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Accepted for Publication: June 23, 2019.

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Published Online: December 9, 2019. doi:10.1001/jamapediatrics.2019.4715

Author Contributions: Drs Cairo and Shi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Cairo, Talano, Moore, Weinberg.
Acquisition, analysis, or interpretation of data: Cairo, Talano, Moore, Shi, Weinberg, Grossman, Shenoy.
Drafting of the manuscript: Cairo, Moore, Weinberg, Shenoy.
Critical revision of the manuscript for important intellectual content: Cairo, Talano, Moore, Shi, Weinberg, Grossman, Shenoy.
Statistical analysis: Cairo, Shi.
Obtained funding: Cairo.
Administrative, technical, or material support: Cairo, Talano, Weinberg.
Supervision: Cairo, Talano, Moore.
Other - Cellular therapy laboratory core: Grossman.
Other - Participated in the trial and helped with data and writing the paper: Shenoy.

Conflict of Interest Disclosures: Dr Cairo reports receiving grants from the US Food and Drug Administration (FDA) (R01FD004090), the Pediatric Cancer Research Foundation (PCRF), Otsuka, and Miltenyi during the conduct of the study. No other disclosures were reported.

Funding/Support: This study was supported by FDA grant R01FD004090 (Dr Cairo) and by the PCRF, Otsuka, and Miltenyi (Dr Cairo). Miltenyi Biotec (Bergisch Gladbach, Germany) supplied the CliniMACS CD34+ reagent system.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: This paper was presented as an oral abstract at the 60th Annual Meeting of the American Society of Hematology; December 1, 2018; San Diego, California.

Additional Contributions: We acknowledge the members of the SCD HAPLO Consortium including Carolyn Keever-Taylor, PhD, Department of Medicine, Medical College of Wisconsin, Milwaukee; Mark C. Walters, MD, and Elliot Vichinsky, MD, Department of Pediatrics, UCSF Benioff Children's Hospital, Oakland, California; Susan K. Parsons, MD, Departments of Medicine and Pediatrics, Tufts Medical Center, Boston, Massachusetts; Suzanne Braniecki, PhD, Allen J. Dozor, MD, and Deborah Friedman, MD, Department of Pediatrics, New York Medical College, Valhalla; Robert C. McKinstry, MD, PhD, Department of Pediatrics and Radiology, Washington University, St. Louis, Missouri; James Verbsky, MD, Department of Pediatrics, Medical College of Wisconsin, Milwaukee; Chitti R. Moorthy, MD, Department of Radiation Medicine, New York Medical College, Valhalla; Janet Ayello, MS, Allyson Flower, MD, Yaya Chu, PhD, Erin Morris, BSN, Harshini Mahanti, MRSC, and Sandra Fabricatore, MSN, Department of Pediatrics, New York Medical College, Valhalla; Olga Militano, PharmD, Children's Oncology Group, Arcadia, California; Liana Klejmont, PharmD, and Carmella van de Ven, MA, Department of Pediatrics, New York Medical College, Valhalla; Lee Ann Baxter-Lowe, PhD, Department of Pathology, Children's Hospital Los Angeles, Los Angeles, California; and Mildred Semidei-Pomales, MS Department of Pediatrics, New York Medical College, Valhalla, for their assistance in the data collection and interpretation. We thank Virginia Davenport, RN, Department of Pediatrics, New York Medical College, Valhalla, for her superb editorial assistance. No compensation was received. We also thank the patients and families who participated in this clinical trial and all the members of the external data safety monitoring committee and external advisory committee.

1. Gladwin MT. Cardiovascular complications and risk of death in sickle-cell disease. *Lancet*. 2016;387(10037):2565-2574. doi:10.1016/S0140-6736(16)00647-4

2. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994;330(23):1639-1644. doi:10.1056/NEJM199406093302303

3. Gluckman E, Cappelli B, Bernaudin F, et al; Eurocord, the Pediatric Working Party of the European Society for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant Research. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood*. 2017;129(11):1548-1556. doi:10.1182/blood-2016-10-745711

4. Talano JA, Cairo MS. Hematopoietic stem cell transplantation for sickle cell disease: state of the science. *Eur J Haematol*. 2015;94(5):391-399. doi:10.1111/ejh.12447

5. Shenoy S, Eapen M, Panepinto JA, et al. A trial of unrelated donor marrow transplantation for children with severe sickle cell disease. *Blood*. 2016;128(21):2561-2567. doi:10.1182/blood-2016-05-715870

6. Geyer MB, Ricci AM, Jacobson JS, et al. T cell depletion utilizing CD34(+) stem cell selection and CD3(+) addback from unrelated adult donors in paediatric allogeneic stem cell transplantation recipients. *Br J Haematol*. 2012;157(2):205-219. doi:10.1111/j.1365-2141.2012.09048.x

Placental Weight and Risk of Neonatal Death

The placenta is a determinant of fetal growth, and infants who are born small for gestational age have an increased risk of infant death.[1,2] Such knowledge suggests that placental factors may be associated with infant death, particularly in deaths shortly after birth.

