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ABSTRACT

OBJECTIVES: The National Patient-Centered Clinical Research Network (PCORnet) supports observational and clinical research using health care data. The PCORnet Antibiotics and Childhood Growth Study is one of PCORnet’s inaugural observational studies. We sought to describe the processes used to integrate and analyze data from children across 35 participating institutions, the cohort characteristics, and prevalence of antibiotic use.

METHODS: We included children in the cohort if they had at least one same-day height and weight measured in each of 3 age periods: 1) before 12 months, 2) 12 to 30 months, and 3) after 24 months. We distributed statistical queries that each institution ran on its local version of the PCORnet Common Data Model, with aggregate data returned for analysis. We defined overweight or obesity as age- and sex-specific body mass index ≥85th percentile, obesity ≥95th percentile, and severe obesity ≥120% of the 95th percentile.

RESULTS: A total of 681,739 children met the cohort inclusion criteria, and participants were racially/ethnically diverse (24.9% black, 17.5% Hispanic). Before 24 months of age, 55.2% of children received at least one antibiotic prescription; 21.3% received a single antibiotic prescription; 14.3% received 4 or more; and 33.3% received a broad-spectrum antibiotic. Overweight and obesity prevalence was 27.6% at age 4 to <6 years (n = 362,044) and 36.2% at 9 to <11 years (n = 58,344).

CONCLUSIONS: The PCORnet Antibiotics and Childhood Growth Study is a large national longitudinal observational study in a diverse population that will examine the relationship between early antibiotic use and subsequent growth patterns in children.

KEYWORDS: antibiotics; body mass index; childhood growth; childhood obesity; electronic health records; research infrastructure

ACADEMIC PEDIATRICS 2018;18:569–576

WHAT’S NEW

The National Patient-Centered Clinical Research Network (PCORnet) provides an unprecedented opportunity to conduct research using health care data. In 35 health care institutions, we assembled a large cohort to examine antibiotics and childhood growth. More than half of children received an antibiotic prescription before 2 years of age.

THE WIDESPREAD AVAILABILITY of health care data through electronic health records (EHRs) and other data sources provide unique opportunities to conduct pragmatic clinical trials and observational studies on a large scale. The National Patient-Centered Clinical Research Network (PCORnet) is a distributed research network that uses health care data to facilitate multisite clinical trials and observational research studies.\(^1\)–\(^3\) PCORnet has 13 clinical data research
To participate in the study, Network Partners had to meet data quality standards that were set forth by the PCORnet Coordinating Center. These included assessments of data model conformance, missing data in required tables and variables, and data plausibility in date and vital measure fields. Required tables included enrollment, encounters, demographics, vital findings, diagnoses, and procedures. The study team additionally required that Network Partners had the capacity to create a pediatric cohort that met the study’s inclusion criteria and that could identify antibiotic prescriptions. Of the 44 institutions initially planned for inclusion, we removed 8 from the study for the following reasons: did not meet Coordinating Center data quality standards (n = 1) or did not meet them by February 1, 2017 (n = 1); did not have access to outpatient prescription medications in their CDM (n = 2); were unable to map their prescribing data to RxNorm codes needed for the study by February 1, 2017 (n = 1); were unwilling to share individual-level data (n = 2); or chose not to participate because the site had a small pediatric population available in their CDM (n = 1). A team of stakeholders from participating CDRNs and 2 of the Patient-Powered Research Networks, including parents, providers, health system representatives, and patient advocates, closely informed the study conception and design, and provided ongoing feedback throughout the study.

The PCORnet CDM consists of 15 tables and over 100 variables available for research. An in-depth assessment of data usability and consistency was necessary before conducting statistical analyses, a process called study-specific data characterization. For the PCORnet Antibiotics and Childhood Growth Study, this process included capturing site-level aggregate data on study-specific variables (eg, demographics, diagnoses, medications, vital signs). The study team analyzed this data to determine which sites met data quality eligibility requirements, while providing initial information on the cohort of interest.

