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Family income in early childhood and subsequent Attention-Deficit/Hyperactivity Disorder: A quasi-experimental study

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Abstract

Background—Studies have found negative associations between socioeconomic position and Attention-Deficit/Hyperactivity Disorder (ADHD), but it is unclear if this association is causal. The aim of this study was to determine the extent to which the association between family income in early childhood and offspring ADHD depends on measured and unmeasured selection factors.

Methods—A total of 811,803 individuals born in Sweden between 1992 and 2000 were included in this nationwide population based cohort study. Diagnosis of ADHD was assessed via the Swedish national Patient Register and the Swedish Prescribed Drug Register. Annual family income during offsprings' first five years in life was collected prospectively from the Swedish Integrated Database for Labour Market Research (LISA) and divided into quartiles by (lower) family disposable income. We predicted ADHD from family income while controlling for covariates and also comparing differently exposed cousins and siblings to control for unmeasured familial confounding.

Results—The crude analyses suggested that children exposed to lower income levels were at increased risk for ADHD (HR_{Quartile1}=2.52; 95% CI, 2.42–2.63; HR_{Quartile2}=1.52; 95% CI, 1.45–1.58; HR_{Quartile3}=1.20; 95% CI, 1.14–1.15). This dose-dependent association decreased after adjustment for measured covariates (HR_{Quartile1}=2.09; 95% CI, 2.00–2.19; HR_{Quartile2}=1.36; 95% CI, 1.30–1.42; HR_{Quartile3}=1.13; 95% CI, 1.08–1.18). Although the association was attenuated in cousin comparisons (HR_{Quartile1}=1.61; 95% CI, 1.40–1.84; HR_{Quartile2}=1.28; 95% CI, 1.12–1.45; HR_{Quartile3}=1.14; 95% CI, 1.01–1.28) and sibling comparison models (HR_{Quartile1}=1.37; 95% CI, 1.07–1.75; HR_{Quartile2}=1.37; 95% CI, 1.12–1.68; HR_{Quartile3}=1.23; 95% CI, 1.04–1.45), it remained statistically significant across all levels of decreased disposable family income.

Conclusions—Our results indicated that low family income in early childhood was associated with increased likelihood of ADHD. The link remained even after controlling for unmeasured selection factors, highlighting family income in early childhood as a potential causal risk factor for ADHD.

Keywords

ADHD; family income; childhood; causality; quasi-experimental approaches

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly heritable neurodevelopmental disorder with an early onset (Biederman & Faraone, 2005; Faraone et al., 2005). Although research has documented a robust negative relationship between family socioeconomic status (SES) and its components (i.e., income, education, and occupation) and offspring ADHD (Biederman, Faraone, & Monuteaux, 2002; Biederman et al., 1995; Counts, Nigg, Stawicki, Rappley, & von Eye, 2005; Hjern, Weitof, & Lindblad, 2010; Scallil et al., 1999), it is possible that unmeasured selection factors accounts for this association; meaning, for example, that genetically influenced parental characteristics (e.g., mental health problems) cause low SES and increase offspring risk of ADHD (Thapar, Cooper, Jefferies, & Stergiakouli, 2012).

Since RCTs are impossible, quasi-experimental designs (e.g., sibling-comparison analyses) that rule out unmeasured selection factors are needed to address if parental SES is a true cause of offspring ADHD (Academy of Medical Sciences Working Group, 2007; Shadish, Cook, & Campbell, 2002). Although no prior study has used quasi-experimental designs to investigate if low family SES influence early-onset, highly heritable neurodevelopmental disorders like ADHD in offspring, such studies have been performed regarding offspring conduct problems. A natural experiment with American Indian families found that increases in income were followed by a significant reduction in their children's conduct problems (Costello, Compton, Keeler, & Angold, 2003). Similarly, a comparison of differentially exposed siblings (who share genetic factor and many of the same unmeasured family characteristics) showed that sibling differences in family income during childhood were associated with sibling differences in conduct problems (D'Onofrio et al., 2009). Similar results have been reported also from other quasi-experimental studies (Dearing, McCartney, & Taylor, 2006; Hao & Matsueda, 2006). Altogether, the findings suggest that the association between family income and conduct problems in offspring partly reflects social causation; that is, low SES causes offspring conduct problems indirectly via environmental adversity and stress that interfere with parenting and limit the resources available for one's children (Costello, et al., 2003; D'Onofrio, et al., 2009).

