JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 24, Number 6, 2014

Pp. 1–9
DOI: 10.1089/cap.2014.0020

Original Article

Cardiovascular Safety of Stimulants in Children with Attention-Deficit/Hyperactivity Disorder: A Nationwide Prospective Cohort Study

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Abstract

Objective: The purpose of this study was to determine whether stimulant users are at higher risk of a later cardiovascular event than are non-users, examining this association in both a national cohort and a population-based sample of children and adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD). We also aim to examine a possible dose-response relationship in such an association.

Methods: We conducted a longitudinal, prospective cohort study of all children born in Denmark between 1990 and 1999. Within this cohort, children with ADHD were identified. Data from national health registers on psychiatric and somatic diagnoses, stimulant prescriptions, cardiovascular risk factors, pre- and perinatal and sociodemographic covariates in all children and their parents were merged, using the unique personal identification number. Hazard ratios (HR) for cardiovascular events were estimated using Cox regression, adjusted for other known risk factors.

Results: In the total population ($n = 714{,}258$ contributing a total of 6,767,982 person-years) use of stimulants increased the risk of a cardiovascular event; adjusted HR = 1.83 (1.10–3.04). In children with ADHD ($n = 8300$) stimulant treatment also increased the risk of a cardiovascular event (adjusted HR = 2.20 [2.15–2.24]), with a complex time-dependent dose-response relationship.

Conclusions: This is the first nationwide cohort study of the cardiovascular safety of stimulants in children and adolescents, and it represents, to our knowledge, the longest prospective follow-up study. Cardiovascular events were rare but twice as likely in stimulant users as in non-users, both in the total national population and in children with ADHD. We found a complex, time- and dose-dependent interrelationship between cardiovascular adverse events and stimulant treatment in children and adolescents. Our results suggest a safety signal with an increased risk of cardiovascular disease associated with stimulant treatment in children and adolescents, even after adjusting for a number of potential confounders.

Introduction

Worldwide, an increasing number of children and adolescents with attention-deficit/hyperactivity-disorder (ADHD) (American Psychiatric Association 2000) are treated with psychostimulants (Lang et al. 2010). Concern regarding the cardiovascular safety of these agents persists, and case reports of sudden death or acute myocardial infarction have been published (Jiao et al. 2009; Ruwald et al. 2012). Stimulants significantly increase blood pressure and heart rate in patients with ADHD (Findling et al. 2001; Samuels et al. 2006; Mick et al. 2013), and although these cardiovascular effects are usually small in magnitude, they contribute to the concern of a possible association with serious adverse cardiovascular events (Graham and Coghill 2008; Graham et al. 2011; Vitiello et al. 2012).

In a review from 2012, Westover and Halm identified 10 population-based observational studies on the cardiovascular risks of stimulant medications (Westover and Halm 2012). The review

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Funding: The study was funded by grants from the Lundbeck Foundation, the Danish Council for Independent Research (Sapere Aude Starting Grant, 10-079597), Centre For Integrated Register-Based Research at Aarhus University (CIRRAU), The Foundation for Psychiatric Research in the Region of Southern Denmark, and Slagtermester Max Wørzner and Inger Wørzners Foundation.

concluded that one of the seven studies in children and adolescents and two of the three in adults found an association. (See Supplementary Table S1 for an overview of these studies. Supplementary material is available in the online version of this article at www.liebertpub.com/jcap). It also concluded that the relationship of time and dose of stimulants to the risk of adverse cardiovascular events is unknown. The reviewed studies had methodological limitations, which made the interpretation of the results difficult, and the authors suggested that in order to overcome these limitations future observational studies should include large population-based samples, use hard clinical outcomes, examine time and dose of stimulants, attempt to control for confounding by indication and contraindication, reduce risk of selection bias by, for example, not only comparing users with non-users, and adjust for confounders by using appropriate statistical approaches and by including sensitivity analyses of subsamples with and without predisposing cardiovascular risk factors (Westover and Halm 2012).

We performed the first nationwide cohort study including a large number of children and adolescents diagnosed with ADHD, with the longest prospective follow-up, and used hard data from the Danish national health registries on measurements of exposure, predictors, potential confounders, effect modifiers, and outcomes, with the following three objectives: 1) To examine whether stimulant use compared with non-use was associated with cardiovascular disease in a total Danish population-sample; 2) to examine the same association in a population-based sample of children and adolescents with a diagnosis of ADHD; and 3) to examine the modifying effect of time and dose of stimulants and later cardiovascular disease.

Methods

Utilizing data from a number of national Danish registries (See Table 1), we applied the unique personal identification number (ID) as a key identifier, to combine and merge data across registries at the level of each individual.

Participants

We identified a cohort of all children born in Denmark between 1990 and 1999 ($n = 714{,}258$) from the Danish Civil Registration System (Pedersen et al. 2006). Within this birth cohort, we identified all children diagnosed with ADHD after the age of 5 years ($n = 8300$), using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (World Health Organization 1993) diagnostic codes of F90.0, F90.1, F90.8, or F90.9, from either the Danish Psychiatric Central Register (DPCR) or the Danish National Hospital Register (DNHR). A total of 419 individuals were diagnosed with ADHD before the age of 5 years, and one additional individual was treated with ADHD medication before the age of 5 years, and these 420 individuals were excluded. We have previously examined the prevalence and predictors of ADHD medications within this cohort (Dalsgaard et al. 2013a, 2014). We collected data on all lifetime

Table 1. The National Registers Providing Data for the Study and the Covered Time Period

