Childhood Asthma in Offspring. J Pediatr. 2020;219:173–9 e1 10.1016/j.jpeds.2019.12.053. [PubMed: 31987655]
17. Sontag-Padilla L, Burns RM, Shih RA, Griffin BA, Martin LT, Chandra A, et al. The Urban Child Institute CANDLE Study: Methodological Overview and Baseline Sample Description Santa Monica, CA: RAND Corporation; 2015 [Available from: https://www.rand.org/pubs/research_reports/RR1336.html.
18. Roy A, Kocak M, Hartman TJ, Vereen S, Adgent M, Piyathilake C, et al. Association of prenatal folate status with early childhood wheeze and atopic dermatitis. Pediatr Allergy Immunol. 2018;29(2):144–50 10.1111/pai.12834. [PubMed: 29168294]
19. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J. 1995;8(3):483–91 10.1183/09031936.95.08030483. [PubMed: 7789502]
20. Rosa MJ, Hartman TJ, Adgent M, Gardner K, Gebretsadik T, Moore PE, et al. Prenatal polyunsaturated fatty acids and child asthma: Effect modification by maternal asthma and child sex. J Allergy Clin Immunol. 2020;145(3):800–7 e4 10.1016/j.jaci.2019.10.039. [PubMed: 31809758]
21. Rusconi F, Galassi C, Forastiere F, Bellasio M, De Sario M, Ciccone G, et al. Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children. Am J Respir Crit Care Med. 2007;175(1):16–21 10.1164/rccm.200512-1978OC. [PubMed: 16998092]
22. Zugna D, Galassi C, Annesi-Maesano I, Baiz N, Barros H, Basterrechea M, et al. Maternal complications in pregnancy and wheezing in early childhood: a pooled analysis of 14 birth cohorts. Int J Epidemiol. 2015;44(1):199–208 10.1093/ije/dyu260. [PubMed: 25626439]
23. Aspberg S, Dahlquist G, Kahan T, Kallen B. Is neonatal phototherapy associated with an increased risk for hospitalized childhood bronchial asthma? Pediatr Allergy Immunol. 2007;18(4):313–9 10.1111/j.1399-3038.2006.00518.x. [PubMed: 17346296]
24. Aspberg S, Dahlquist G, Kahan T, Kallen B. Confirmed association between neonatal phototherapy or neonatal icterus and risk of childhood asthma. Pediatr Allergy Immunol. 2010;21(4 Pt 2):e733–9 10.1111/j.1399-3038.2010.01038.x. [PubMed: 20444150]
25. Haataja P, Korhonen P, Ojala R, Hirvonen M, Paassilta M, Gissler M, et al. Asthma and atopic dermatitis in children born moderately and late preterm. Eur J Pediatr. 2016;175(6):799–808 10.1007/s00431-016-2708-8. [PubMed: 26898703]
26. Risnes KR, Belanger K, Murk W, Bracken MB. Antibiotic exposure by 6 months and asthma and allergy at 6 years: Findings in a cohort of 1,401 US children. Am J Epidemiol. 2011;173(3):310–8 10.1093/aje/kwq400. [PubMed: 21190986]
27. Kumar R, Ouyang F, Story RE, Pongracic JA, Hong X, Wang G, et al. Gestational diabetes, atopic dermatitis, and allergen sensitization in early childhood. J Allergy Clin Immunol. 2009;124(5):1031–8 e1–4 10.1016/j.jaci.2009.06.052. [PubMed: 19733904]
28. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The Pathophysiology of Gestational Diabetes Mellitus. Int J Mol Sci. 2018;19(11) 10.3390/ijms19113342.
29. Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EA. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. Am J Obstet Gynecol. 1991;165(6 Pt 1):1667–72 10.1016/0002-9378(91)90012-g. [PubMed: 1750458]

30. Taricco E, Radaelli T, Rossi G, Nobile de Santis MS, Bulfamante GP, Avagliano L, et al. Effects of gestational diabetes on fetal oxygen and glucose levels in vivo. BJOG. 2009;116(13):1729–35 10.1111/j.1471-0528.2009.02341.x. [PubMed: 19832834]

## Highlights

Gestational diabetes is associated with perinatal complications and childhood morbidities such as obesity and type 2 diabetes. Findings from epidemiologic studies investigating maternal diabetes and childhood wheeze/asthma have been inconsistent.

After adjusting for a rich set of potential confounders, this study found strong associations between gestational diabetes and childhood asthma and wheeze in a predominantly African-American/Black pregnancy cohort.

Exposure to gestational diabetes *in utero* may increase a child's likelihood of developing wheeze or asthma; gestational diabetes is a possible modifiable risk factor for these outcomes.

