Attention Deficit Disorder, Stimulant Use, and Childhood Body Mass Index Trajectory

WHAT'S KNOWN ON THIS SUBJECT: Childhood attention-deficit/hyperactivity disorder has been associated with both childhood and adult obesity, whereas treatment with stimulants has been associated with delayed child growth. No longitudinal studies with details about dates of diagnosis, treatment, and duration of stimulant use have been published.

WHAT THIS STUDY ADDS: Using electronic health record data, this was the first study to evaluate the independent associations of attention-deficit/hyperactivity disorder diagnosis, stimulant treatment, age at first stimulant use, and duration of stimulant use on longitudinal BMI trajectories throughout childhood and adolescence.

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KEY WORDS

adolescent, attention deficit disorder with hyperactivity, BMI, child, central nervous system stimulants, epidemiology, longitudinal studies

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder

EHR—electronic health record

ICD-9-CM—*International Classification of Diseases, Ninth Revision, Clinical Modification*

Dr Schwartz conceptualized and designed the study, assisted in acquisition of the data and data analysis, interpreted the data, and wrote the first draft of the manuscript; Dr Bailey-Davis assisted in interpretation of the data and development of the first draft of the manuscript; Dr Bandeen-Roche assisted in the design of the data analysis, analysis and interpretation of the data, and revision of the manuscript; Drs Hirsch, Nau, Liu, and Glass assisted in interpretation of the data and revision of the manuscript; Mr Pollak assisted in analysis and interpretation of the data and revision of the manuscript; and all authors approved the final manuscript as submitted.

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abstract

BACKGROUND: Childhood attention-deficit/hyperactivity disorder (ADHD) has been associated with childhood and adult obesity, and stimulant use with delayed childhood growth, but the independent influences are unclear. No longitudinal studies have examined associations of ADHD diagnosis and stimulant use on BMI trajectories throughout childhood and adolescence.

METHODS: We used longitudinal electronic health record data from the Geisinger Health System on 163 820 children ages 3 to 18 years in Pennsylvania. Random effects linear regression models were used to model BMI trajectories with increasing age in relation to ADHD diagnosis, age at first stimulant use, and stimulant use duration, while controlling for confounding variables.

RESULTS: Mean (SD) age at first BMI was 8.9 (5.0) years, and children provided a mean (SD) of 3.2 (2.4) annual BMI measurements. On average, BMI trajectories showed a curvilinear relation with age. There were consistent associations of unmedicated ADHD with higher BMIs during childhood compared with those without ADHD or stimulants. Younger age at first stimulant use and longer duration of stimulant use were each associated with slower BMI growth earlier in childhood but a more rapid rebound to higher BMIs in late adolescence.

CONCLUSIONS: The study provides the first longitudinal evidence that ADHD during childhood not treated with stimulants was associated with higher childhood BMIs. In contrast, ADHD treated with stimulants was associated with slower early BMI growth but a rebound later in adolescence to levels above children without a history of ADHD or stimulant use. The findings have important clinical and neurobiological implications. *Pediatrics* 2014;133:668–676

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common pediatric psychiatric disorders, with a prevalence in the United States approaching 9%.¹ As a likely consequence of this, stimulants, the most common therapy for ADHD,² are the second most commonly prescribed medications among children.³ National data reveal that the prevalence of stimulant use has increased rapidly over the past 30 years. From 2007 to 2010, 4.2% of children younger than 18 years had been prescribed stimulants within the past 30 days; this represented more than a fivefold increase in such use since 1988 to 1994.³

There is substantial evidence that stimulant use is associated with growth deficits and some evidence of growth delays in ADHD.⁴ However, increasingly, and paradoxically, concerns have been raised about a possible link between ADHD and obesity. Cross-sectional studies in children have reported an association between ADHD and obesity,^{5–7} and childhood ADHD may be a risk factor for adult obesity.^{2,8,9} The risk of obesity associated with ADHD may be reduced or eliminated among children who have received stimulants as treatment for ADHD.^{6,7,10} However, the independent contributions of ADHD and the medications used to treat it have not been fully elucidated.

ADHD and stimulant use are promising avenues of research regarding the childhood obesity epidemic. In seeking explanations for the rapid increase in obesity rates over the past several decades, it is important to evaluate the role of risk factors that have also increased in prevalence within a similar time frame. ADHD and stimulant use meet this criterion and, given the limitations of previous studies that showed an association between ADHD and obesity, now merit a careful evaluation of their relative and independent contributions to BMI trajectories in children.