Danish Civil Registration System (DCRS): 1974–2010
- Identification of the unique personal identification (ID) number as a key identifier of all live-born children in Denmark between January 1, 1990 and December 31, 1999
- Identification of both parents of children in this cohort

Danish Psychiatric Central Register (DPCR): 1960–2010
- ID number
- Lifetime ICD-10 psychiatric diagnoses from all inpatient admissions (since 1960) and outpatient contacts (since 1995) of all children in the cohort and their parents
- Information on date of admission, date of discharge, identification of the hospital, ICD-10 diagnoses, and conditions of admission (voluntary or coercive) for all contacts

Integrated Database for Longitudinal Labour Market Research (IDA): 1980–2010
- ID number
- Age of mother and father
- Level and length of education of mother and father
- Parental employment status of mother and father on November 1 for each calendar year
- Length of unemployment periods for mothers and fathers during each calendar year
- Gross income of both parents for each calendar year

Danish Medical Birth Register (MBR): 1973–2010
- ID number
- Apgar score
- Birth weight
- Birth complications
- Maternal smoking during pregnancy

Danish National Hospital Register (DNHR): 1980–2010
- ID number
- Lifetime ICD-10 cardiovascular diseases (I00-I99) from all inpatient admissions (since 1980) and outpatient contacts (since 1995) for all children in the cohort and their parents
- Holds information on ICD-10 diagnoses, the date of admission, date of discharge, and ID of the hospital

Danish Register of Medical Product Statistics (DRMPS): 1995–2008
- ID number for each prescription
- All prescriptions for all children in the cohort and their parents
- Information on the anatomical therapeutic chemical (ATC-code), the date of purchase, defined daily doses (DDD), and brand name

We included the following ATC-codes for stimulants treatment:
- Amphetamine (N06BA01)
- Dexamphetamine (N06BA02)
- Methylphenidate (N06BA04)

Cardiovascular risk factors, either in the child or in one of the parents:
- Any cardiovascular disease in parents (I00–I99)
- Any respiratory disease in parents (J00–J99)
- Congenital cardiovascular disease (Q20–28)
- Any cardiovascular disease in the child before the age of 5
- Fragile X (Q99.2)
- Down syndrome (Q90.x)
- Diabetes (E10–14)
- Cardiovascular medication (ATC-C code)
- Respiratory medication (ATC-R ode)
- Neuroleptics (ATC-N05A code)

ICD 10, International Statistical Classification of Diseases and Related Health Problems, 10th revision.

psychiatric and somatic diagnoses, cardiovascular risk factors, and drug prescriptions, as well as data concerning relevant socio-demographic variables. See Table 2 for baseline characteristics.

Cardiovascular risk factors and definition of outcome

Risk factors for cardiovascular diseases were measured before the age of 5 years, and were defined as a diagnosis of congenital heart disease, cardiovascular disease, Fragile X, Down syndrome, or diabetes, or a prescription for the child of neuroleptics or cardiovascular or respiratory medication (anatomical therapeutic chemical [ATC] codes N05A, R, or C, respectively; except C05A) for the child. Parental cardiovascular disease, respiratory disease, or diabetes or prescriptions with an ATC-code N05A, R, or C (except C05A), were also considered cardiovascular risk factors. The ICD-10 and ICD-9 diagnoses are shown in Supplementary Table S2 (see the online article for supplementary material at http://www.liebertonline.com/jcap). The outcome in this study was defined as the child having a hospital contact (inpatient ward, outpatient clinic, or visit to an emergency ward) with a diagnosis of a cardiovascular disease, defined as an I00-I99 diagnosis in the DNHR. In the main analyses, we differentiated these outcome contacts from other contacts, for example, those resulting from ADHD or follow-up of ADHD treatment, by including only 1) outcome data from the DNHR, which includes contacts from departments dealing with somatic health (and we did not include outcome data from the DPCR) and 2) outcome contacts with a cardiovascular diagnosis.

Stimulant treatment

The Danish Register of Medical Product Statistics gave data on all drug purchases for cohort members and their parents. Stimulant treatment was defined as purchase of a drug containing amphetamine (N06BA01), dexamphetamine (N06BA02), or methylphenidate (N06BA04). A lifetime history of drug utilization was constructed based on dates of prescriptions of medication as well as the number of defined daily doses (DDD) of 30 mg of methylphenidate purchased each day for a child from the age of 5 years, onwards. The history of drug utilization, including timing and dosing, was estimated by combining data on intervals between prescriptions and number of DDDs per prescription, and date of discontinuation of treatment was estimated based on number of DDDs on the last prescription, and extrapolating the estimated dose from the period preceding the last prescription. The daily dosage of methylphenidate was divided into three groups – >0 but <15 mg/day, between 15 and 30 mg/day, and >30 mg/day – and was measured at three points in time: At the date of the cardiovascular event, and 3 and 12 months prior to this date.

Potentially confounding risk factors

Additional risk factors included early measurements of perinatal and child health (e.g., maternal smoking during pregnancy, length of gestation, birth complications, low birth weight, Apgar score, number of injuries resulting in hospital contacts, and visits to emergency wards before the child was 5 years of age) and comorbid psychiatric conditions (Dalsgaard et al. 2002; Linnet et al. 2003). We also included data on any psychiatric diagnoses in parents. In addition, we included a number of demographic and socioeconomic background variables: Gender, region, and year of birth for the child, and age, education, and occupation for the parents.