Previously, low placental weight has been associated with increased risk of fetal death[3] and with cerebral palsy in infants.[4] By contrast, in preterm-born children, high placental weight and high placental weight relative to birth weight increased the risks.[3,4] These previous findings suggest that placental weight may be associated with neonatal death and that associations may differ by gestational age at birth.

Therefore, we studied the association of placental weight with the risk of neonatal death. We also studied whether placental weight relative to birth weight was associated with neonatal death.

Methods | We used data from the Medical Birth Registry of Norway during January 1999 to December 2015, including all singleton infants in Norway without congenital malformations (n = 868 617) and all singleton infants with congenital malformations (n = 38 229). The study was approved by the Norwegian Data Inspectorate. The use of data from the Medical Birth Registry of Norway is regulated by law and the study was recommended by its advisory committee.

We grouped the distribution of placental weight (in grams) into quartiles within 2-week intervals of gestational age at birth. The associations of low (first quartile) and high (fourth quartile) placental weight with neonatal death were estimated as crude and adjusted odds ratios (aOR) with 95% confidence intervals. The second and third quartiles combined were used as the reference category. We made separate analyses among children born preterm (gestational weeks 29-36) and children born at term (gestational weeks 37-42) and we repeated the analyses using quartiles of placental weight relative to birth weight (placental weight/birth weight, in grams) as the exposure. Adjustments were made for offspring sex, parity (0 or ≥1), pregnancy after in vitro fertilization (yes/no), maternal age (years), maternal smoking (yes/no), preeclampsia (yes/no), and maternal diabetes (yes/no).

Results | *Infants Without Congenital Malformations*. In total, 492 of 868 617 infants without congenital malformations (0.06%) died

Table 1. Odds Ratios of Neonatal Death Among 868 617 Infants Without Congenital Malformations According to Gestational Age–Specific Quartiles of Placental Weight, Birth Weight, and Placental to Birth Weight Ratio[a]

	Neonatal Death											
	Placental Weight				Birth Weight				Placental to Birth Weight Ratio			
	No.		OR (95% CI)		No.		OR (95% CI)		No.		OR (95% CI)	
Quartile	Yes	No	Crude	Adjusted	Yes	No	Crude	Adjusted	Yes	No	Crude	Adjusted
Gestational Age, 29-36 wk (n = 39 641)												
First	41	9345	1.45 (0.98-2.16)	1.56 (1.05-2.32)	42	9668	1.14 (0.78-1.67)	1.29 (0.87-1.90)	29	9936	0.79 (0.51-1.21)	0.78 (0.51-1.21)
Second to third	62	20 535	1 [Reference]	1 [Reference]	76	20 020	1 [Reference]	1 [Reference]	74	19 934	1 [Reference]	1 [Reference]
Fourth	69	9589	2.38 (1.69-3.36)	2.31 (1.63-3.27)	54	9781	1.45 (1.03-2.06)	1.38 (0.97-1.97)	69	9599	1.94 (1.39-2.69)	1.94 (1.40-2.70)
Gestational Age, 37-42 wk (n = 828 976)												
First	89	204 898	1.18 (0.91-1.54)	1.18 (0.90-1.53)	116	206 442	1.95 (1.51-2.52)	1.90 (1.47-2.45)	80	207 495	1.07 (0.82-1.41)	1.09 (0.83-1.43)
Second to third	151	411 649	1 [Reference]	1 [Reference]	120	416 265	1 [Reference]	1 [Reference]	149	414 620	1 [Reference]	1 [Reference]
Fourth	80	212 109	1.03 (0.78-1.35)	1.03 (0.78-1.35)	84	205 949	1.42 (1.07-1.87)	1.43 (1.08-1.90)	91	206 541	1.23 (0.96-1.59)	1.20 (0.93-1.56)

Abbreviation: OR, odds ratio.

[a] Adjustments were made for offspring sex, parity (0 or ≥1), pregnancy after in vitro fertilization (yes/no), maternal age (years), maternal smoking (yes/no), preeclampsia (yes/no), and maternal diabetes (yes/no).

