NEW RESEARCH

Check for updates

Associations Between Attention-Deficit/Hyperactivity Disorder (ADHD), ADHD Medication, and Shorter Height: A Quasi-Experimental and Family-Based Study

Rickard Ahlberg, MSc, Miguel Garcia-Argibay, PhD, Ebba Du Rietz, PhD, Agnieszka Butwicka, MD, PhD, Samuele Cortese, MD, PhD, Brian M. D'Onofrio, PhD, Jonas F. Ludvigsson, MD, PhD, Henrik Larsson, PhD

Objective: The association between attention-deficit/hyperactivity disorder (ADHD) and shorter height is unclear. This study examined the risk of shorter height in individuals with ADHD, and the influence of prenatal factors, ADHD medication, psychiatric comorbidity, socioeconomic factors, and familial liability.

Method: We drew on Swedish National Registers for 2 different study designs. First, height data for 14,268 individuals with ADHD and 71,339 controls were stratified into 2 groups: (1) before stimulant treatment was introduced in Sweden, and (2) after stimulant treatment was introduced in Sweden. Second, we used a family-based design including 833,172 relatives without ADHD with different levels of relatedness to the individuals with ADHD and matched controls.

Results: ADHD was associated with shorter height both before (below-average height: OR = 1.31, 95% CI = 1.22-1.41) and after (below-average height: OR = 1.21, 95% CI = 1.13-1.31) stimulants for ADHD were introduced in Sweden, and was of similar magnitude in both cohorts. The association between ADHD and shorter height attenuated after adjustment for prenatal factors, psychiatric disorders, and socioeconomic status. Relatives of individuals with ADHD had an increased risk of shorter height (below-average height in full siblings: OR = 1.14, 95% CI = 1.09-1.19; maternal half siblings: OR = 1.10, 95% CI = 1.01-1.20; paternal half siblings: OR = 1.15, 95% CI = 1.07-1.24, first full cousins: OR = 1.10, 95% CI = 1.08-1.12).

Conclusion: Our findings suggest that ADHD is associated with shorter height. On a population level, this association was present both before and after ADHD medications were available in Sweden. The association between ADHD and height was partly explained by prenatal factors, psychiatric comorbidity, low socioeconomic status, and a shared familial liability for ADHD.

Key words: ADHD; adult height; ADHD medication

J Am Acad Child Adolesc Psychiatry 2023;62(12):1316-1325.

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder characterized by developmentally inappropriate, persistent, and impairing levels of inattention and/or hyperactivity-impulsivity.[1,2] The estimated pooled prevalence is around 6% to 7% in children and 2% to 3.5% in adults.[3-5] Because ADHD is associated with an increased risk for a range of adverse functional and somatic outcomes, the need for an effective and safe management of this condition is highly relevant.[6-9] Evidence from short-term (<1 year) double-blind randomized controlled trials (RCTs) show large effect sizes for stimulant and moderate effect sizes for non-stimulant medications.[10-14] The potential benefits of ADHD medication must, however, be considered in the light of possible risks.

One of the most commonly reported risks associated with the use of ADHD medication is growth deficit in height and weight,[15] but available studies on growth during ADHD treatment have provided mixed findings. Indeed, clinical guidelines and systematic reviews of the literature on the possible effects of ADHD medication on growth have concluded that more work is needed to clarify the effects of medication from childhood to adulthood.[15,16] A recent systematic review and meta-analysis of 18 studies (n = 34 to 1,758) focusing on long-term methylphenidate exposure showed that long-term treatment with methylphenidate might be associated with a growth deficit, in particular with respect to

height; however, effect sizes were found to be small (standardized mean difference = 0.27, 95% CI = 0.16-0.38) and of possible minimal clinical impact.[17] Importantly, the systematic review by Carucci *et al.*[17] highlighted that the included studies generally did not adequately describe or measure possible confounders such as genetic factors, prenatal factors, or socioeconomic factors. This means that a possible association between ADHD medication and short height in persons with ADHD is still an area that needs further research.