Statistics

Data on exposure (stimulant treatment) and outcome (cardiovascular events) were treated as time-dependent variables, and we used Cox regression to estimate the impact of stimulant treatment and dosage on the hazard ratio (HR) for a cardiovascular event; 95% confidence intervals (CIs) were calculated for HRs. Subjects were followed until the date of outcome or censored at the date of death or at the end of our observation (December 31, 2008), whichever came first. In sensitivity analyses, we stratified on the presence of a risk factor for cardiovascular diseases. We also performed analyses on a subset of the sample, excluding patients who had serious cardiovascular events or who died during follow-up. In a small proportion of the ADHD sample ($<1\%$) we did not have complete data concerning all of the covariates. However, stepwise inclusion of covariates in the model did not change the estimated hazard ratios. We also included a covariate for missing data in the adjusted analyses. The statistical package SAS 9.2 was used in the analyses (SAS Institute Inc. 2000). The study was approved by the DCPR (7-505-29-1470/1) and by the Danish Data Protection Agency (2010-41-4766).

Results

Stimulant use versus non-use in the national population

Among 714,258 subjects (6,767,982 person-years), with each subject contributing with a mean of 9.5 years of observation, a total of 5734 individuals had a cardiovascular event (84 events per 100,000 person-years). There was an increased risk of any cardiovascular event in stimulant users compared with non-users in the total population, with an adjusted HR of 1.83 (95% CI 1.10–3.04).

Use of stimulants versus non-use in subjects with ADHD

Among children with ADHD ($n=8{,}300$) we identified 111 cardiovascular events (170 events per 100,000 person-years). In children with ADHD, stimulant use versus non-use was associated with an increased hazard for a cardiovascular event (adjusted HR = 2.34 [1.15–4.75]). The 111 cardiovascular events in children with ADHD included hypertension (8%), ischemic heart disease (2%), pulmonary heart disease ($<1\%$), arrhythmias (23%), cardiac arrest ($<1\%$), heart failure (2%), heart disease caused by rheumatic fever (2%), heart disease not otherwise specified (NOS) (14%), cerebrovascular disease (9%), and cardiovascular disease NOS (40%).

Change of dosage through the study period

For 57% of children with ADHD, who were treated with stimulants and experiencing a cardiovascular event, stimulant dose had been reduced during the 12 months prior to the event. Only 30% of children without a cardiovascular event had experienced a decrease in stimulant dose within the last year ($\chi^2=9.35$, $df=2$, $p=0.0022$). Similarly, significantly more children with a cardiovascular event discontinued stimulant treatment or had their dose reduced from high/medium to low; 43% compared with only 24% among those who did not have a cardiovascular event ($\chi^2=5.64$, $df=2$, $p=0.017$). For additional data on dose changes during follow-up, see Supplementary Table S3 (see the online article for supplementary material at http://www.liebertonline.com/jcap).

Table 2. Demographic, Perinatal and Clinical Characteristics of ADHD Sample at Baseline

	Not treated with stimulants (n = 2818)[a]		*Treated with stimulants (n = 5482)*[a]	
Variable	*Mean (SD)*	n *(%)*	*Mean (SD)*	n *(%)*
ADHD and treatment				
Age at ADHD diagnosis	10.01 (3.22)		10.03 (3.00)	
Age at initiation of stimulant treatment	-		10.48 (2.88)	
Duration of stimulant treatment, years	-		2.45 (2.11)	
Child[b]				
5 min Apgar score	9.74 (1.17)		9.76 (1.07)	
Gestation length (weeks)	39.25 (2.40)		39.29 (2.28)	
Gender (male)		**2203 (78.2%)**		**4511 (82.3%)**
Birth weight < 1500 g		50 (1.9%)		68 (1.3%)
Birth weight 1500–2500 g		161 (6.0%)		326 (6.2%)
Birth weight > 2500 g		2452 (92.1%)		4831 (92,5%)
Complications at birth		792 (28.1%)		1634 (29.8%)
Congenital heart disease at birth (Q20–28)		60 (2.1%)		93 (1.7%)
Cardiovascular disease before age 5		40 (1.4%)		69 (1.3%)
Fragile X syndrome		0 (0.0%)		2 (0.0%)
Down syndrome		5 (0.2%)		2 (0.0%)
Diabetes		1 (0.0%)		3 (0.1%)
Neuroleptic treatment before age 5		0 (0.0%)		3 (0.1%)
Heart medication before age 5		**15 (0.5%)**		6 (0.1%)
Comorbid psychiatric condition		1750 (62.1%)		3450 (62.9%)
Affective disorder and anxiety		**275 (9.8%)**		**459 (8.4%)**
Number of psychiatric diagnoses	2.19 (1.33)		2.17 (1.28)	
Number of injuries before age 5	**1.01 (1.44)**		**1.15 (1.58)**	
Number of hospital contacts before age 5	4.95 (4.97)		4.99 (5.18)	
Mother[b]				
Age, mean (SD)	**32.13 (5.21)**		**31.79 (5.03)**	
Length of education (years)	11.52 (2.37)		11.52 (2.35)	
Income (1,000 $/year 2004)	**38.3 (16.0)**		**39.3 (15.4)**	
Married/cohabiting with the child's father		1698 (61.9%)		3266 (61.1%)
High school or less		1297 (48.3%)		2502 (47.5%)
Unemployed < 13 weeks		2237 (81.6%)		4,395 (82.2)
Unemployed 13–26 weeks		268 (9.8%)		508 (9.5%)
Unemployed > 26 weeks		237 (8.6%)		441 (8.3%)
Employed in November		**1707 (62.3%)**		**3350 (66.1%)**
Psychiatric diagnosis		347 (12.3%)		623 (11.4%)
Cardiovascular disease		171 (6.1%)		330 (6.0%)
Respiratory disease		565 (20.1%)		1157 (21.1%)
Smoking during pregnancy		299 (12.7%)		558 (12.2%)
Heart medication		257 (9.1%)		444 (8.1%)
Diabetes		30 (1.1%)		53 (1.0%)
Father[b]				
Age, mean (SD)	35.10 (6.33)		34.81 (6.01)	
Length of education (years)	**11.47 (2.44)**		**11.35 (2.38)**	
Income (1,000 $/year 2004)	57.3 (33.2)		58.0 (33.9)	
High school or less		1032 (41.4%)		2069 (42.4%)
Unemployed < 13 weeks		2271 (88.4%)		4472 (89.0%)
Unemployed 13–26 weeks		152 (5.9%)		267 (5.3%)
Unemployed > 26 weeks		146 (5.7%)		286 (5.7%)
Employed in November		2151 (83.7%)		4291 (85.4%)
Psychiatric diagnosis		279 (10.5%)		546 (10.6%)
Cardiovascular disease		170 (6.4%)		330 (6.4%)
Respiratory disease		427 (16.0%)		816 (15.8%)
Heart medication		121 (4.5%)		249 (4.8%)
Diabetes		28 (1.1%)		42 (0.8%)