Table 2. Odds Ratios of Neonatal Death in 38 229 Infants With Congenital Malformations According to Gestational Age–Specific Quartiles of Placental Weight, Birth Weight, and Placental to Birth Weight Ratio[a]

	Neonatal Death											
	Placental Weight				Birth Weight				Placental to Birth Weight Ratio			
	No.		OR (95% CI)		No.		OR (95% CI)		No.		OR (95% CI)	
Quartile	Yes	No	Crude	Adjusted	Yes	No	Crude	Adjusted	Yes	No	Crude	Adjusted
Gestational Age 29-36 wk (n = 4187)												
First	79	1042	1.93 (1.39-2.68)	2.02 (1.45-2.82)	99	1132	2.22 (1.63-3.04)	2.47 (1.80-3.39)	45	946	1.05 (0.72-1.52)	1.04 (0.72-1.52)
Second to third	71	1808	1 [Reference]	1 [Reference]	72	1831	1 [Reference]	1 [Reference]	83	1826	1 [Reference]	1 [Reference]
Fourth	65	1122	1.48 (1.05-2.08)	1.47 (1.04-2.08)	44	1009	1.11 (0.76-1.63)	1.10 (0.75-1.63)	87	1200	1.60 (1.17-2.17)	1.59 (1.17-2.17)
Gestational Age 37-42 wk (n = 34 042)												
First	102	8606	1.93 (1.46-2.55)	1.96 (1.48-2.60)	138	9242	2.80 (2.13-3.66)	2.93 (2.23-3.85)	55	8123	1.14 (0.82-1.59)	1.14 (0.82-1.59)
Second to third	99	16 127	1 [Reference]	1 [Reference]	86	16 096	1 [Reference]	1 [Reference]	98	16 539	1 [Reference]	1 [Reference]
Fourth	51	9057	0.92 (0.65-1.29)	0.89 (0.64-1.26)	28	8452	0.62 (0.40-0.95)	0.58 (0.38-0.90)	99	9128	1.83 (1.38-2.42)	1.82 (1.37-2.41)

Abbreviation: OR, odds ratio.

[a] Adjustments were made for offspring sex, parity (0 or ≥1), pregnancy after in vitro fertilization (yes/no), maternal age (years), maternal smoking (yes/no), preeclampsia (yes/no), and maternal diabetes (yes/no).

during the neonatal period. Among the preterm born infants, high (aOR, 2.31; 95% CI, 1.63-3.27) and low placental weight (aOR, 1.56; 95% CI, 1.05-2.32) increased the risk of neonatal death (**Table 1**). Also, high placental weight relative to birth weight increased the risk of neonatal death among preterm-born children (aOR, 1.94; 95% CI, 1.40-2.70). Among the infants born at term, placental weight was not associated with neonatal death.

Infants With Congenital Malformations. In total, 467 of the 38 229 infants with congenital malformations (1.22%) died during the neonatal period. Among the preterm-born infants, the associations of placental weight with neonatal death displayed similar patterns as for infants without congenital malformation (**Table 2**). However, in term-born infants with congenital malformations, low placental weight increased the risk of neonatal death (aOR, 1.96; 95% CI, 1.48-2.60). Although the placental weight was low among the infants who died, birth weight was relatively lower. Thus, high placental weight relative to birth weight increased the risk of neonatal death in term-born infants with congenital malformations (aOR ,1.82; 95% CI, 1.37-2.41).

Discussion | We found that high placental weight increased the risk of neonatal death in preterm-born infants. This finding is novel and difficult to explain. It is possible that underlying adverse intrauterine conditions, such as fetoplacental hypoxemia, could induce biological responses that result in placental enlargement,[5] and also increase the risk of preterm birth and neonatal death.

Conclusions | We found that preterm born infants with either high or low placental weight had an increased risk of neonatal death. In term-born infants, low placental weight was associated with an increase in the risk of neonatal death among infants with congenital malformations. These findings may help to identify infants at increased risk of neonatal death.

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Published Online: December 2, 2019. doi:10.1001/jamapediatrics.2019.4556

Author Contributions: Drs Dypvik and Eskild had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Obtained funding: Eskild.
Administrative, technical, or material support: Eskild.
Supervision: Saugstad, Eskild.

Conflict of Interest Disclosures: Drs Dypvik and Larsen reported grants from South-Eastern Norway Regional Health Authority during the conduct of the study. No other disclosures were reported.