We tested the hypothesis that family income in early childhood has a causal effect on subsequent offspring ADHD in a large population-based cohort of children. We focused on early postnatal effects of family income on ADHD because recent research suggests that environmental exposures early in life may program biological and behavioral responses with long-term effects (Swanson & Wadhwa, 2008). We explored the impact of confounding by (a) controlling for measured covariates, (b) by comparing full cousins (offspring of full-siblings) within extended families, a design that rules out all unmeasured factors that make cousins similar and (c) by comparing full siblings within nuclear families, a design that rules out all unmeasured factors that make siblings similar (D'Onofrio, Lahey, Turkheimer, & Lichtenstein, In press; Lahey & D'Onofrio, 2010).

METHODS

Sample

We merged information from eight government-maintained population registers through each individual's unique personal identification number: (1) the Swedish Medical Birth Registry included data on more than 99% of pregnancies in Sweden from 1973 onwards; (2) the Multi-Generation Register contained information about biological and adoptive relationships for individuals living in Sweden since 1933; (3) the Cause of Death Register provided data on principal and contributing causes of death since 1958; (4) the Migration Register supplied data on dates for migration in or out of Sweden; (5) the Integrated

Database for Labour Market Research (LISA) provided annual information on family income, unemployment status, and social welfare benefits since 1990 for all individuals from 16 years of age that were registered in Sweden as of December 31 each year; (6) the National Patient Register provided data on psychiatric inpatient care since 1973 (ICD-8 to ICD-10) and outpatient care since 2001 (ICD-10) (WHO, 1992); and, finally, (7) the Swedish Prescribed Drug Register provided data on dispensed pharmaceuticals in the entire population of Sweden since July 2005, including drug identity (Anatomical Therapeutic Chemical [ATC-codes]) and dates of dispensed prescriptions (Wettermark et al., 2007).

We used a birth cohort of 811,803 children born 1992–2000 and included in the Medical Birth Registry. This cohort represented 90.7 % of the targeted population (N=895,243). We excluded children from multiple births (n=26,706), with serious malformations at birth (n=30,859), who were stillborn before or during delivery (n=2,776), who died before the age of 5 (n=2,607), or who emigrated from the country before the age of 5 (n=4,236). Of the remaining 828,059 offspring, those who had missing data on family disposable income (n=7,351), sex (n=104), parity (n=23) or who could not be linked to both biological parents (n=8,521) or had been diagnosed with ADHD and/or were treated with stimulants or non-stimulants before age 5 years (n=257) were excluded from analyses. In addition, we excluded those who were missing. For the within-family analyses, we identified 430,344 full biological siblings nested within 202,408 nuclear families and 470,117 cousins nested within 194,728 extended families in our sample.

The study was approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden.

Measures

Exposure—Annual data on family income from the LISA register were used as our main exposure; the mean disposable family income between ages 0 and 5. Income was inflation-adjusted to values in 1990 according to Statistics Sweden's consumer price index and also reverse-coded, log transformed and standardized (i.e., mean = 0 and SD = 1) prior to analysis. The average family income during the first five years was used to create categorical (quartiles) and dichotomized (median split) exposure variables based on sample distribution.

Covariates—Offspring sex, birth year, and parity were included in all models. Maternal country of birth (divided into Sweden, other Nordic country, Non-Nordic country), parental age (five categories; <20, 20–25, 25–30, 30–35 and >35) at the time of the first-born child, and parental history of hospitalization for a mental disorder (ICD8–9: 290–315; ICD10: F00–F99), were included as measured nuclear family confounders (i.e., all siblings in the same family were similarly exposed to the confounder).

Outcome—Children treated with stimulant or non-stimulant medication for ADHD (methylphenidate [N06BA04]; atomoxetine [N06BA09]; amphetamine [N06BA01]; dexamphetamine [N06BA02]) at any time between July 2005 and July 2010 were identified via Prescribed Drug Register. The authority to prescribe ADHD medications in Sweden is restricted to specialist physicians familiar with the treatment of this disorder. Children obtaining a diagnosis of hyperkinetic disorder between 2001 and 2010 were identified via the National Patient Register (ICD-10: F90). No distinction was made between primary and secondary diagnoses. In the total sample of 811,803 children, 21,796 (2.68%) received a diagnosis of hyperkinetic disorder from outpatient care or received stimulant or non-stimulant treatment at any time during follow-up.