ADHD might be associated with growth dysregulation even in medication-naive individuals, with both height suppression and growth spurt, depending on age.[18-22] Research on the reasons underpinning the association between ADHD and shorter height is limited. Height suppression and/or accelerated growth in ADHD may reflect an inherent characteristic of the disorder itself, with possible disruption of the neuroendocrinological system.[23] Along this line, Nemet *et al.*[24] recently reported reduced growth hormone secretion among children with ADHD. Furthermore, ADHD and height are both strongly influenced by genetic factors,[2,25] and the association between ADHD and height might be due to common genetic alterations.[26-28] Finally, as indicated in reviews and meta-analyses on the association between ADHD medication and shorter height, prenatal (eg, birth weight), psychiatric, and somatic covariates may confound the association between ADHD and shorter height, so this needs to be controlled for.[17,29,30] Low birth weight is associated with ADHD[31] and also with height deficit.[32] Studies have found an association between depression and height in individuals both with and without ADHD, [33,34] which may indicate that comorbid depression plays a role in the association between ADHD and height. Associations between ADHD and somatic disorders have also been found.[35] It is possible that these somatic conditions (eg, hypothyroidism, inflammatory bowel disease, celiac disease) or the medications used to treat them account for some of the association between ADHD and shorter height,[36,37] so this indicates the need for appropriate adjustments.

To test these hypotheses, the present study used a linkage of the Swedish military service conscription register and several other national registers to compare the height of individuals with ADHD before (treatment-naive cohort) and after (potentially treated cohort) ADHD medication was introduced as a treatment alternative in Sweden. We then explored the role of prenatal factors, psychiatric and somatic comorbidity, and socioeconomic factors in the potentially treated cohort. Then, to assess the role of shared familial factors, we used a family-based design to explore whether relatives (who themselves did not have a diagnosis of ADHD) of individuals with ADHD are at increased risk for shorter than expected height.

METHOD

Data Sources and Measures

We used data from a record linkage of Swedish national registers. Individuals with at least 1 diagnosis of ADHD in the Swedish National Patient Register (NPR), which includes inpatient diagnoses from 1987 and outpatient diagnoses from 2001, were identified by using *International Classification of Diseases* (*ICD*) diagnostic codes (*ICD-9*: code 314; *ICD-10*: code F90). ADHD case inviduals were those who had received an ADHD diagnosis in the NPR and who also had participated in the Swedish military conscription at any time between 1968 and 2010. The NPR was also used to measure psychiatric and somatic comorbidities with known negative effect on growth. Psychiatric comorbidity was defined as having a diagnosis of anxiety (*ICD-9*: 300; *ICD-10* F30-F31), depression (*ICD-9*: 296D, 300E; *ICD-10*: F32-F34), or substance use disorder (*ICD-9*: 291, 292, 303-305; *ICD-10*: F10-F18). Somatic comorbidity was defined by a diagnosis of fetal alcohol syndrome (*ICD-9*: 760W, Q860), inflammatory bowel disease (*ICD-9*: 555, 556; *ICD-10*: K50, K51, K523), celiac disease (*ICD-9*: 579A; *ICD-10*: K900), or hypothyroidism (*ICD-9*: 244, 243; *ICD-10*: E00, E01, E02, E03). The Swedish Prescribed Drug Register was used to obtain data on dispensed medications, including the following: amphetamine (Anatomical Therapeutic Chemical classification system [ATC)] codes: N06BA01, N06BA02; methylphenidate (N06BA04); atomoxetine (N06BA09); and lisdexamfetamine (N06BA12).

The Swedish Medical Birth Register was used to obtain valid information about birthweight from 1973.[38] In line with previous research,[39,40] birthweight was categorized into low (500-2,499 g), normal (2,500-4,199 g), and high (4,200-6,000 g). The Integrated Database for Labour Market Research (LISA) register provided information about the highest parental education level and was used as an indicator of socioeconomic status (SES).

We also used the Swedish Military Service Conscription Register (SMSCR), which contains medical and psychological examinations of all Swedish men up until 2007 at an approximate age of 18 years.[41] Measurements of height from the medical examination were extracted for this study. To compare height in individuals with ADHD before and after ADHD medication was introduced in Sweden, a drug-naive cohort and a potentially treated cohort were created by stratifying individuals with ADHD and matched controls into 2 groups based on calendar year for conscription. The treatment-naive cohort consisted of inviduals conscripting between 1968 and 1991 (before ADHD medication was introduced in Sweden) and the potentially treated cohort

consisted of individuals conscripting between 1992 and 2010 (after ADHD medication was introduced). In 1991, a nationally funded randomized controlled trial on the effects of stimulant medication on ADHD symptoms in children was started in Sweden.[42] Before that study, ADHD medication were very rare in Sweden; but after that RCT, prescriptions started to rise.[43,44] Using the Swedish Total Population Register, we identified up to 5 controls for each ADHD case individual. The controls also had to participate in the Swedish military conscription and were matched on sex, birth year, and county.