Funding/Support: The study received funding from grant 272901 from the South-Eastern Regional Health Authorities of Norway.

Role of the Funder/Sponsor: The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

1. Baer RJ, Rogers EE, Partridge JC, et al. Population-based risks of mortality and preterm morbidity by gestational age and birth weight. *J Perinatol*. 2016;36(11):1008-1013. doi:10.1038/jp.2016.118

2. Altman M, Edstedt Bonamy AK, Wikström AK, Cnattingius S. Cause-specific infant mortality in a population-based Swedish study of term and post-term births: the contribution of gestational age and birth weight. *BMJ Open*. 2012;2(4):e001152. doi:10.1136/bmjopen-2012-001152

3. Haavaldsen C, Samuelsen SO, Eskild A. Fetal death and placental weight/birth weight ratio: a population study. *Acta Obstet Gynecol Scand*. 2013;92(5):583-590. doi:10.1111/aogs.12105

4. Strand KM, Andersen GL, Haavaldsen C, Vik T, Eskild A. Association of placental weight with cerebral palsy: population-based cohort study in Norway. *BJOG*. 2016;123(13):2131-2138. doi:10.1111/1471-0528.13827

5. Eskild A, Strøm-Roum EM, Haavaldsen C. Does the biological response to fetal hypoxia involve angiogenesis, placental enlargement and preeclampsia? *Paediatr Perinat Epidemiol*. 2016;30(3):305-309. doi:10.1111/ppe.12283

Association Between Use of Multiple Classes of Antibiotic in Infancy and Allergic Disease in Childhood

Antibiotic administration negatively affects the microbiome by decreasing bacterial diversity, and this has been associated with allergic disease.[1-3] Exposure to multiple classes of antibiotics may lead to even greater perturbations to the gut biome than 1 class alone. The purpose of this study is to determine whether exposure to multiple antibiotic classes in infancy is associated with a higher risk of developing allergic disease in early childhood.

Methods | This retrospective cohort study was conducted with a previously collected cohort of 798 426 children who were Department of Defense Tricare beneficiaries.[1] These children had a birth medical record in the Military Health System database between October 1, 2001, and September 30, 2013, with continued enrollment from 35 days of age or younger until at least 1 year of age. Children with an initial birth stay in the hospital of more than 7 days or a diagnosis with an outcome allergic condition within the first 6 months of life were excluded. Exposures were defined as having any dispensed prescription for penicillin, penicillin with a β-lactamase inhibitor, cephalosporin, sulfonamide, or macrolide in the first 6 months of life.

The main outcomes were the presence of any allergic disease, food allergy, anaphylaxis, asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, or contact dermatitis. Cox proportional hazards modeling was performed. The first model used exposure to specific classes of antibiotics to analyze the development of any allergic disease. The second model used antibiotic classes as an ordinal variable representing the number of antibiotic classes prescribed in the first 6 months. Adjusted hazard ratios represented the association of an increase in the number of classes of antibiotic with each of the outcomes. Models were adjusted for cesarean delivery, prematurity, sex, antacid medication exposure (proton pump inhibitors or histamine-2 receptor antagonists), and total days of supplied antibiotics. The study was reviewed and approved by the institutional review board of the Uniformed Services University, with a waiver of informed consent because data were deidentified. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc), and 2-tailed *P* values less than .05 were considered significant. Data were collected from October 1, 2001, to September 30, 2013. Data analysis occurred from February 2019 to May 2019.

Results | Among the 798 426 children in the cohort (including 400 323 male children [50.1%]), there were 162 605 filled prescriptions for antibiotics (penicillin, 96 793 prescriptions [59.5%]; macrolide, 21 347 prescriptions [13.1%]; cephalosporin, 21 284 prescriptions [13.1%]; penicillin with β-lactamase inhibitor, 15 811 prescriptions [9.7%]; sulfonamides, 6212 prescriptions [3.8%]). There were 664 710 children (83.3%) prescribed no classes of antibiotic, 109 341 children (13.7%) prescribed 1 class, 20 358 (2.5%) prescribed 2 classes, 3543 (0.44%) prescribed 3 classes, and 474 children (0.06%) prescribed 4 or more classes of antibiotics during the first 6 months of life. Data for children in the cohort were available for a median of 4.6 (interquartile range, 2.5-7.9) years.

All types of antibiotic classes assessed were associated with significant increased adjusted hazard ratios (aHRs) for any outcome allergic disease (**Table 1**). The aHRs were lowest for sulfonamides (1.06 [95% CI, 1.03-1.10]) and 1.19 or greater for all