Bold indicates a significant difference between the never and ever stimulant group at the 5% level.
[a]For some baseline variables missing data.
[b]Covariates measured when the child was 4 years of age, unless otherwise specified.
ADHD, attention-deficit/hyperactivity disorder.

Dose-response relationship in the adjusted analyses

We did, in the adjusted survival analyses, find a dose-response relationship, with high doses associated with an increased risk of cardiovascular events (see Table 3). Specifically, children prescribed >30 mg of methylphenidate per day 12 months prior to the event had a higher risk than children not in treatment (adjusted HR = 2.24 [1.20–4.20]).

In contrast, examining the dose at the time of the cardiovascular event, we found an inverse relationship between cardiovascular events and the current dose, with the highest risk in the group of children being prescribed the lowest dose (see Table 4).

Sensitivity analyses

In the stratified analyses, children with known predisposing cardiovascular risk factors were at similar risk of a cardiovascular event (adjusted HR = 2.01, [1.98–2.06]) as children with no known predisposing cardiovascular risk factors treated with the same dose (adjusted HR = 2.46, [2.40–2.51]). Among children with ADHD, five had experienced a serious cardiovascular event, including cardiac arrest, uncompensated heart disease, and ischemic heart disease. None of these children had been treated with stimulants. When excluding these cases, the HRs remained unchanged (data not shown). During the study period, six children died, but none of them died from cardiovascular causes. All six had previously been treated with stimulants and three were still receiving treatment at the time of death. None of these six cases had ever received a cardiovascular diagnosis. The HRs remained unchanged when excluding these cases from the analyses (data not shown). For a tabulation of dose changes in these six individuals, see Supplementary Table S4 (see the online article for supplementary material at http://www.liebertonline.com/jcap).

Discussion

In this large nationwide cohort study, we found that stimulant treatment increased the risk of cardiovascular events both in the total national population and in a population-based sample of children and adolescents with ADHD. This is consistent with some of the findings in one of the seven previous studies within this age group (Winterstein et al. 2007), although we found a higher estimated risk (2.2 vs. 1.2). Compared with the study by Winterstein et al., the observation period of our study was much longer (9.5 vs. 2.3 years) and this may explain the difference in estimated risk. Furthermore, our prospective follow-up may also offer less biased results than the previous retrospective studies in children and adolescents (Winterstein et al. 2007, 2009; Cooper et al. 2011; Schelleman et al. 2011; Olfson et al. 2012) and in adults (Holick et al. 2009; Habel et al. 2011; Schelleman et al. 2012). Only two of the previous studies included patients with ADHD and estimated the effect of treatment (Winterstein et al. 2007; Olfson et al. 2012), whereas the rest of the previous studies compared users to non-users, essentially comparing patients with ADHD to normal controls without ADHD. These two groups are likely to differ in a number of ways in addition to their treatment status, and hence would not have comparable cardiovascular risk profiles. There is some evidence to suggest that ADHD may be more prevalent in children with a cardiovascular disease than in the general population (Vetter et al. 2008). In a recent study of 13,460 new stimulant users, 2% had a preexisting cardiovascular disorder compared with only 1.2% of non-users (Kraut et al. 2013).

We also found that children without predisposing cardiovascular risk factors were at increased risk of a cardiovascular event. This is in contrast to the negative findings in a smaller study, which excluded children with previous cardiovascular symptoms or diagnosis, rather than adjusting or stratifying for such a preexisting risk (Olfson et al. 2012). Similarly to many previous studies, we have adjusted risk estimates for child cardiovascular risk factors, but in addition, we were also able to follow parents prospectively and adjust for a large number of covariates in parents, including parental cardiovascular risk, and socioeconomic and psychiatric history; hence our results may offer a less biased estimate of the association.