Statistical analyses

Cox proportional regression was used to obtain hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for the associations between family income in early childhood and subsequent offspring ADHD. This approach enabled us to take time at risk into account. The participants entered the study at their 5th birthday and were subsequently followed up for a median time of 8.9 years. The maximum follow-up time was 13 years. Those who migrated or died during follow-up period were censored.

In addition to a crude model (Model I; adjusted for sex, birth year, and parity) we also adjusted for the specified measured nuclear family confounders (Model II). To explore the effect of unmeasured selection factors, we used stratified Cox regression models for cousin and sibling comparisons with a separate stratum for each set of full cousins and siblings, respectively. The cousin comparison model (Model III) controlled for measured covariates (sex, birth year, parity and nuclear family confounders) and also for all unmeasured selection factors that are constant within extended families. The sibling comparisons (Model IV) controlled for measured covariates (sex, birth year, parity) and all unmeasured selection factors that are constant within nuclear families.

We conducted sensitivity analyses to assess the potential effect of birth order on the studied associations. We also performed analyses stratified on birth-year to check for period effects. Further, we explored the generalizability of our results by restricting the analyses to single-children families.

All models were fitted in Stata 12.1 (Statacorp, 2011).

RESULTS

Demographic characteristics of the sample are presented in Table 1. ADHD seemed to be associated with lower disposable family income in childhood and with measured covariates and family-wide confounders.

HRs with corresponding 95% CIs for the effect of family income in early childhood on offspring ADHD are presented in Table 2. The crude association (Model I) for the categorical family disposable income measure suggested that offspring exposed to lower levels of family income in early childhood were at increased risk for ADHD ($HR_{\text{Quartile1}}=2.52$; $HR_{\text{Quartile2}}=1.52$; $HR_{\text{Quartile3}}=1.20$). This dose-dependent association decreased marginally in Model II after adjustment for measured covariates ($HR_{\text{Quartile1}}=2.09$; $HR_{\text{Quartile2}}=1.36$; $HR_{\text{Quartile3}}=1.13$). When fitting the cousin comparison model (Model III) to adjust for the measured covariates and unmeasured selection factors within extended families the association was further attenuated, but remained statistically significant ($HR_{\text{Quartile1}}=1.61$; $HR_{\text{Quartile2}}=1.28$; $HR_{\text{Quartile3}}=1.14$). Finally, in sibling comparisons the association remained statistically significant across all levels of the categorical family income measure (Model IV: $HR_{\text{Quartile1}}=1.37$; $HR_{\text{Quartile2}}=1.37$; $HR_{\text{Quartile3}}=1.23$), indicating that family income in early childhood influence subsequent offspring ADHD even after controlling for all unmeasured selection factors that are constant within nuclear families.

A similar pattern of associations was observed for the binary family income exposure variable (Table 2). That is, the effect of family income in early childhood on subsequent offspring ADHD remained statistically significant even after adjustment for measured covariates (Model II: $HR=1.57$), unmeasured selection factors within extended families (Model III: $HR=1.27$) and unmeasured selection factors that are constant within nuclear families (Model IV: $HR=1.14$).

Sensitivity analysis

To explore our assumptions and test the robustness of the findings, we conducted sensitivity analyses with the binary family income exposure variable.

First, crude analyses (Model I) stratified on parity revealed similar results across strata ($HR_{\text{Parity1}}=1.90$; 95% CI, 1.81–1.99; $HR_{\text{Parity2}}=1.79$; 95% CI, 1.70–1.87; $HR_{\text{Parity3}}=1.76$; 95% CI, 1.64–1.89; $HR_{\text{Parity4}}=1.60$; 95% CI, 1.46–1.76), suggesting limited birth order effects.

Second, crude analyses (Model I) stratified on birth year revealed similar results across strata (HRs ranged from 1.76 to 2.10 for birth years 1992–2000), suggesting limited bias from period effects.

Third, and finally, the crude association (Model I) between parental disposable income and offspring ADHD was similar when restricting analyses to single-children families ($HR=1.93$; 95% CI, 1.84–2.01), indicating that the sibling comparison results are generalizable to a broader family context.

DISCUSSION

This study is the first to use quasi-experimental designs to test if family income in early childhood influences subsequent offspring ADHD. In a very large birth cohort with population-based data from national registers, cousins within the extended family and siblings within the same nuclear family who were differentially exposed to family income during early childhood differed in ADHD risk. Thus, even though selection factors seem to explain part of the association, the present results are consistent with a causal effect of family income on offspring ADHD.