The national Multi-Generation Register (MGR) was used to create a family-based design. The register was used to enable identification of male full siblings, half siblings, and cousins of the individuals with ADHD and the matched controls. Only male relatives with height data from the conscript register were included.

Statistical Analyses

We first compared the mean height between individuals with ADHD and their matched controls. We then stratified individuals into 2 groups depending on the year of military conscription; 1968 to 1991 (stimulant-naive cohort: conscripted before ADHD medication was introduced in Sweden) and 1992 to 2010 (potentially treated cohort: conscripted after ADHD medication was introduced). To allow for non-linear effects and to facilitate clinical interpretability, height measurements were categorized into 5 groups as follows: (1) 150 to 165 cm (far below average; below −2 SD); (2) 166 to 172 cm (below average; −1 SD to −2 SD); (3) 173 to 185 cm (average; above −1 SD); (4) 186 to 192 cm (above average; +1 SD to +2 SD); and (5) 194 to 209 cm (far above average; above +2 SD). Group 3 (average) was used as reference group. These groupings of height by standard deviations above or below average is the standard way to categorize height in Swedish schools and in the Swedish military, and has been used in earlier epidemiological research on the association between height and various outcomes.[45-47]

Conditional logistic regression was used to quantify the association between ADHD and categorical defined height within individuals. The results were presented as odds ratios (ORs) with 95% CIs. We first compared the strength of the crude associations between ADHD and height in the drug-naive cohort and the potentially treated cohort. We then explored the role of confounders in the potentially treated cohort using 4 separate models: model 1 adjusted for prenatal factors (ie, birth weight), model 2 for medical comorbidity, model 3 for psychiatric comorbidity, and model 4 for SES. Because of the lack of complete data in the stimulant-naive cohort, it was not possible to assess the role of confounding in that cohort. The coverage in the registers is very low before 1992. We performed a sensitivity analysis in which all individuals with ADHD had a prescription for ADHD medication (Table S1, available online). ADHD medication use was classified categorically based on information about prescriptions (ie, at least 1 prescription = yes; no prescription = no). We also performed a sensitivity analysis with ADHD measured continuously instead of categorically (Table S2, available online).

To study familial liability between ADHD and height, we used data for full siblings, maternal and paternal half siblings, and full cousins. We used conditional logistic regression to estimate the odds of shorter or taller height in relatives without ADHD of individuals with ADHD compared to relatives of controls (who themselves did not have a diagnosis of ADHD). These analyses were based on relatives of all individuals in the treatment-naive and potentially treated cohorts (ie, individuals conscripting between 1968 and 2010). This was done separately for the different degrees of relatedness (ie, full siblings, half siblings, and cousins).

All analyses were performed in SAS 9.4 (SAS Institute Inc) with a robust sandwich estimator to supply standard errors corrected for the dependence between repeated observations within families.[48,49]

Ethical Considerations

The use of Swedish register data does not require informed consent. This study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr2013/862–31/5).

RESULTS

Descriptive Statistics

The study included 14,268 individuals diagnosed with ADHD and 71,339 matched controls; all individuals were male. The mean height in the treatment-naive sample was 178.12 cm (SD = 6.60) for individuals with ADHD and 179.27 cm (SD = 6.51) for controls. In the potentially treated sample, the mean height for individuals with ADHD was 178.89 cm (SD = 6.84) and was 179.64 cm (SD = 6.66) for controls. In all, 89.7% and 88.52% of the individuals in the ADHD medication–naive sample and the potentially treated sample, respectively, received their ADHD diagnoses in outpatient psychiatric care. About

78% of the individuals with ADHD in the potentially treated sample had a prescription for ADHD medication. The family-based analyses included a total of 833,172 relatives with different levels of family relatedness to the individuals with ADHD and the controls. Table 1 provides further descriptive data.