Importantly, we also found a dose-response relationship between stimulant treatment and cardiovascular events. Children with ADHD previously treated with high doses were 2.2 times more likely to experience a cardiovascular event than were children with ADHD who were treated with smaller doses. In contrast, when these analyses were performed using the stimulant dosage at the time of the cardiovascular event, we found a significant inverse dose-response relationship. Only one previous study has examined a dose-response relationship, and found current treatment with methylphenidate to be associated with an increased risk of serious cardiovascular events and death in adults with ADHD, with an HR for all causes of death of 1.74 (1.60–1.89) compared with non-users (Schelleman et al. 2012). Similar to our findings, the study found that the risk was inversely related with current dose. Specifically, adults with ADHD treated with <20 mg of methylphenidate per day had double the risk of sudden death as patients treated with >20 mg per day. We also found an inverse dose-response relationship with current dose, and our data suggest that high doses of methylphenidate followed by a lower dose may contribute to an increased long-term risk of adverse cardiovascular events.

A possible biological mechanism for the time-dose-response relationship in our study may involve alterations to cardiac sympathetic function via altered striatal dopamine transporter levels in the brain, mediated through treatment and discontinuation of treatment with stimulants. Drug-näive adults with ADHD have higher density of dopamine transporters (DAT) in striatum (Dresel et al. 2000; Krause et al. 2000), and exposure to stimulants further increases density of DAT in the striatum even after discontinuation of the medication (Fusar-Poli et al. 2012). In animals, DAT are not only found in the central nervous system but also in the myocardium (Palomar et al. 2011). The corrected cardiac repolarization time (QTc interval) is inversely correlated with striatal DAT density (Kauppila et al. 2009). Reports on whether stimulants prolong the QTc interval in patients with ADHD during active treatment are inconsistent (Vetter et al. 2008; Arcieri et al. 2012; Hamilton et al. 2012; Martinez-Raga et al. 2013); and little is known on the effect of discontinuation of stimulant treatment on QTc interval. Animal studies have found that stimulants prolong action potential duration and resting membrane potential in sinoatrial cells (Aileru and Carpentier 1996), affect action-potential repolarization in ventricular myocytes (Casis et al. 2000), affect cell membranes in the myocardium (Henderson and Fischer 1995), and have dose-related structural effects on capillary endothelial cells (Bahcelioglu et al. 2009). Drug-näive children with ADHD have higher heart rates than controls (Huang and Tsai 2011; Imeraj et al. 2011; Buchhorn et al. 2012a) and reduced heart rate variability (HRV), which is normalized by methylphenidate (Buchhorn et al. 2012b).

Hence, theoretically, discontinuation of treatment may shorten the QTc interval or result in reemergence of HRV in children with ADHD. Short QT syndrome is known to be clinically associated with atrial and ventricular fibrillation, syncope, and sudden cardiac

Table 3. Adjusted Hazard Ratios for Cardiovascular Disease in Children with ADHD

Variable	*Hazard ratio*	*95% Confidence interval*	
Medicine dosage (12 months before the cardiovascular event)			
No stimulant medication(reference)	1		
Dosage < 15 mg methylphenidate	1.43	0.57	3.59
Dosage 15–30 mg methylphenidate	1.67	0.84	3.32
Dosage > 30 mg methylphenidate	**2.24**	**1.20**	**4.21**
Child[a]			
Male (0/1)	0.71	0.45	1.11
5 min Apgar score	0.50	0.04	6.02
Birth weight < 1500 g	0.33	0.04	2.71
Birth weight 1500–2500 g	1.07	0.52	2.19
Birth weight > 2500 g (reference)	1.00		
Gestation length (weeks)	1.00	0.94	1.07
Child health missing	0.67	0.05	9.43
Complications at birth	1.21	0.80	1.85
Heart disease at birth (Q20–28)	**4.57**	**2.29**	**9.10**
Cardiovascular disease before age 5	**2.77**	**1.22**	**6.32**
Diabetes	**38.65**	**4.44**	**336.78**
Treatment with heart medication before age 5	0.86	0.13	5.70
Any comorbid psychiatric condition	1.20	0.68	2.13
Number of comorbid psychiatric diagnoses	**1.21**	**1.05**	**1.39**
Comorbid affective or anxiety disorder	1.52	0.87	2.64
Number of injuries before age 5	0.97	0.82	1.14
Number of contacts with a hospital before age 5	**1.04**	**1.02**	**1.07**
Number of visits to the emergency ward before age 5	1.11	0.98	1.27
Mother[a]			
Age	1.00	0.95	1.04
Educational level, high school or less	1.00	0.54	1.84
Length of education (years)	1.04	0.92	1.19
Unemployed < 13 weeks	0.90	0.46	1.78
Unemployed 13–26 weeks	0.70	0.27	1.79
Unemployed > 26 weeks (reference)	1		
Employed in November	1.16	0.71	1.91
Psychiatric diagnoses	0.88	0.46	1.67
Cardiovascular disease	1.31	0.61	2.83
Respiratory disease	0.66	0.38	1.13
Smoking during pregnancy	1.50	0.59	3.83
Data on smoking missing	1.29	0.61	2.76
Diabetes	0.80	0.10	6.39
Cardiovascular medication (ATC-C code)	0.81	0.38	1.74
Data on mother missing	2.66	0.37	19.22
Father[a]			
Age	1.02	0.99	1.04
Educational level, high school or less	1.02	0.54	1.95
Length of education (years)	0.98	0.85	1.13
Unemployed < 13 weeks	1.09	0.46	2.57
Unemployed 13–26 weeks	1.86	0.64	5.41
Unemployed > 26 weeks (reference)	1		
Employed in November	1.64	0.82	3.29
Psychiatric diagnosis	0.92	0.46	1.84
Cardiovascular disease	0.78	0.33	1.85
Respiratory disease	0.91	0.51	1.60
Diabetes	1.95	0.46	8.25
Cardiovascular medication (ATC-C code)	2.17	0.96	4.92
Data on father missing	1.75	0.25	12.23
Regions[a]			
Northern Jutland	0.68	0.25	1.83
Central Jutland	0.88	0.52	1.49
Southern Jutland	0.72	0.39	1.32
Zealand	1.37	0.78	2.41
Copenhagen area (reference)	1		

Observations: Days 23,736,162 /Individuals 8295.
Bold indicates a significant difference between the never and ever stimulant group at the 5% level.
[a]Covariates measured when the child was 4 years of age, unless otherwise specified.
ADHD, attention-deficit/hyperactivity disorder; ATC-C, anatomical therapeutic chemical code C.