We used longitudinal electronic health record (EHR) data from a large, integrated health system to examine these relations for the first time.

METHODS

Study Population and Design

Data were obtained from children and adolescents (hereafter referred to as just children) with a primary care provider in the Geisinger Health System. These children represent the general population in the region.^{11,12} The study area included 37 counties in central and northeastern Pennsylvania and consisted of 1288 communities (defined as townships, boroughs, or census tracts in cities^{11,13,14}). Only children whose home address could be geocoded to the street level were included in the analysis. The study was approved by institutional review boards at Geisinger Health System and Johns Hopkins Bloomberg School of Public Health.

Data Collection

We collected data on 257 729 children who were 2 to 18 years of age between January 2001 and February 2012. Of these, 206 395 had at least 1 height and weight measured in the clinical setting, after deleting biologically implausible values. A total of 173 048 children were successfully geocoded as previously reported^{13,14} and 163 820 were included in the analysis after exclusion of 2-year-olds because of difficulties in measuring height at this age. Data were obtained on sociodemographics, encounters, vital signs, laboratory tests, procedures, and medications. All orders and encounters were accompanied by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes.

Variable Creation

Diagnosis of ADHD was based on ICD-9-CM codes 314.0 to 314.9 for outpatient

encounters or medication orders. Stimulant use was based on physician orders for medications that occurred before the date of the last BMI measurement for each child. Relevant medications were identified by searching by name, class, and subclass codes. Duration of stimulant use was based on the dates of physician orders. Because most of the agents of interest are Schedule II Controlled Substances, physician orders must be written monthly. Each monthly order was assumed to cover all days in the month; multiple orders for the same drug from the same encounter were allocated to subsequent months. Comorbidities (ICD-9-CM code), including asthma (493.x), diabetes (250.x), psychoses (290.x–299.x), depression (311), adjustment reaction and disorders (309.x), and anxiety (300.x), were considered present if there were 3 or more outpatient encounters or medication orders with the code. Medical assistance for health insurance was used as a surrogate for low family socioeconomic status.

Data Analysis

In longitudinal studies of childhood growth, there are several options for analysis, including untransformed BMI, BMI percentiles, or BMI z scores.¹⁵ We modeled untransformed BMI values, because when modeling trajectories of change, this measure, as opposed to BMI z scores (which are age-adjusted, cross-sectional deviations from national norms), yields estimates that are more interpretable, precise, and sensitive to factors that alter change.^{16,17} Age (years) was modeled as duration between the child's date of birth and the date of BMI measurement. Only the first BMI measurement for a child in an age-year was used. When height and weight were not measured in the same visit, we matched values within 3 months.¹⁵

The goal of the analysis was to determine to what degree ADHD diagnosis,

stimulant use, age of first use, and duration of use were associated with BMI trajectories, while controlling for potential confounding variables. SAS (SAS Institute, Inc, Cary, NC) and Stata (Stata Corp, College Station, TX) were used for data analysis. We used mixed effects linear regression models with BMI as the dependent variable to model growth curve trajectories of BMI by age. Models included fixed-effects terms for age, age², and age³ (with mean-centered age at 10.7 years), as well as gender, race/ethnicity (African American, Hispanic, and other versus white), community type (borough or census tract versus township), and medical assistance. Community type was included because of previous associations of residential locations with obesity.^{18,19} Random effects included subject-specific intercepts and coefficients for age and age² to accommodate serial correlations and allow trajectories to vary across children. Random effects were allowed to covary via an unstructured covariance matrix, and fitting was accomplished by restricted maximum likelihood estimation. Because we observed inequality of the individual-level error variances by age, we used a group effect for age groups of 3 to 5, 5 to 8, and >8 years that allowed for heterogeneity in residual variances across groups. To model differences in BMI trajectories by demographic characteristics, models included cross-products of gender and medical assistance with all 3 age terms as fixed effects, and of race/ethnicity with age and age².