DISTRIBUTED STATISTICAL NETWORK QUERIES

Sites extract data from their local EHR systems and other health care data repositories, such as insurance claims, and transform those data to meet CDM standards. The PCORnet distributed research network model addresses governance and privacy concerns by allowing institutions to maintain data locally, rather than create a network-wide centralized database. Queries written to conform to the CDM standards are distributed to Network Partners for local execution, resulting in the return of standardized output that can be aggregated with other partners. To produce statistical query packages for distribution, either for data characterization or study analyses, PCORnet follows a standard workflow, informed by the setup of the US Food and Drug Administration’s Sentinel program. The Sentinel program utilizes claims data from health insurers to examine drug safety across the United States. The workflow begins with the development of scientific specifications that describe the purpose of the query and the intended analyses, which serves as a blueprint for the programming team. The programmers then develop a SAS statistical query to capture relevant data from...
Network Partners or to conduct analyses (SAS Institute, Cary, NC). Study teams are also responsible for generating and reviewing codes for relevant variables used for the query. This study used International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), and SNOMED-CT codes for diagnoses, and RxNorm and National Drug Code (NDC) codes for medications.

After query program development has been completed and tested with simulated data at the PCORnet Coordinating Center and at sites for beta testing, the program is distributed to the network via the PopMedNet Query Tool. Once results are returned from all responding sites, responses are collapsed into a single summary report for review and analysis by the study team (Supplemental Fig. 1) in the case of aggregated data, and into analytic files for other types of data, such as patient-level data.

Study Cohort

The PCORnet Antibiotics and Childhood Growth study cohort included children from birth to <11 years of age. Inclusion criteria were one or more encounters with same-day length/height and weight measured in each of the following intervals: 0 to 12 months, 12 to <30 months, and 24+ months of age. The latter 2 age periods overlapped to allow for the possibility that children had their 2-year-old well-child visit soon after their second birthday. Thus, children with only 2 measures were eligible for inclusion if the second was between 24 and 30 months of age. Less than 1% of the children met the cohort criteria with only 2 measures. Children were excluded from the cohort if they did not have a male or female designation for sex. Most Network Partners had data available from 2009 or 2010 until mid-to late 2016, with a few exceptions. Only one had data that began before 2000; another Network Partner’s data availability ended in 2015.

Variables and Data Analysis

All data presented here were from descriptive analyses of all participating institutions. We presented some descriptive data anonymously at the Network Partner level for those 23 Network Partners that had at least 5000 children in the cohort. Demographics were defined according to the PCORnet CDM standards. Drug codes for antibiotics were identified using a two-pronged approach. First, we captured NDC codes for antibiotics using the functional classification system from First Databank. Crosswalks available from the National Library of Medicine were used to convert the NDC code list into RxNorm codes, the prescription classification system used for this study. Second, to identify additional systemic antibiotic codes in RxNorm, we separately captured RxNorm semantic clinical drug form (SCDF) terms using the Anatomic Therapeutic Classification system. Under the RxNorm hierarchy, we also collected all less specific codes that were related to the SCDF terms to maximize capture of antibiotics; these included drug component, ingredient, brand name, multi-ingredient, and precise ingredient codes. We further captured more specific codes related to the SCDF terms, including semantic clinical drug or pack and semantic branded drug or pack codes. During manual review of these lists, we excluded antiprotozoal medications, antibiotics not available in the United States, veterinary medicines, and most intravenous medications. This led to a final antibiotic list of oral medications and intravenous or intramuscular ceftriaxone and penicillin, medications likely to be prescribed in the outpatient or emergency department setting. This restriction ensured consistency across the network—several did not have inpatient medications—and allowed this study to focus on antibiotics whose use we believed could be potentially more modifiable than most intravenous medications.

Network Partners did not routinely have days supplied available for prescriptions. Thus, we defined exposure to antibiotics by the number of episodes of antibiotics prescribed. The time window for an antibiotic episode was 7 days, such that any antibiotic prescriptions within a 7-day period of another prescription were joined together into a single episode. Narrow-spectrum antibiotics included amoxicillin, penicillin, and dicloxacillin; broad-spectrum antibiotics included all others, including penicillin combinations, such as amoxicillin/clavulanic acid. To define whether the episode was for a broad- or narrow-spectrum antibiotic, we used the highest spectrum antibiotic prescribed within the episode.

Diagnostic codes were identified for potential confounders or effect modifiers, such as asthma and prematurity, as well as diagnoses for chronic conditions. For complex chronic conditions, we used the list of ICD-9-CM code clusters developed by Feudtner et al. Using these diagnoses, we added to the list by searching an Optum database to ensure that we captured all relevant codes for these diagnoses. For those sites that used only SNOMED-CT codes for diagnoses, we translated the final ICD-9-CM code list to SNOMED-CT using an established crosswalk.