Table 4. Dose-Response Relationship in the Association Between Stimulant Treatment and an Adverse Cardiovascular Event in Children with ADHD

	Adjusted hazard ratio[a]	*95% confidence interval*	
Stimulant dosage at the time of the adverse cardiovascular event ($n = 8300$)			
Non-user (reference)	1		
Dosage < 15 mg methylphenidate	**2.31**	**1.18**	**4.53**
Dosage 15–30 mg methylphenidate	1.28	0.65	2.53
Dosage > 30 mg methylphenidate	1.08	0.54	2.14
Stimulant dosage 3 months before the adverse cardiovascular event ($n = 8298$)			
Non-user (reference)	1		
Dosage < 15 mg methylphenidate	**2.04**	**1.01**	**4.12**
Dosage 15–30 mg methylphenidate	1.42	0.74	2.73
Dosage > 30 mg methylphenidate	0.82	0.37	1.81
Stimulant dosage 12 months before the adverse cardiovascular event ($n = 8295$)			
Non-user (reference)	1		
Dosage < 15 mg methylphenidate	1.43	0.57	3.59
Dosage 15–30 mg methylphenidate	1.67	0.84	3.32
Dosage > 30 mg methylphenidate	**2.24**	**1.20**	**4.21**

Bold indicates a significantly increased hazard ratio compared to the reference group.

[a]Hazard ratios were adjusted for all covariates mentioned in Table 3.

ADHD, attention-deficit/hyperactivity disorder.

death (Schimpf et al. 2008), and reduced HRV is also a known risk factor for cardiovascular events (Tsuji et al. 1996).

Whether a decrease from high doses of stimulants can have enduring effects on cardiac sympathetic function via altered striatal DAT and whether a dose reduction or discontinuation can possibly affect the QT interval may be worthy of further investigations. More research is needed to gain a clearer understanding of the interactions among stimulant dosage, dosage changes, and length of exposure on cardiac, sympathetic, parasympathetic, and striatal function.

As with other registry-based studies, our study has a number of methodological weaknesses. Systematic information bias may be one limitation of using register data, particularly if cardiovascular disease was diagnosed preferentially in one group compared with the other. All subjects identified as having an ADHD diagnosis in this study were followed at an outpatient clinic at a hospital department where, in principle, they were eligible for pharmacological intervention. However, cardiovascular symptoms may have been more likely identified in children receiving pharmacological treatment, and minor cardiovascular symptoms may have led to a reduction of dose. In an attempt to adjust for group differences, we have, in our data set, included a number of potential confounding covariates including a rich set of background variables indicating the severity of the symptoms and geographical variation in pharmacological treatment practices, as well as potential predisposition for cardiovascular disease. In addition, diagnoses in the registers are clinical diagnoses, not the result of systematic well-described uniform assessments. However, the validity of the clinical ADHD diagnoses in the registers has been shown to be good (Linnet et al. 2009; Dalsgaard et al. 2013b). This was not a randomized controlled trial. Nationwide register-based cohort studies, on the other hand, offer alternative opportunities to study large samples less prone to selection bias for long periods, without attrition, and with the ability to adjust the analyses for a number of important covariates that may act as potential confounders. Still, our results on the inverse relationship between stimulant dose and risk of cardiovascular events may be biased by residual confounding, and should be interpreted cautiously and in light of this.

Conclusions

We present the first nationwide cohort study of the cardiovascular safety of stimulants, and, to our knowledge, the longest prospective follow-up study of this. Cardiovascular events were rare, but associated with stimulant treatment, with a 1.8-fold increased risk in the total population and a 2.2-fold increased risk in children and adolescents with ADHD. Our study of a possible dose-response relationship suggests a complex, time- and dose-dependent interrelationship between cardiovascular adverse events and stimulant treatment and cardiovascular effects of discontinuation of stimulant treatment in children and adolescents with ADHD.

Clinical Significance

If replicated in other studies, our findings may be of public health significance, especially given the increasing use of psychostimulants. Our findings may also be relevant for future revisions of the international treatment guidelines with regard to the use of high doses of methylphenidate, and regarding the recommendation of drug holidays.

Acknowledgments

We thank Niels Gregersen for help in data management, and Emily Leckman-Westin for help in revising an earlier draft of the manuscript. We also thank the funding sources for financial support for the study, namely the Lundbeck Foundation, the Danish Council for Independent Research (Sapere Aude Starting Grant, 10-079597), Centre For Integrated Register-Based Research at Aarhus University (CIRRAU), The Foundation for Psychiatric Research in the Region of Southern Denmark and Slagtermester Max Wørzner and Inger Wørzners Foundation.

Disclosures

No competing financial interests exist.

References

Aileru AA, Carpentier RG: Mechanisms of the in vitro effects of amphetamine on rat sinus node automaticity and membrane potentials of atrial fibers. J Electrocardiol 29:123–130, 1996.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision. Washington, DC; American Psychiatric Association, 2000.