ADHD diagnosis (ever versus never), age at first stimulant use (quartiles), and duration of stimulant use (quartiles [1–2, 3–6, 7–19, and 20–120 months] and also as a single ordinal variable [0–4] to assess the statistical significance of trends) were then added to the model, alone and in combination as main effects and with cross-products

with the 3 age terms. Models were evaluated for goodness of fit, normality of residuals, and homoscedasticity; fit was also evaluated by comparing regression lines to lowess lines on added variable plots. To evaluate robustness of findings to assumptions of normality and homoscedasticity, models were repeated by using *ln*-transformed BMI and also a Huber-White estimator.²⁰ As there were no substantive differences, only the results of the primary models are presented.

RESULTS

Description of Study Population

The 163 820 children included approximately equal numbers of boys and girls, with a mean age at first BMI of almost 9 years, and 91% were white (Table 1). There were 1 to 13 BMI observations per subject with a total of 524 862 observations in the analysis. On average, children had just over 3 yearly BMI measurements, with an average duration between first and last measurements of 2.9 years. The mean (SD, range) duration from first contact with the health care system to the last (before age 19) was 4.88 (3.47, 0–11.51) years. Geocoded and nongeocodable children were not notably different, but children with and without ADHD had several differences (Table 1). Thirty percent of children resided in boroughs (generally walkable small towns), 15% in census tracts in cities, and 55% in townships (include rural and suburban areas).

A total of 13 789 (8.4%) children had encounter diagnoses for ADHD (24.1% with only 1 diagnosis and 58.6% with ≥ 4); 11 080 (6.8%) had an order for stimulants; and 15 473 (9.5%) had either a stimulant order or an ADHD diagnosis. Among the children with only 1 ADHD diagnosis, 71.4% were never treated for ADHD. There were 201 854 orders for medications used in the analysis,

including 105 504 for methylphenidate, 68 323 for dextroamphetamine/amphetamine, 12 380 for atomoxetine, 5297 for dexmethylphenidate, and the remainder mainly for dextroamphetamine or lisdexamfetamine dimesylate. The mean (median) stimulant duration was 426.3 (182.6) days. The median age at first stimulant order was 8.5 years. Children who had ever had a stimulant order were more likely to have received medical assistance, 54% compared with 32% for children without stimulant orders ($P < .0001$).

Average BMI Growth Trajectories

The average trajectory of BMI increase with age (“BMI growth”) was curvilinear (Fig 1, by race/ethnicity). On average, girls had higher BMIs than boys at all ages (all age cross-products $P < .0001$). Although the average BMI growth trajectory did not differ in Hispanic children (compared with white children, $P > .10$), there was evidence that the trajectory did differ in African American children (cross-product for age $P < .0001$, for age² $P = .07$), with apparent divergence by age 5 years and widening as children got older. Children who had ever received medical assistance had higher BMIs at all ages compared with children who had not, with apparent divergence of the growth trajectories after age 8 years (all cross-product $P < .0001$).

BMI Trajectories by ADHD Diagnosis and Stimulant Use Categories

We compared the BMI trajectories of children who never received an ADHD diagnosis and never had a physician order for stimulants (referred to as “controls”) with 3 groups: (1) those with a diagnosis of ADHD but without physician orders for stimulants, (2) those with orders for stimulants but without an ADHD diagnosis, and (3) those with both stimulant orders and ADHD diagnoses (Table 2 and Fig 2).

TABLE 1 Summary Statistics for Children Eligible for Phase I Analysis (Age 3 to 18 y at Any Time Between 2001 and 2012 With Valid BMI), by ADHD and Geocoding Status