TABLE 1 Distribution of Study Variables in Individuals With ADHD and Controls

Characteristic	ADHD		Controls	
Height data 1968-2010				
Subjects, n (%)	14,268	(100.00)	71,339	(100.00)
Height, cm, mean (SD)				
150-165	363	(2.54)	1,142	(1.60)
166-172	2,254	(15.80)	9,071	(12.72)
173-185	9,561	(67.01)	48,444	(67.91)
186-192	1,810	(12.69)	10,893	(15.27)
193-209	280	(1.96)	1,789	(2.51)
Height, cm at conscription	178.51	(6.74)	179.47	(6.57)
Anxiety disorder	1,708	(11.97)	365	(0.51)
Depression	6,100	(42.75)	2,335	(3.30)
Substance use disorder	6,367	(44.62)	2,879	(4.04)
Hypothyroidism	148	(1.04)	184	(0.26)
Inflammatory bowel disease	233	(1.63)	856	(1.20)
Celiac disease	36	(0.25)	145	(0.20)
Height data 1968-1991				
Subjects, n (%)	7,016	(100.00)	35,079	(100.00)
Height, cm, mean (SD)				
150-165	183	(2.61)	599	(1.71)
166-172	1,185	(16.89)	4,596	(13.10)
173-185	4,744	(67.62)	24,061	(68.59)
186-192	801	(11.42)	5,027	(14.33)
193-209	103	(1.47)	796	(2.27)
Height, cm, at conscription	178.12	(6.60)	179.27	(6.51)
Anxiety disorder	1,708	(11.97)	365	(0.51)
Depression	6,100	(42.75)	2,335	(3.30)
Substance use disorder	6,367	(44.62)	2,879	(4.04)
Hypothyroidism	148	(1.04)	184	(0.26)
Inflammatory bowel disease	233	(1.63)	856	(1.20)
Celiac disease	36	(0.25)	145	(0.20)
Height data 1992-2010				
Subjects, n (%)	7,251	(100.00)	36,254	(100.00)
Height, cm, mean (SD)				
150-165	180	(2.48)	579	(1.60)
166-172	1,069	(14.74)	4,461	(12.30)
173-185	4,816	(66.42)	24,368	(67.21)
186-192	1,009	(13.92)	5,793	(15.98)
193-209	177	(2.44)	1,053	(2.90)
Height, cm, at conscription	178.89	(6.84)	179.64	(6.66)
Anxiety disorder	1,708	(11.97)	365	(0.51)
Depression	6,100	(42.75)	2,335	(3.30)
Substance use disorder	6,367	(44.62)	2,879	(4.04)
Hypothyroidism	148	(1.04)	184	(0.26)
Inflammatory bowel disease	233	(1.63)	856	(1.20)
Celiac disease	36	(0.25)	145	(0.20)

Note: ADHD = attention-deficit/hyperactivity disorder.

TABLE 2 Odds Ratios (OR) With Their 95% CIs for Categorical Height in ADHD Case Individuals Compared to Controls for Individuals Conscripting Between 1968 and 1991[a] or between 1992 and 2010

Height, cm	Height data 1968-1991, OR (95% CI) Crude	Height data 1992-2010, OR (95% CI), Crude	Height data 1992-2010, Adjusted OR (95% CI), Prenatal[b]	Height data 1992-2010, Adjusted OR (95%CI), Medical[c]	Height data 1992-2010, Adjusted OR (95% CI), Psychiatric[d]	Height data 1992-2010, Adjusted OR (95% CI), SES[e]
150-165	1.55 (1.31-1.83)	1.58 (1.33-1.87)	1.38 (1.11-1.72)	1.58 (1.33-1.87)	1.54 (1.23-1.92)	1.32 (1.09-1.58)
166-172	1.31 (1.22-1.41)	1.21 (1.13-1.31)	1.18 (1.09-1.28)	1.21 (1.13-1.31)	1.15 (1.04-1.27)	1.11 (1.02-1.20)
173-185	Ref	Ref	Ref	Ref	Ref	Ref
186-192	0.81 (0.74-0.87)	0.88 (0.82-0.95)	0.92 (0.85-1.00)	0.88 (0.82-0.95)	0.97 (0.88-1.06)	0.96 (0.88-1.04)
193-209	0.65 (0.53-0.80)	0.85 (0.72-1.00)	0.94 (0.79-1.16)	0.85 (0.72-1.00)	0.90 (0.73-1.11)	0.97 (0.81-1.15)