Many prior studies have reported that SES is negatively associated with ADHD (Biederman, et al., 2002; Biederman, et al., 1995; Counts, et al., 2005; Hjern, et al., 2010; Scahill, et al., 1999), but none of these focused on early postnatal effects of family income. More importantly, none of the prior studies used quasi-experimental designs to account for unmeasured selection factors. Nevertheless, the present findings are consistent with research on family income using quasi-experimental designs, which supports that causal effects account for the observed increased risk of offspring conduct problems (Costello, et al., 2003; D'Onofrio, et al., 2009). A causal hypothesis is supported also by recent cognitive neuroscience research that provides plausible neural pathways through which exposure to low SES could influence ADHD risk. For example, there is increasing evidence that the prefrontal working memory system, an important neuronal ADHD endophenotype (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Castellanos & Tannock, 2002), is strongly associated with low SES. (Hackman, Farah, & Meaney, 2010) Clearly, future studies needs to assess plausible pregnancy-related (e.g., infections and poor nutrition during pregnancy) and postnatal risks (e.g., impaired parenting, lower cognitive stimulation in the home or neighborhood or day care characteristics) to identify factors that mediate the association between family income and ADHD (Conger & Donnellan, 2007).

The quasi-experimental designs used in this study cannot establish causality, but can greatly reduce the number of alternative explanations to what appear to be causal effects (Donovan & Susser, 2011; Lahey & D'Onofrio, 2010). First, recall bias is unlikely to explain our results, since our family income measures were recorded prospectively. Second, rather than solely relying on the use of measured covariates, the comparison of differentially exposed full siblings controlled for unmeasured selection factors that may have accounted for the association between family income in early childhood and offspring ADHD. Third, the

combined use of cousin and sibling comparisons accompanied by sensitivity analyses allowed us to address concerns about the generalizability of findings from sibling studies (Frisell, Oberg, Kuja-Halkola, & Sjolander, 2012; Talati & Weissman, 2010), and to rule out birth order and period effects as alternative explanations.

The current study also has limitations that should be considered. First, it was not possible to classify ADHD cases according to the three DSM-IV ADHD subtypes (i.e., combined, primarily hyperactive-impulsive and primarily inattentive type), because these specific diagnoses were not recorded across the registers. However, prior research suggests that most measures of psychosocial adversity have subtype-general rather than subtype-specific effects (Lee et al., 2008).

Second, we have not examined the validity of the national register-based diagnoses of ADHD using comparisons with research diagnoses based on independent semi-structured interviews and/or medical records. However, detailed psychiatric symptom data from 19,150 twins (born 1992–2001) from the Swedish Twin Registry allowed us to explore the validity of register-based ADHD diagnoses. Twins' ADHD symptoms were assessed using a well-validated measure of 96 specific child psychiatric symptoms (Hansson, Svanstrom Rojvall, Rastam, Gillberg, & Anckarsater, 2005; Larson et al., 2010). In total, 2.62% ($n=501$) of these twins were diagnosed with ADHD via the national patient registers or were on stimulant/non-stimulant medication. The mean parent-rated ADHD symptom score of these 501 twins (9.05, $SD=5.32$) was substantially higher (Cohen's $d = 1.74$) than that of the total sample (mean=1.73, $SD=2.68$). About 70% of the twins with a national register-based ADHD diagnosis were identified as screen-positive for parent-rated ADHD. Very similar results were obtained when the validity checks were restricted to either ADHD cases ascertained via clinical ICD diagnoses (i.e., the Patient Register) or via ADHD medication treatment (i.e., the Prescribed Drug Register). Further, we recently explored prescriptions patterns of ADHD drugs from 2005 to 2009 in a total population cohort of almost 5 million individuals, aged 8–45 years (41,000 patients were dispensed an ADHD drug) (Zetterqvist, Asherson, Halldner, Langstrom, & Larsson, 2012). The results provide support for using medication for ADHD as a proxy for ADHD, as the observed patterns of medication use follow epidemiological patterns of diagnosis prevalence—higher prevalence among children than among adults and higher among males than females (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Simon, Czobor, Balint, Meszaros, & Bitter, 2009). In addition, prior epidemiological studies in Sweden using the Patient Register and the Prescribed Drug Register to measure ADHD reported expected associations to criminality (Lichtenstein et al., 2012) and also to early environmental risks such as maternal smoking during pregnancy (Lindblad & Hjern, 2010), prematurity (Lindstrom, Lindblad, & Hjern, 2011), and psychosocial adversity (Hjern, et al., 2010).