Study Variable	Home Address Geocoded, <i>n</i> = 163 820		Home Address Not Geocoded, <i>n</i> = 31 427	<i>P</i> Value ^a
	Never ADHD Diagnosis, <i>n</i> = 150 031	Ever ADHD Diagnosis, <i>n</i> = 13 789		
Age at first BMI, y, mean (SD)	9.4 (5.2)	8.3 (4.2)	9.8 (5.1)	<.0001
Race/ethnicity, %				<.0001
White	91.1	93.2	89.4	
Black	4.7	4.6	5.0	
Hispanic	1.2	1.1	1.6	
Other	1.7	1.6	1.8	
Missing	1.3	1.3	2.1	
Gender, female, %	51.7	28.1	48.6	<.0001
Medical assistance for health insurance, % ^b	32.2	50.5	33.3	<.0001
Age at last BMI, y, mean (SD)	12.1 (5.2)	12.9 (4.2)	12.1 (5.1)	<.0001
Duration between first and last BMI, y, mean (SD)	2.7 (3.1)	4.6 (3.2)	2.4 (2.9)	<.0001
No. of annual BMIs available for analysis, mean (SD), range	3.1 (2.3)	4.7 (2.8)	2.8 (2.2)	<.0001
BMI measurements by age, %				
3	23.4	21.1	19.7	
4	23.7	25.8	20.1	
5	23.2	30.7	20.2	
6	17.9	31.4	16.1	
7	16.7	34.1	15.4	
8	16.2	35.7	15.1	
9	15.8	35.9	15.1	
10	15.9	36.0	15.2	
11	19.9	37.8	18.3	
12	18.0	34.9	16.8	
13	17.4	30.7	16.4	
14	17.8	28.7	17.1	
15	20.7	26.7	19.3	
16	23.0	25.9	21.5	
17	19.7	21.1	18.3	
18	17.3	15.2	16.5	
Residential community, %				<.0001
Township	55.2	50.5	Not available ^c	
Borough	29.9	33.3		
City	14.9	16.2		
BMI, first, mean (SD)	19.7 (5.3)	18.7 (4.6)	19.9 (5.3)	<.0001
BMI, last, mean (SD)	21.4 (6.0)	21.9 (6.1)	21.4 (5.9)	<.0001

^a Comparing geocoded children who never and ever had an ADHD diagnosis.^b See Methods for definition of medical assistance.^c Without successful geocoding, this could not be accurately determined.

Compared with controls, those in group 3 had slower rates of BMI growth in early childhood but more rapid rates during adolescence (*P* values for main effect and 3 cross-products with age < 0.0001), with BMIs eventually exceeding those in controls. In contrast, those with a di-

agnosis of ADHD and without any stimulant orders (group 1) had more rapid BMI growth after age 10 years compared with controls (age cross-product *P* < .0001). Children in group 2 had an average BMI trajectory that was intermediate between groups 1 and 3 but lower than controls.

BMI Trajectories by Age at First Stimulant Use and Duration

Younger age at first stimulant order was associated with slower BMI growth in early childhood, but the earlier stimulants were ordered, the earlier and stronger that BMI growth “re-bounded” and eventually exceeded values in controls (Table 3 and Fig 3). Examination of diagnostic plots suggested that data were sparse at age 17 and 18 years for children in the earliest age at first stimulant order group and that the high BMIs at these ages predicted by the model were somewhat overestimated.

Longer stimulant use duration evidenced consistent and strong impacts on BMI trajectories (Table 4 and Fig 4). There was a trend toward lower average BMIs (at the mean age) across the 4 duration quartile groups (β coefficients across quartiles = -0.38 , -0.50 , -0.64 , and -1.21 , respectively, Table 4). This trend continued within the quartile of the longest duration of use. In addition, longer duration of stimulant use was associated with slower BMI growth at younger ages, but with more rapid acceleration of BMI growth at older ages (Fig 4). To evaluate trends further, duration of stimulant use was re-parameterized by replacing the 4 groups with a single variable coded 0 to 4 (0 for controls and 1–4 for the 4 quartiles of duration) along with cross-products with the 3 age terms. This analysis demonstrated that, with increasing duration of stimulant use, there was a consistent dose-response relation in terms of lower average BMIs (at the median age), slower early BMI growth, and increasing rates of BMI growth with later ages. After inclusion of comorbidities in the models, no substantive changes in these associations were observed.

Several sensitivity analyses were performed. To further explore BMI trajectories by age at first stimulant order

FIGURE 1

BMI trajectories (predicted values from regression model with modeled lines) by race/ethnicity from model without any ADHD diagnosis or stimulant order variables. The predicted BMI values were from the fixed portion of the model using observed population means for gender and medical assistance.

and stimulant use duration, we divided each of these variables into tertiles and modeled trajectories in the 9 resulting groups. There was a mean (SD) of 1231.1 (335.8) children in each of the 9 groups.

The results suggested there were independent influences of age at first stimulant order and duration of stimulant use, with trends across tertiles for both variables. When regression

models were repeated with non-stimulant ADHD medications removed, associations with age at first ADHD medication use and duration of use strengthened, and BMI trajectories in children treated only with non-stimulants were similar to those in untreated ADHD. When children treated with ADHD medications and other psychotropic medications were separately categorized (51.4% of children ever treated with ADHD medications were also ever treated with another psychotropic), associations with ADHD medications strengthened, as other psychotropic medication use was generally associated with accelerated BMI growth.