Note: ADHD = attention-deficit/hyperactivity disorder; Ref = reference; SES = socioeconomic status.
[a]*For individuals conscripting between 1968 and 1991, only crude associations are presented because of limited data on the selected covariates before 1992.*
[b]*Birth weight.*
[c]*Inflammatory bowel disease, celiac disease, hypothyroidism.*
[d]*Anxiety disorders, depression, substance use disorder.*
[e]*Highest parental education.*

Height of Individuals With ADHD Compared to Controls

Table 2 shows that the crude associations between ADHD and shorter height were similar in the treatment-naive cohort (far below average height: unadjusted OR = 1.55, 95% CI = 1.31-1.83; below average height: unadjusted OR = 1.31, 95% CI = 1.22-1.41) and the potentially treated cohort (far below average height: unadjusted OR = 1.58, 95% CI = 1.33-1.87; below average height: unadjusted OR = 1.21, 95% CI = 1.13-1.31). In the potentially treated cohort (Table 2), the adjusted models show that prenatal factors, psychiatric comorbidity, and SES attenuated associations between ADHD and shorter height. This pattern of similar associations between ADHD and height in the treatment-naive cohort and in the treated cohort were also found in a sensitivity analysis in which all individuals had been prescribed ADHD medication (Table S1, available online). A similar pattern was also found in a sensitivity analysis with height as a continuous instead of a categorical outcome (Table S2, available online).

Familial Liability for Association Between ADHD and Height

Full siblings of individuals with ADHD had increased odds of being shorter than average (far below average height: OR = 1.18, 95% CI = 1.05-1.32; below average height: OR: 1.14, 95% CI = 1.09-1.19) compared to full siblings of matched controls (Table 3). Maternal (far below average height: OR = 1.18, 95% CI = 0.96-1.47; below average height: OR: 1.10, 95% CI = 1.01-1.20) and paternal (far below average height: OR = 1.40, 95% CI = 1.16-1.69; below average height: OR: 1.15, 95% CI = 1.07-1.24) half siblings of individuals with ADHD had an increased odds of being shorter and decreased odds of being taller compared to maternal and paternal half siblings of matched controls. Full cousins of individuals with ADHD also had increased odds of being shorter than average (far below average height: OR = 1.20, 95% CI = 1.14-1.27; below average height: OR = 1.10, 95% CI = 1.08-1.12) compared to full cousins of matched controls.

DISCUSSION

This study investigated the association between ADHD and shorter-than-expected height in a treatment-naive cohort and a potentially treated cohort by using data from the Swedish National Conscript Register. We also used a family-based design to estimate the potential familial overlap between ADHD and shorter-than-expected height. To our knowledge, this is the largest epidemiological study to date on the association between ADHD and height. Our findings suggest that ADHD is associated with shorter height. We found that the association between ADHD and shorter height was similar in magnitude in the treatment-naive cohort and the potentially treated cohort. The association between ADHD and shorter-than-expected height attenuated after controlling for prenatal factors, psychiatric disorders, and SES. Furthermore, relatives of individuals with ADHD (who themselves did not have a diagnosis of ADHD) were on average shorter than relatives of individuals without ADHD. Our findings suggest that the

TABLE 3 Categorical Height in Relatives of Individuals With ADHD Compared to Relatives of Controls