Arcieri R, Germinario EAP, Bonati M, Masi G, Zuddas A, Vella S, Chiarotti F, Panei, Italian Attention-Deficit/Hyperactivity Disorder Regional Reference Centers: Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. J Child Adolesc Psychopharmacol 22:423–431, 2012.

Bahcelioglu M, Gozil R, Take G, Elmas C, Oktem H, Kadioglu D, Calguner E, Erdogan D, Sargon MF, Yazici AC, Tas M, Bardakci Y, Senol S: Dose-related immunohistochemical and ultrastructural changes after oral methylphenidate administration in cerebrum and cerebellum of the rat. World J Biol Psychiatry 10:531–543, 2009.

Buchhorn R, Conzelmann A, Willaschek C, Stork D, Taurines R, Renner TJ: Heart rate variability and methylphenidate in children with ADHD. Atten Defic Hyperact Disord 4:85–91, 2012a.

Buchhorn R, Muller C, Willaschek C, Norozi K: How to predict the impact of methylphenidate on cardiovascular risk in children with attention deficit disorder: Methylphenidate improves autonomic dysfunction in children with ADHD. ISRN Pharm 2012:170935, 2012b.

Casis O, Espiña L, Gallego M: Effects of amphetamine on calcium and potassium currents in rat heart. J Cardiovasc Pharmacol 36:390–395, 2000.

Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC, Murray KT, Quinn VP, Stein CM, Callahan ST, Fireman BH, Fish FA, Kirshner HS, O'Duffy A, Connell FA, Ray WA: ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med 365:1896–1904, 2011.

Dalsgaard S, Leckman JF, Nielsen HS, Simonsen M: Gender and injuries predict stimulant medication J Child Adolesc Psychopharmacol. 2014 [Epub ahead of print].

Dalsgaard S, Mortensen PB, Frydenberg M, Thomsen PH: Conduct problems, gender and adult psychiatric outcome of children with attention-deficit hyperactivity disorder. Br J Psychiatry 181:416–421, 2002.

Dalsgaard S, Nielsen HS, Simonsen M: Five-fold increase in national prevalence rates of attention-deficit/hyperactivity disorder medications for children and adolescents with autism spectrum disorder, attention-deficit/hyperactivity disorder, and other psychiatric disorders: A Danish register-based study. J Child Adolesc Psychopharmacol 23:432–439, 2013a.

Dalsgaard S, Humlum MK, Nielsen HS, Simonsen M. Common Danish standards in prescribing medication for children and adolescents with ADHD. Eur Child Adolesc Psychiatry DOI: 10.1007/s00787-013-0508-5, 2013b.

Dresel S, Krause J, Krause KH, LaFougere C, Brinkbaumer K, Kung HF, Hahn K, Tatsch K: Attention deficit hyperactivity disorder: binding of [99mTc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment. Eur J Nucl Med 27:1518–1524, 2000.

Findling RL, Short EJ, Manos MJ: Short-term cardiovascular effects of methylphenidate and Adderall. J Am Acad Child Adolesc Psychiatry 40:525–529, 2001.

Fusar–Poli P, Rubia K, Rossi G, Sartori G, Balottin U: Striatal dopamine transporter alterations in ADHD: Pathophysiology or adaptation to psychostimulants? A meta-analysis. Am J Psychiatry 169:264–272, 2012.

Graham J, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, Dopfner M, Hamilton R, Hollis C, Holtmann M, Hulpke–Wette M, Lecendreux M, Rosenthal E, Rothenberger A, Santosh P, Sergeant J, Simonoff E, Sonuga–Barke E, Wong IC, Zuddas A, Steinhausen HC, Taylor E: European guidelines on managing adverse effects of medication for ADHD. Eur Child Adolesc Psychiatry 20:17–37, 2011.

Graham J, Coghill D: Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. CNS Drugs 22:213–237, 2008.

Habel LA, Cooper WO, Sox CM, Chan KA, Fireman BH, Arbogast PG, Cheetham TC, Quinn VP, Dublin S, Boudreau DM, Andrade SE, Pawloski PA, Raebel MA, Smith DH, Achacoso N, Uratsu C, Go AS, Sidney S, Nguyen–Huynh MN, Ray WA, Selby JV: ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. JAMA. 306:2673–2683, 2011.

Hamilton RM, Rosenthal E, Hulpke–Wette M, Graham JG, Sergeant J: Cardiovascular considerations of attention deficit hyperactivity disorder medications: A report of the European Network on Hyperactivity Disorders work group, European Attention Deficit Hyperactivity Disorder Guidelines Group on attention deficit hyperactivity disorder drug safety meeting. Cardiol Young 22:63–70, 2012.

Henderson TA, Fischer VW: Effects of methylphenidate (Ritalin) on mammalian myocardial ultrastructure. Am J Cardiovasc Pathol 5:68–78, 1995.

Holick CN, Turnbull BR, Jones ME, Chaudhry S, Bangs ME, Seeger JD: Atomoxetine and cerebrovascular outcomes in adults. J Clin Psychopharmacol 29:453–460, 2009.

Huang YS, Tsai MH: Long-term outcomes with medications for attention-deficit hyperactivity disorder: Current status of knowledge. CNS Drugs 25:539–554, 2011.

Imeraj L, Antrop I, Roeyers H, Deschepper E, Bal S, Deboutte D: Diurnal variations in arousal: a naturalistic heart rate study in children with ADHD. Eur Child Adolesc Psychiatry 20:381–392, 2011.