DISCUSSION

This is the first study to use longitudinal data from an EHR in a large population of children ages 3 to 18 years to examine the impact of ADHD diagnosis and treatment on BMI trajectories. We have made several observations that dramatically strengthen the evidence base regarding ADHD, stimulant use, childhood BMI trajectories, and obesity risk. The data suggest that children with unmedicated ADHD have faster rates of BMI growth after approximately age 10 years compared with controls with neither a history of ADHD nor stimulant use; children with ADHD treated with stimulants have reduced rates of BMI growth in early to mid-childhood but experience a “BMI rebound” in late childhood, after which BMI growth accelerates, leading to BMIs in late adolescence that are higher than those in controls. The findings are consistent with and may partially explain observed associations of childhood ADHD with adult obesity.^{2,8,9} The associations of stimulants with BMI growth trajectories were robust to the metric used, with evidence of dose-response relations for both age at first stimulant order and stimulant use duration, and after adjustment for many relevant

TABLE 2 Adjusted^a Associations Comparing Groups With Different Patterns of ADHD Diagnosis and Stimulant Use (With Controls Without ADHD Diagnosis or Stimulant Use) With BMI Trajectories in Children in the Geisinger Health System, 2001–2012

Variable	β	SE	P value
Intercept	19.7808	0.0200	<.0001
Age	0.8641	0.0033	<.0001
Age ²	0.0166	0.0004	<.0001
Age ³	−0.0051	0.0001	<.0001
Diag-NoMeds ^b	0.0624	0.0724	.39
Diag-NoMeds × age	0.0574	0.0133	<.0001
Diag-NoMeds × age ²	0.0018	0.0015	.24
Diag-NoMeds × age ³	−0.0010	0.0002	<.0001
Meds-NoDiag ^b	−0.2866	0.1102	.009
Meds-NoDiag × age	0.0015	0.0182	.93
Meds-NoDiag × age ²	0.0158	0.0021	<.0001
Meds-NoDiag × age ³	0.0004	0.0003	.21
Diag+meds ^b	−0.7616	0.0473	<.0001
Diag+meds × age	−0.0570	0.0070	<.0001
Diag+meds × age ²	0.0223	0.0008	<.0001
Diag+meds × age ³	0.0014	0.0001	<.0001

^a In addition to variables in the table, the model included gender, gender*age, gender*age², gender*age³, race/ethnicity (separate terms for black, Hispanic, and other), race/ethnicity*age, race/ethnicity*age², medical assistance, medical assistance*age, medical assistance*age², medical assistance*age³, and community type (borough, census tract).

^b Diag-NoMeds indicates children who only had encounters with ADHD diagnoses without a record of stimulants for treatment; Meds-NoDiag indicates children who only had orders for stimulants without a record of ADHD diagnosis; Diag+meds indicates children who had both encounters of diagnoses for ADHD as well as orders for stimulants. For each group, BMI trajectories were modeled with linear, quadratic, and cubic terms for age.

FIGURE 2

BMI trajectories (predicted values from regression model with modeled lines) for different groups characterized by ADHD diagnosis and stimulant orders (plot of model from Table 2). Different dashed lines identify children who had ADHD diagnostic codes only ("ADHD Dx Without Stimulant Use"), stimulant orders only ("Stimulant Use Without ADHD Dx"), or both ("ADHD Dx With Stimulant Use"), compared with children without a history of ADHD or stimulant use (solid line). The predicted BMI values were from the fixed portion of the model using observed population means for gender, race/ethnicity, and medical assistance.

TABLE 3 Adjusted^a Associations of Age at First Stimulant Order (Compared With Controls Without Stimulant Use) With BMI Trajectories in Children in the Geisinger Health System, 2001–2012