Third, national guidelines for medication of ADHD, issued by the National Board of Health and Welfare in 2002, stated that medication should be reserved for cases where other supportive interventions have failed, indicating that ADHD drug treatments most likely represent an indicator of the more severe cases of ADHD. This may suggest that our results are less generalizable to the entire population of subjects with ADHD.

Conclusion

We found that reduced family income in early childhood is associated with increased risk for ADHD. The association remained even after controlling for unmeasured selection factors, which highlight family income in early childhood as a potential causal risk factor to ADHD.

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Abbreviations

(LISA)	Integrated Database for Labour Market Research
(ADHD)	Attention-Deficit/Hyperactivity Disorder
(HR)	hazard ratio

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Key points

- Studies have found negative associations between socioeconomic position and Attention-Deficit/Hyperactivity Disorder (ADHD), but it is unclear if this association is causal.
- Quasi-experimental analyses indicated that cousins within the extended family and siblings within the same nuclear family who were differentially exposed to family income during early childhood differed in ADHD risk.
- Although selection factors seem to explain part of the association, the present results are consistent with a causal effect of family income on offspring ADHD.

Table 1

Demographic characteristics of offspring and families.

Variable	N	%	ADHD (%)
<i>Total sample</i>	811,803	100	2.68
Main exposure			
<i>Disposable family income, mean through ages 0 to 5</i>			
Quartile 1 (lowest)	202,950	25	4.31
Quartile 2	202,951	25	2.73
Quartile 3	202,951	25	2.09
Quartile 4 (highest)	202,951	25	1.60
Covariates included in all models			
<i>Sex</i>			
Male	415,139	51.14	3.91
Female	396,664	48.86	1.40
<i>Parity</i>			
First born	329,970	40.65	2.73
Second born	329,970	37.23	2.53
Third born	124,034	15.28	2.66
Fourth+ born	55,578	6.85	3.34
<i>Birth year</i>			
1992–1995	408,076	50.27	2.99
1996–2000	403,727	49.73	2.37
Nuclear family confounders			
<i>Maternal country of origin</i>			
Sweden	683,449	84.26	2.85
Other Nordic country	23,899	2.95	2.61
Non-Nordic country	103,805	12.80	1.63
<i>Maternal age at first-born child</i>			
Less than 20 years old	15,813	1.95	5.79
20 to 25 years old	144,449	17.79	3.79
25 to 30 years old	287,310	35.39	2.53
30 to 35 years old	241,589	29.76	2.21
35 years or older	122,642	15.11	2.28
<i>Paternal age at first-born child</i>			
Less than 20 years old	4,003	0.49	5.82
20 to 25 years old	71,514	8.81	4.30
25 to 30 years old	232,037	28.58	2.85
30 to 35 years old	266,668	32.85	2.33
35 years or older	237,581	29.27	2.38
<i>Parental mental disorder</i>			
No history of mental disorder	649,927	80.06	1.99
Any lifetime mental disorder	161,876	19.94	5.48

Table 2

Hazard ratios (HRs) with corresponding 95% confidence intervals for disposable family income and subsequent offspring ADHD.

Mean family income, years 0–5	Model I	Model II	Model III	Model IV
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
<i>Categorical exposure</i>				
Quartile 1 (lowest)	2.52 [2.42; 2.63]	2.09 [2.00; 2.19]	1.61 [1.40; 1.84]	1.37 [1.07; 1.75]
Quartile 2	1.52 [1.45; 1.58]	1.36 [1.30; 1.42]	1.28 [1.12; 1.45]	1.37 [1.12; 1.68]
Quartile 3	1.20 [1.14; 1.25]	1.13 [1.08; 1.18]	1.14 [1.01; 1.28]	1.23 [1.04; 1.45]
Quartile 4 (highest)	-	-	-	-
<i>Binary exposure (median split)</i>	1.82 [1.77; 1.87]	1.57 [1.52; 1.62]	1.27 [1.16; 1.39]	1.14 [1.00; 1.30]

Note:

Model I: Adjusted for sex, birth year, and parity.

Model II: Model I + adjusted for mother's country of birth (Sweden, other Nordic country, Non-Nordic country), parental history of mental disorders and ages at birth of first child.

Model III: Cousin comparisons + adjusted for all other confounders in Model I and II.

Model IV: Sibling comparisons + adjusted for sex, birth year and parity.