Jiao X, Velez S, Ringstad J, Eyma V, Miller D, Bleiberg M: Myocardial infarction associated with adderall XR and alcohol use in a young man. J Am Board Fam Med 22:197–201, 2009.

Kauppila E, Vanninen E, Kuusela T, Kaurijoki S, Karhunen L, Pietilainen KH, Rissanen A, Kaprio J, Tiihonen J, Kuikka J: Cardiac repolarization and striatal dopamine transporter function are interrelated. Nucl Med Commun 30:713–717, 2009.

Krause KH, Dresel SH, Krause J, Kung HF, Tatsch K: Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: Effects of methylphenidate as measured by single photon emission computed tomography. Neurosci Lett 285:107–110, 2000.

Kraut AA, Langner I, Lindemann C, Banaschewski T, Petermann U, Petermann F, Mikolajczyk RT, Garbe E: Comorbidities in ADHD children treated with methylphenidate: a database study. BMC Psychiatry 13:11, 2013.

Lang HC, Scheffler RM, Hu TW: The discrepancy in attention deficit hyperactivity disorder (ADHD) medications diffusion: 1994–2003: A global pharmaceutical data analysis. Health Policy 97:71–78, 2010.

Linnet KM, Dalsgaard S, Obel C, Wisborg K, Henriksen TB, Rodriguez A, Kotimaa A, Moilanen I, Thomsen PH, Olsen J, Jarvelin MR: Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: Review of the current evidence. Am J Psychiatry 160:1028–1040, 2003.

Linnet KM, Wisborg K, Secher NJ, Hove Thomsen P, Obel C, Dalsgaard S, Henriksen TB: Coffee consumption during pregnancy and the risk of hyperkinetic disorder and ADHD: A prospective cohort study. Acta Paediatr 98:173–179, 2009.

Martinez–Raga J, Knecht C, Szerman N, Martinez MI: Risk of serious cardiovascular problems with medications for attention-deficit hyperactivity disorder. CNS Drugs 27:15–30, 2013.

Mick E, McManus DD, Goldberg RJ: Meta–analysis of increased heart rate and blood pressure associated with CNS stimulant treatment of ADHD in adults. Eur Neuropsychopharmacol 23:534–541, 2013.

Olfson M, Huang C, Gerhard T, Winterstein AG, Crystal S, Allison PD, Marcus SC: Stimulants and cardiovascular events in youth with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 51:147–156, 2012.

Palomar AR, Larios BN, De Sanchez VC, Perez LM, Lopez Fde L, Flores G, Gomez–Villalobos Mde J: Expression and distribution of dopamine transporter in cardiac tissues of the guinea pig. Neurochem Res 36:399–405, 2011.

Pedersen CB, Gøtzsche H, Møller JØ, Mortensen PB: The Danish Civil Registration System – A cohort of eight million persons. Dan Med Bull 53:441–449, 2006.

Ruwald MH, Ruwald AC, Tonder N: Methylphenidate induced ST elevation acute myocardial infarction [in Danish]. Ugeskr Laeger 174:647–648, 2012.

Samuels JA, Franco K, Wan F, Sorof JM: Effect of stimulants on 24-h ambulatory blood pressure in children with ADHD: A double-blind, randomized, cross-over trial. Pediatr Nephrol 21:92–95, 2006.

SAS Institute Inc.: SAS (release 9.2). Cary, NC: SAS Institute Inc.; 2000.

Schelleman H, Bilker WB, Kimmel SE, Daniel GW, Newcomb C, Guevara JP, Cziraky MJ, Strom BL, Hennessy S: Methylphenidate and risk of serious cardiovascular events in adults. Am J Psychiatry 169:178–185, 2012.

Schelleman H, Bilker WB, Strom BL, Kimmel SE, Newcomb C, Guevara JP, Daniel GW, Cziraky MJ, Hennessy S: Cardiovascular events and death in children exposed and unexposed to ADHD agents. Pediatrics 127:1102–1110, 2011.

Schimpf R, Borggrefe M, Wolpert C. Clinical and molecular genetics of the short QT syndrome. Curr Opin Cardiol 23:192–198, 2008.

Tsuji H, Larson MG, Venditti FJ, Jr., Manders ES, Evans JC, Feldman CL, Levy D: Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 94:2850–2855, 1996.

Vetter VL, Elia J, Erickson C, Berger S, Blum N, Uzark K, Webb CL: Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder [corrected]: A scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. Circulation 117:2407–2423, 2008.

Vitiello B, Elliott GR, Swanson JM, Arnold LE, Hechtman L, Abikoff H, Molina BS, Wells K, Wigal T, Jensen PS, Greenhill LL, Kaltman JR, Severe JB, Odbert C, Hur K, Gibbons R: Blood pressure and heart rate over 10 years in the multimodal treatment study of children with ADHD. Am J Psychiatry 169:167–177, 2012.

Westover AN, Halm EA: Do prescription stimulants increase the risk of adverse cardiovascular events? A systematic review. BMC Cardiovasc Disord 12:41, 2012.

Winterstein AG, Gerhard T, Shuster J, Johnson M, Zito JM, Saidi A: Cardiac safety of central nervous system stimulants in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics 120:e1494–e1501, 2007.

Winterstein AG, Gerhard T, Shuster J, Saidi A: Cardiac safety of methylphenidate versus amphetamine salts in the treatment of ADHD. Pediatrics 124:e75–80, 2009.

World Health Organization: The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. Geneva: World Health Organization; 1993.

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