**Table 1.**

Characteristics of eligible dyads in the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) cohort

| Characteristic | Gestational Diabetes (−) | Gestational Diabetes (+) | Total |
|---|---|---|---|
| n (%) | 1045 (94.4) | 62 (5.6) | 1107 (100) |
| **Maternal Characteristics** | | | |
| Race, n (%) † | | | |
| African-American/Black | 688 (66.0) | 36 (58.1) | 724 (65.5) |
| White/Other | 355 (34.0) | 26 (41.9) | 381 (34.5) |
| Education, n (%) †* | | | |
| ≤ High School | 606 (58.0) | 27 (43.5) | 633 (57.2) |
| > High School | 438 (42.0) | 35 (56.5) | 473 (44.8) |
| Gestational hypertension, yes, n (%) †,§* | 94 (9.0) | 11 (17.7) | 105 (9.5) |
| Asthma history, yes, n (%) † | 120 (11.6) | 7 (11.5) | 127 (11.6) |
| Nulliparous, yes, n (%) | 417 (39.9) | 21 (33.9) | 438 (39.6) |
| Cesarean delivery, yes, n (%) | 380 (36.4) | 29 (46.8) | 409 (36.9) |
| Prenatal smoking, yes, n (%) † | 89 (8.5) | 9 (14.5) | 98 (8.9) |
| Age, median (IQR), years * | 26 (22, 30) | 31 (25, 34) | 26 (22, 30) |
| Household-size adjusted income, median (IQR) †,‡ | 13,043 (4709, 28,571) | 18,750 (8333, 28571) | 13,397 (5110, 28571) |
| SES composite, median (IQR) * | −0.10 (−0.63, 0.85) | 0.20 (−0.35, 1.12) | −0.09 (−0.60, 0.85) |
| Pre-pregnancy BMI, median (IQR) †* | 26 (22, 32) | 30 (26, 33) | 26 (22, 32) |
| Total weight gain, median (IQR), kg †* | 14 (10, 19) | 11 (8, 15) | 14 (10, 18) |
| **Child Characteristics** | | | |
| Sex, male, n (%) | 515 (49.3) | 36 (58.1) | 551 (49.8) |
| Age at visit, median (IQR), years | 4.2 (4.1, 4.5) | 4.2 (4.1, 4.7) | 4.2 (4.1, 4.5) |
| Gestational weeks, median (IQR) * | 39 (38, 40) | 39 (38, 39) | 39 (38, 40) |
| Birth weight, median (IQR), g * | 3250 (2971, 3563) | 3362 (3033, 3803) | 3260 (2974, 3572) |
| **Child Respiratory Outcomes** | | | |
| Current wheeze, yes, n (%) †* | 190 (18.3) | 19 (30.6) | 209 (19.0) |
| Current asthma, yes, n (%) †,¶* | 156 (15.0) | 17 (27.4) | 173 (15.7) |
| Diagnosed asthma, yes, n (%) †* | 139 (13.4) | 16 (25.8) | 155 (14.1) |

* p <0.05 for Wilcoxon rank sum or Pearson $X^2$ test. IQR = Interquartile Range; kg = kilograms; BMI = body mass index (kilograms/meters$^2$)

† missing data: maternal race n = 2; maternal education n = 1; household-size adjusted income n = 7; gestational hypertension n = 2; total weight gain n = 65; asthma history n = 8; prenatal smoking n = 1; pre-pregnancy BMI n = 3; child BMI at assessment n = 82; diagnosed asthma n = 6; current wheeze n = 7; current asthma n = 5

‡ household income was reported at enrollment (n = 1031) or obtained from a later CANDLE study visit, if missing.

[§] pre-eclampsia or gestational hypertension

[¶] Subjects that were missing responses for one (n = 17) or two (n = 1) of the defining criteria for current asthma and had one negative response to the remaining criteria were treated as non-asthma subjects. Subjects missing responses for all three criteria were treated as missing.

**Table 2.**

Risk ratios (RR) and 95% confidence intervals for the association between gestational diabetes and childhood respiratory outcomes.

| | n | RR (95% CI) |
|---|---|---|
| **Current Wheeze** | | |
| Unadjusted | 1100 | 1.67 (1.13, 2.49) |
| Adjusted * | 1087 | 1.85 (1.23, 2.78) |
| **Current Asthma** | | |
| Unadjusted | 1102 | 1.83 (1.19, 2.81) |
| Adjusted * | 1089 | 2.01 (1.30, 3.10) |
| **Diagnosed Asthma** | | |
| Unadjusted | 1101 | 1.93 (1.23, 3.02) |
| Adjusted * | 1088 | 2.13 (1.35, 3.38) |

*Adjusted for age (continuous years), race (African American/Black; White or Other), prenatal smoking (yes/no), pre-pregnancy body mass index (BMI) (continuous kg/$m^2$), parity (0/≥1), maternal asthma history (yes/no), SES composite score (continuous) and infant sex (male/female)