Height data, cm, 1968-2010	ADHD–relative pairs, n/ total (%)	Control–relative pairs, n/ total (%)	OR (95%CI)
Male relatives			
Full siblings			
150-165	359/18,588 (1.93)	1,535/92,939 (1.65)	1.18 (1.05-1.32)
166-172	2,715/18,588 (14.61)	11,934/92,939 (12.84)	1.14 (1.09-1-19)
173-185	12,586/18,588 (67.71)	63,053/92,939 (67.84)	Ref
186-192	2,491/18,588 (13.40)	13,997/92,939 (15.06)	0.89 (0.85-0.93)
193-209	437/18,588 (2.35)	2,420/92,939 (2.60)	0.90 (0.81-1.00)
Maternal half siblings			
150-165	107/5,351 (2.00)	454/26,755 (1.70)	1.18 (0.96-1-47)
166-172	814/5,351 (15.21)	3,703/26,755 (13.84)	1.10 (1.01-1.20)
173-185	3,676/5,351 (68.70)	18,437/26,755 (68.91)	Ref
186-192	653/5,351 (12.20)	3,635/26,755 (13.59)	0.90 (0.82-0.99)
193-209	101/5,351 (1.89)	526/26,755 (1.97)	0.96 (0.77-1.20)
Paternal half siblings			
150-165	140/6,888 (2.03)	502/34,400 (1.46)	1.40 (1.16-1.70)
166-172	1,006/6,888 (14.61)	4,405/34,400 (12.79)	1.15 (1.07-1.24)
173-185	4,704/6,888 (68.29)	23,630/34,400 (68.61)	Ref
186-192	921/6,888 (13.37)	5,091/34,400 (14.78)	0.91 (0.84-0.98)
193-209	117/6,888 (1.70)	812/34,400 (2.36)	0.72 (0.59-0.88)
First full cousins			
150-165	1,657/106,147 (1.56)	6,925/530,735 (1.30)	1.20 (1.14-1.27)
166-172	14,087/106,147 (13.27)	64,098/530,735 (12.08)	1.10 (1.08-1.12)
173-185	72,642/106,147 (68.44)	364,499/530,735 (68.68)	Ref
186-192	15,294/106,147 (14.41)	81,71/530,735 (15.40)	0.94 (0.92-0.96)
193-209	2,467/106,147 (2.32)	13,502/530,735 (2.54)	0.92 (0.88-0.96)

Note: ADHD = attention-deficit/hyperactivity disorder; OR = odds ratio; Ref = reference.

observed association between ADHD and shorter height at age 18 years is in part explained by confounding, including a shared familial liability for ADHD.

We found that individuals with ADHD were on average shorter at 18 years of age compared to individuals without ADHD. Importantly, we also found this in individuals with ADHD before ADHD medications were introduced in Sweden. Individuals with ADHD conscripting at age 18 between 1968 and 1991 (n = 7,016) were on average 1.15 cm shorter than matched controls (n = 35,079) conscripting during the same time. Individuals with ADHD conscripting between 1992 and 2010 (n = 7,251) when ADHD medication was available in Sweden were on average 0.75 cm shorter than matched controls (n = 36,254) conscripting during the same time. Earlier findings on height in treatment-naive individuals with ADHD have been mixed. In a longitudinal study of a birth cohort (N = 5,718) including 101 stimulant-naive individuals with ADHD, no significant differences in adult height were found.[50] Similarly, in an analysis of data from the National Epidemiological Survey on Alcohol and Related Conditions study (NESARC), no significant differences in adult height between 591 never-treated individuals with ADHD and 34,652 individuals without ADHD were found.[51] In contrast to our large study with 14,268 individuals with ADHD and 71,339 controls, limited power might explain why several previous studies did not find a statistically significant association between ADHD and shorter height.[50-52] There are, however, exceptions. In a recent study of 650 adolescents (80%-90% having reached puberty) with ADHD, of whom 283 were stimulant naive, a significant association between ADHD and shorter height were found.[21] As in our study, ADHD medication use was not associated with shorter height. The Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder (MTA) study indicated that ADHD is associated with a growth spurt, possibly leading individuals with ADHD to reach their final adult height earlier than individuals without ADHD.[22] However, a limitation of our study was that we lacked a measure of pubertal timing or repeated assessments of height, so it remains unclear whether the participants in our study actually had reached their final adult height. In a follow-up in

the MTA study of 112 individuals with ADHD at age 18 years, the average height was 1.29 cm greater in the negligibly treated group compared to a naturalistic comparison group.[53] Even though the average height of the non-ADHD controls in our sample were comparable to the naturalistic comparison group in the MTA study, differences was observed when comparing the average height of our potentially treated ADHD group and the different ADHD groups (eg, negligibly treated group) of the MTA study. These conflicting results need to be resolved in future research.