Computation of body mass index (BMI) z scores utilized the World Health Organization (WHO) growth standards for children <24 months of age: underweight if age- and sex-specific BMI was <2.3rd percentile, normal weight if 2.3rd to <97.7th percentile, and overweight/obesity if ≥97.7th percentile. We used the US Centers for Disease Control and Prevention National Health and Nutrition Examination Survey (NHANES) 2000 growth charts to classify weight status of children ≥24 months of age: underweight if <5th percentile, normal weight 5th to <85th, overweight 85th to <95th percentile, obesity ≥95th percentile, and severe obesity ≥120% of the 95th percentile. We removed implausible values of BMI z scores less than −5 and greater than 8, accounting for the recommended bounds for both the WHO (~−5, +5) and Centers for Disease Control and Prevention (~−4, +8). We utilized a SAS-based summary program to aggregate data across responding Network Partners and format into a readable Excel (Microsoft, Redmond, Wash) report for analyses and characterization.

Results

The final study cohort included 681,739 children, which was 38% of all children who had at least one same-day height/weight measurement at <12 months of age and 71% of children who also had at least one additional same-day
Among all children in the cohort, 55.2% received at least one prescription for antibiotics (Table 2). Among the 23 Network Partners with at least 5000 children, 16 had higher rates of prescribing for narrow-spectrum antibiotics (Fig. 1B). Nearly a quarter of children (23.4%) received 1 narrow-spectrum antibiotic, and 3.4% received 4+ prescriptions compared to 16.8% and 5.9% for broad-spectrum antibiotics (Table 2). Amoxicillin/clavulanic acid and azithromycin were prescribed at least once for 14.3% and 9.2% of children, respectively.

Mean BMI z score was −0.30 (WHO, SD 1.31) at 0 to <6 months of age, rising to 0.59 (NHANES, SD 1.18) at 9 to 11 years of age. The prevalence of overweight and obesity across age groups was 3.7% among 0- to 6-month-olds, 27.6% among 4- to <6-year-olds, and 36.2% among 9- to <11-year-olds (Fig. 2, Supplemental Tables 3 and 4). The prevalence of severe obesity was 2.5% and 6.8%, respectively, for 4- to <6-year-olds and 9- to <11-year-olds. There was a range in prevalence of overweight
and obesity across the 23 Network Partners with at least 5000 children in the cohort (Supplemental Fig. 3). For example, prevalence of obesity among 4- to 6-year-olds had a range of 5% to 22%.

**DISCUSSION**

Using the PCORnet data network infrastructure, we assembled a study cohort of 681,739 children with multiple measures of height and weight captured in EHRs across 35 health care institutions. More than half of these children had height and weight data at ages 4 to <6 years and 9% at ages 9 to <11 years. The cohort has broad diversity in geography, demographics, and care settings, and provides a rich data source for the longitudinal study of childhood growth.

PCORnet’s architecture strikes a balance between facilitating large-scale collaborative research and managing institutional risks. The PCORnet Antibiotics and Childhood Growth Study, engaging 28 (34%) of 82 Network Partners, provides an early test of the network, including valuable information about network governance and operations, patient engagement, use of prescribing and anthropometric data, and population characteristics. Most contributing health care institutions in the network are anchored by large hospitals in urban or suburban areas, which may explain the high rates of complex chronic conditions. Overall, however, the clinical data collected align well with expectations for pediatric populations.

Results from this descriptive study demonstrate that PCORnet is well suited for pediatrics observational epidemiologic research, with the capacity to create large cohorts for the study of health care exposures and outcomes. PCORnet can also provide meaningful national surveillance data on health care utilization and outcomes. In this cohort, over half of included children received at least one prescription for antibiotics by their second birthday. While recommended first-line antibiotics were most common, one third of children received at least one broad-spectrum antibiotic, and 1 in 7 received 4+ courses. This results in a significant exposed group for both antibiotics overall and for subset analyses by type and extent of exposure. The rate of antibiotic exposure is comparable to prior studies.\textsuperscript{18–20}

Anthropometric measures for this cohort are similar to national survey estimates. For most age categories, the median BMI $z$ score is slightly positive. Prevalence of obesity in our cohort was 13.1% from ages 4 to <6 years and 20.0% from ages 9 to <11 years. Prevalence of obesity among 4- to 6-year-olds had a range of 5% to 22%.
Ages 9 to <11 years, compared to 9% among 2- to <6-year-olds and 18% among 6- to <12-year-olds in NHANES data spanning 2011 to 2014. Prevalence of severe obesity was 2.5% for 4- to <6-year-olds and 6.8% for 9- to <11-year-olds, compared to 1.7% for 2- to <6-year-olds and 4.3% for 6- to <12-year-olds in NHANES 2011–2014. The slightly higher prevalence in our cohort may reflect differences in age ranges, given the higher prevalence of childhood obesity as age increases or differences in patient mix between those children continuously enrolled in PCORnet health systems versus the US population. It may also reflect characteristics of the cohort, which includes a larger proportion of African American children and children living in urban settings than the US population.