Variable	β	SE	P Value
Intercept	19.7797	0.0198	<.0001
Age	0.8658	0.0033	<.0001
Age ²	0.0167	0.0004	<.0001
Age ³	−0.0051	0.0001	<.0001
STIMAgeG1 ^b	−0.8837	0.0877	<.0001
STIMAgeG1 × age	0.0010	0.0141	.94
STIMAgeG1 × age ²	0.0530	0.0027	<.0001
STIMAgeG1 × age ³	0.0041	0.0003	<.0001
STIMAgeG2 ^b	−0.6755	0.0829	<.0001
STIMAgeG2 × age	−0.0509	0.0116	<.0001
STIMAgeG2 × age ²	0.0260	0.0016	<.0001
STIMAgeG2 × age ³	0.0024	0.0002	<.0001
STIMAgeG3 ^b	−0.7384	0.0828	<.0001
STIMAgeG3 × age	−0.0552	0.0121	<.0001
STIMAgeG3 × age ²	0.0194	0.0014	<.0001
STIMAgeG3 × age ³	0.0021	0.0002	<.0001
STIMAgeG4 ^b	−0.4403	0.0961	<.0001
STIMAgeG4 × age	−0.0261	0.0158	.10
STIMAgeG4 × age ²	0.0022	0.0026	.39
STIMAgeG4 × age ³	0.0019	0.0004	<.0001

^a In addition to variables in the table, the model included gender, gender*age, gender*age², gender*age³, race/ethnicity (separate terms for black, Hispanic, and other), race/ethnicity*age, race/ethnicity*age², medical assistance, medical assistance*age, medical assistance*age², medical assistance*age³, and community type (borough, census tract).

^b STIMAgeGx indicates age of first stimulant medication order; G1 through G4 represent the 4 quartiles of age of first stimulant order compared with children not taking stimulants as the reference group.

potential confounding variables. Findings strengthened after accounting for ADHD medications that were not stimulants, and for the common use of other psychotropic medications in children with ADHD, as these were associated with accelerated weight gain. The study overcomes many of the limitations of previous research, including those of cross-sectional designs, self-reported height and weight, lack of consideration of the independent roles of diagnoses and medication use, lack of consideration of duration of medication use, and incomplete consideration of other obesity risk factors.

Normative growth patterns for children demonstrate accelerated growth starting at age 5 years, with resultant steady increases in BMI until peak growth rate occurs at ~13 to 14 years.²¹ Factors that lead to early acceleration of BMI growth are generally recognized as obesogenic.^{21,22} With stimulant use, child growth deficits in height and weight have been observed; however, growth deficits show attenuation over time. Children "catch-up" to their prestimulant growth pattern within 2 to 3 years whether stimulant use continues or not.⁴ Slower BMI growth seems to be most pronounced when stimulants are started earlier and for children who are taller or heavier when stimulant therapy is initiated.^{4,23,24}

Suggested mechanisms for stimulant-influenced growth deficits may provide insight into observed BMI rebound by late childhood. Stimulants may function in multiple ways to alter usual growth. At the simplest level, their anorexic effects may reduce energy consumption and directly result in weight loss. However, growing literature suggests more complex effects on hepatic growth factor and cartilage and up- and downregulation of a variety of receptors and neurotransmitters involved throughout the growth system. These effects could plausibly result in initial growth

FIGURE 3

BMI trajectories (predicted values from regression model with modeled lines) by quartiles of age at first stimulant medication order without other ADHD diagnosis or stimulant order variables in the model (plot of model from Table 3). Different dashed lines identify children whose first stimulant order was before age 7.1, 7.1 to 9.3, 9.3 to 12.3, and 12.3 to 18.9 years, compared with children without a history of ADHD or stimulant use (solid line). The predicted BMI values were from the fixed portion of the model using observed population means for gender, race/ethnicity, and medical assistance.

TABLE 4 Adjusted^a Associations of Duration of Stimulant Orders (Compared With Controls Without Stimulant Use) With BMI Trajectories in Children in the Geisinger Health System, 2001–2012

Variable	β	SE	P Value
Intercept	19.7824	0.0198	<.0001
Age	0.8665	0.0033	<.0001
Age ²	0.0167	0.0004	<.0001
Age ³	−0.0051	0.0001	<.0001
STIMDurG1 ^b	−0.3757	0.0759	<.0001
STIMDurG1 × age	0.0177	0.0124	.16
STIMDurG1 × age ²	0.0137	0.0014	<.0001
STIMDurG1 × age ³	0.0001	0.0002	.72
STIMDurG2	−0.4960	0.0941	<.0001
STIMDurG2 × age	−0.0118	0.0143	.41
STIMDurG2 × age ²	0.0174	0.0016	<.0001
STIMDurG2 × age ³	0.0007	0.0002	.005
STIMDurG3	−0.6446	0.0865	<.0001
STIMDurG3 × age	−0.0133	0.0127	.30
STIMDurG3 × age ²	0.0181	0.0015	<.0001
STIMDurG3 × age ³	0.0005	0.0002	.01
STIMDurG4	−1.2063	0.0835	<.0001
STIMDurG4 × age	−0.1501	0.0110	<.0001
STIMDurG4 × age ²	0.0326	0.0013	<.0001
STIMDurG4 × age ³	0.0030	0.0002	<.0001