Our family-based analyses indicate a role of shared familial factors for the association between ADHD and shorter height, but observed differences in effect size across different relatives provide little information about the origin of the familial liability. The observed familial overlap may reflect genetic factors, which would be consistent with the notion that ADHD and height are both highly heritable.[2,54] This is also in line with a recent study reporting a significant negative association between ADHD polygenetic risk scores and height[55]; however, after controlling for educational achievement, this significant association was no longer significant. The findings on polygenic risk scores for ADHD and height has recently been described as mixed.[27]

Controlling for psychiatric comorbidity attenuated the association between ADHD and shorter height to some extent, which is in line with research that has found an association between depression and height in individuals both with and without ADHD.[33,34] Future studies could test whether depression, and possibly antidepressant medication, mediates the association between ADHD and shorter height.[56,57] Finally, we found that adjustment for SES also attenuated the association between ADHD and shorter height, which is consistent with previous findings of an association between low SES and shorter height.[58,59]

A full mechanistic understanding of why treatment-naive individuals with ADHD are shorter than expected, as in our cohort, is currently lacking. Our results points to the influence of shared familial factors, psychiatric comorbidity, and SES. On a biological level, there are indications that children with ADHD have an increased risk of failing growth hormone stimulation[60] and have reduced exercise-induced growth hormone secretion.[24] The etiology of growth hormone deficiency in individuals with ADHD and in general are not fully known, however.[61,62] This is an area for future research.

These results indicate that for the average individual with a diagnosis of ADHD, shorter height is probably explained by familial and/or confounding factors. In terms of clinical relevance, our finding of similar associations between ADHD and height in the treatment-naive cohort and in the treated cohort, and also in the sensitivity analysis restricted to individuals ever prescribed ADHD medication, indicate that ADHD medication does not seem to explain the association between ADHD and shorter height in our study. However, height should still be monitored in pediatric settings, as there might be certain ADHD treatment patterns and/or subgroups of ADHD medication–treated individuals who could show height suppression.[63] Clinicians should be aware of potential differences in growth patterns between individuals with and without ADHD. It could be important to consider relatives' measures (eg, midparental height, height of siblings) and growth patterns prior to ADHD medication in a comprehensive evaluation of growth development in children with ADHD. As such, children with ADHD should be compared to their relatives and to themselves before medication, not only to the standard growth curves for the population. It is also important to highlight that our findings do not rule out the possibility that some individuals are particularly vulnerable to the effects of the ADHD medications. Therefore, our data should not be interpreted as evidence supporting the notion that monitoring of height is not warranted.

The results of our study should be considered in light of some limitations. Our sample included only male patients and their relatives, and might not generalize to female patients. The Swedish Conscript Register predominantly contains men, as military service in Sweden was mandatory for male individuals until 2010. However, studies on ADHD medication containing both male and female patients have not found any gender effect on growth parameters.[53,63,64] The coverage of the Swedish Conscript Register is low after 2005; a minority of Swedish male individuals conscripted after that. This could have introduced selection effects in the data. Population-based register studies with data from psychiatric services (registered in the national patient register) are known to have low rates of some psychiatric disorders. This is because many people with anxiety and depressive disorders seek help from primary care rather than from psychiatric services. The national patient register in Sweden (and in the other Scandinavian countries) does not contain data from primary care. For people attending psychiatric specialist services, however, psychiatric comorbidity is quite often high, potentially due to referral bias. There is also a possibility of other cohort effects associated with ADHD, height, and our selected covariates. The average heights in the general population have increased in the last 150 years and are still increasing.[65] Accordingly, we found a mean difference of 0.4 cm between our 2 cohorts, with the older cohort being shorter. Considering socioeconomic development throughout time and the known association between socioeconomic factors and differences in height, it is possible that this association is stronger in our older cohort compared to

our newer cohort.[66,67] We did, however, control for socioeconomic factors in both of our cohorts, which indicates that socioeconomic differences within our cohorts is not a major contribution to our findings. There is still a possibility, however, of residual confounding from other social factors, such as factors associated with changes in the school and health care systems. Another limitation is the lack of detailed measures of ADHD medication (eg, dosage or exact duration), meaning that the amount of stimulant treatment in our potentially treated cohort is unknown. Our sensitivity analysis of medication use is a categorical (yes/no) measure of medication prescription/no prescription. It is possible that the association between ADHD medication and height is detectable only in the group with the most frequent use, as in the MTA study.[53,63] However, our finding that ADHD is associated with shorter height even in a treatment-naive cohort suggests that confounding by indication should be considered regardless of frequency and duration of medication use. Finally, our results may not be generalizable to countries with a different health care system where there is a stronger selection of ADHD in terms of access to the health care system for children due, for instance, to lack of resources or high health care fees. In Sweden, the health care system, being free of charge, will include most children, which is a strength of this study.[68]

In conclusion, in the largest study to date on the association between ADHD and shorter height, we found that the association between ADHD and shorter height was similar in magnitude in a treatment-naive cohort and a potentially treated cohort. The associations between ADHD and shorter height were partly explained by SES, prenatal factors, and psychiatric comorbidity. Family-based analyses further indicated a shared familial liability between ADHD and shorter height.