The objective of the PCORnet Antibiotics and Childhood Growth Study is to better characterize the relationship between antibiotics and childhood obesity in the United States. This study is powered to examine multiple potential associations of antibiotics and weight, including the effects of types, timing, and frequency of antibiotic use in the first 2 years of life on BMI, obesity, and growth. Quantifying the precise effect size of this association will provide pertinent information to patients and clinicians regarding potential obesogenic risks of antibiotic prescriptions. Compared to prior studies that have examined the relationship between antibiotic use and growth in children, this cohort provides the largest and most diverse population for study. Prior reports have included single health system or single region studies in the United States, including children in Northern California (260,556 children) or central Pennsylvania (142,824 children), as well as smaller European national studies such as in England (11,532 children) or Denmark (28,354 children). Representation of African American children in this cohort is higher than the entire US population (25% vs 12%); the proportion of patients identifying as Hispanic is similar to the US population. This cohort demonstrates a modest overrepresentation of several chronic conditions, which may be due to the inclusion of several large health systems providing tertiary care. Also, the prevalence of chronic disease could have been higher solely...
because the cohort includes children who have received health care services.

In addition to the overrepresentation of urban environments and chronic conditions, it is important to note several other limitations. Most significantly, available data did not include other variables that influence the risk of childhood obesity, including maternal health or gestational factors, as well as environmental, social, behavioral, and dietary factors. The PCORnet study will address the absence of gestational data by linking maternal and child health records for a subset of the cohort, allowing inclusion of maternal BMI, child birth weight, and maternal weight gain. Another limitation was that antibiotic exposure was measured using prescribing records, which may overestimate exposure in cases where children do not complete prescribed courses of antibiotics. Prescribing records also may underestimate exposure because some prescribing may occur in health care settings not covered by a contributing institution and would therefore be missed. Similarly, our identification of chronic conditions relies on one or more occurrences of diagnosis codes recorded during clinical encounters and may overestimate prevalence due to use of these codes to rule out diagnoses. When we capture and analyze individual-level data on participants, rather than aggregate data only (as used herein), we will be able to compensate for this by requiring repeated presence of codes, consistent with the chronic nature of the conditions.

More generally, the use of routine clinical data for the study may result in missingness (eg, patients with race or Hispanic ethnicity not recorded), misestimation (eg, higher use of diagnostic codes when ruling out conditions), or loss of detail (eg, use of ICD-9-CM in billing data, losing specificity of diagnoses primarily recorded in the EHR). These limitations are common to studies using EHR and administrative data.

**CONCLUSIONS**

The PCORnet Antibiotics and Childhood Growth cohort demonstrates the capacity of PCORnet to facilitate capture of data on large pediatric populations for research, including early childhood growth, chronic conditions, infectious diagnoses, and antibiotic usage. This study provides valuable surveillance information on antibiotic utilization and weight, and it is the largest study to date to examine the relationship between antibiotic use in early life on weight outcomes in childhood. The large sample size and detailed clinical data will allow us to examine relationships among the type, timing, and level of antibiotic exposure to determine whether these factors are related to weight outcomes. PCORnet can provide significant opportunities to explore precise research inquiries in pediatrics.

**ACKNOWLEDGMENTS**

The views expressed in this article do not necessarily represent the views of the US Government, the Department of Health and Human Services, or the National Institutes of Health. This work was supported through the Patient-Centered Outcomes Research Institute (PCORI) Program Award (OBS-1505-30069). All statements in this article are solely those of the authors and do not necessarily represent the views of PCORI, its Board of Governors, or Methodology Committee. The PCORnet Childhood Antibiotic Study Team includes a diverse group of investigators, research staff, clinicians, community members, and parent caregivers. All members of the team including the study’s Executive Antibiotic Stakeholder Advisory Group contributed to the study design, data acquisition, and interpretation of results. The Study Team thanks the leaders of the participating PCORnet CDRNs, Patient Powered Research Networks, and PCORnet Coordinating Center, as well as members of the PCORI team, for their support and commitment to this project.

**SUPPLEMENTARY DATA**

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.acap.2018.02.008.

**REFERENCES**


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