^a In addition to variables in the table, the model included gender, gender*age, gender*age², gender*age³, race/ethnicity (separate terms for black, Hispanic, and other), race/ethnicity*age, race/ethnicity*age², medical assistance, medical assistance*age, medical assistance*age², medical assistance*age³, and community type (borough, census tract).

^b STIMDurGx indicates duration of stimulant medication orders with duration based on method of allocating more than 1 prescription on the same day to subsequent months; G1 through G4 represent the 4 quartiles of stimulant duration compared with children not taking stimulants as the reference group.

retardation, possible tolerance to growth inhibition over time, and then rebound growth.^{2,4,24–28}

Temporary growth retardation related to stimulant therapy may partly explain altered growth trajectories among children with ADHD, but alternate hypotheses may also implicate the pathophysiology of ADHD.²⁵ Although direct evidence is generally lacking,⁴ several hypotheses have been considered. A dysmaturity hypothesis suggested that among some children with ADHD, development and rate of growth may be delayed in early life, but this may lessen with age.²⁵ This hypothesis was explained by the fact that height, but not weight, retardation was observed in young children with ADHD but not among older children at 4-year follow-up, and no association was found between height deficits and stimulant use.²⁵ Our findings do not support this hypothesis; children with an ADHD diagnosis and without any stimulant orders had higher BMIs. Psychological hypotheses have been offered, including deficient inhibitory control, poor executive functions, and inability to monitor eating behaviors.^{2,10,29–32} Regarding neurobiological correlates, dysfunction of fronto-striatal dopaminergic pathways has been implicated in ADHD,³⁰ as well as in obesity³³; whereas stimulant therapy may function in the short-term to minimize this dysfunction, its long-term effect may diminish.

Our findings suggest that children with ADHD are at increased risk for obesity. Consistent with current guidelines, clinicians should assess and evaluate BMI at least annually and implement the indicated intervention to prevent obesity.³⁴ It should be noted that behavioral therapy, specifically parent training, can be effective³⁵ for ADHD management and has no known BMI rebound effect. Future research should examine how obesity prevention interventions may be best tailored and delivered to

FIGURE 4

BMI trajectories (predicted values from regression model with modeled lines) by quartiles of stimulant order duration without other ADHD diagnosis or stimulant order variables in the model (plot of model from Table 4). Different dashed lines identify children with 1 to 2 months, 3 to 6 months, 7 to 19 months, and 20 months to 10 years of stimulant use, compared with children without a history of ADHD or stimulant use (solid line). The predicted BMI values were from the fixed portion of the model using observed population means for gender, race/ethnicity, and medical assistance.

families with children who have ADHD and comorbidities.

This study had several strengths, including study of children who represent the general population in the region, longitudinal and detailed health information, measured height and weight, a large sample size, the inclusion of

boys and girls, and a rigorous approach to data analysis. Among limitations, the study had limited diversity by race/ethnicity, so findings may not be generalizable to more diverse populations. BMI data were not complete for all children at all ages and no information was available on medication

adherence. Although the EHR data were extensive, we cannot exclude the possibility that children received diagnosis or treatment of ADHD by outside providers. EHR data also do not allow perfect ascertainment of diagnosis and treatment indications, but 91.6% of stimulant orders had an associated ICD-9-CM code for ADHD, and most of the remaining stimulant orders were for children who had a previous encounter with an ICD-9-CM code for ADHD.

CONCLUSIONS

The findings suggest that stimulant use, rather than ADHD itself, is most strongly associated with growth trajectories in childhood, early BMI rebound, and later obesity. Stimulants appear to slow the rate of BMI growth in early to mid-childhood and then to accelerate growth rates in later childhood, generally after discontinuation of the medication. The findings have relevance to concerns raised about growth rate and its potential adverse long-term consequences. Our findings should motivate greater attention to the possibility that longer-term stimulant use plays a role in the development of obesity in children.

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