Accepted April 12, 2023.

This article was published online and copyedited by Deputy Editor Melissa P. DeBellis, MD.

Mr. Ahlberg, Dr. Garcia-Argibay, and Prof. Larsson are with the School of Medical Sciences, Örebro University, Örebro, Sweden. Drs. Garcia-Argibay, Du Rietz, Butwicka, and Cortese, Prof. D'Onofrio, Larsson, and Ludvigsson are with Karolinska Institutet, Stockholm, Sweden. Dr. Butwicka is also with Child and Adolescent Psychiatry, Stockholm, Stockholm Health Care Services, Region Stockholm, Sweden. Prof. D'Onofrio is also with Indiana University, Bloomington, Indiana. Prof. Ludvigsson is also with Örebro University Hospital, Örebro University, Örebro, Sweden. Dr. Cortese is with the Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life sciences, University of Southampton, Southampton, United Kingdom; Solent NHS Trust, Southampton, United Kingdom; Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, United Kingdom; Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, United Kingdom; Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York City, New York; the Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, United Kingdom.

Henrik Larsson acknowledges financial support from the Swedish Research Council (2018-02599) and the Swedish Brain Foundation (FO2021-0115). Angelica Butwicka is supported by Stiftelsen Söderström Königska Sjukhemmet (SLS-969059), the Swedish Research Council (2017-00788), and Stockholm Region (ALF/FoUU clinical research appointment 2018-0718). Ebba Du Rietz received financial support from the Swedish Research Council for Health, Working Life and Welfare (FORTE) (2019-01172), the Swedish Society for Medical Research (SSMF) (PD20-0036), Fredrik & Ingrid Thurings Stiftelse (2021-00638), and The Strategic Research Area in Epidemiology and Biostatistics (SFOepi).

The research was performed with permission from the Regional Ethical Review Board in Stockholm.

Dr. Garcia-Argibay served as the statistical expert for this research.

Author Contributions

Conceptualization: Ahlberg, Garcia-Argibay.
Data curation: Garcia-Argibay.
Formal analysis: Ahlberg, Garcia-Argibay.
Funding acquisition: Larsson.
Methodology: Ahlberg, Garcia-Argibay, Larsson.
Software: Garcia-Argibay.
Supervision: Du Rietz, Larsson.
Validation: Garcia-Argibay.
Writing — original draft: Ahlberg, Du Rietz, Larsson.
Writing — review and editing: Ahlberg, Garcia-Argibay, Du Rietz, Butwicka, Cortese, D'Onofrio, Ludvigsson.

Disclosure: Dr. Du Rietz has served as a speaker for Shire Sweden AB, a Takeda Pharmaceutical Company, outside of this work. Dr. Cortese has declared honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), and from Healthcare Convention for educational activity on ADHD. Prof. Ludvigsson has coordinated a study on behalf of the Swedish IBD quality register (SWIBREG). That study received funding from Janssen corporation. He has also received financial support from MSD developing a paper reviewing national healthcare registers in China and is currently discussing potential research collaboration with Takeda. Prof. Larsson has reported receiving grants from Shire Pharmaceuticals, personal fees from and serving as a speaker for Medice, Shire/Takeda Pharmaceuticals and Evolan Pharma AB, and sponsorship for a conference on attention-deficit/hyperactivity disorder from Shire/Takeda Pharmaceuticals, and Evolan Pharma AB, all outside the submitted work. Drs. Garcia-Argibay and Butwicka, Prof. D'Onofrio, and Mr. Ahlberg have reported no biomedical financial interests or potential conflicts of interest.

Correspondence to Rickard Ahlberg, MSc, Örebro University, Fakultetsgatan 1, 702 81, Örebro, Sweden; e-mail: rickardahlberg@oru.se

https://doi.org/10.1016/j.jaac.2023.03.015

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association; 2013.
2. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. Mol Psychiatry. 2019;24(4):562-575. https://doi.org/10.1038/s41380-018-0070-0
3. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int J Epidemiol. 2014;43(2):434-442. https://doi.org/10.1093/ije/dyt261