**Attention-deficit/hyperactivity disorder as a novel risk factor for cardiovascular diseases: a nationwide population-based cohort study**

**Authors and affiliations**

Lin Li,1,2 Zheng Chang,2 Jiangwei Sun,3 Miguel Garcia-Argibays,1 Ebba Du Rietz,2 Maja Dobrosavljevic, 1 Isabell Brikell, 2 Tomas Jernberg,4 Marco Solmi,5,6,7,8 Samuele Cortese,8,9,10 Henrik Larsson 1,2

1. School of Medical Sciences, Örebro University, Örebro, Sweden
2. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
3. The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
4. Department of Clinical Sciences, Danderyd University Hospital, Stockholm, Sweden
5. Department of Psychiatry, University of Ottawa, Ontario, Canada
6. Department of Mental Health, The Ottawa Hospital, Ontario, Canada
7. Ottawa Hospital Research Institute (OHRI) Clinical Epidemiology Program University of Ottawa, Ontario, Canada
8. Centre for Innovation in Mental Health-Developmental Lab, School of Psychology, University of Southampton, and NHS Trust, Southampton, United Kingdom
9. Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York City, New York, USA
10. Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK

\*Correspondence to: Lin Li, PhD, Nobels väg 12a, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden. Phone: +46 019 302191. E-mail: lin.li @ki.se

**ABSTRACT**

Accumulating evidence suggests a higher risk of cardiovascular diseases among individual with psychiatric disorders, but very little is known about the risks of overall and specific groups of cardiovascular diseases in attention-deficit/hyperactivity disorder (ADHD). To fill the knowledge gap, we investigated the prospective associations between ADHD and a wide range of cardiovascular diseases in adults. In this nationwide population-based cohort study, we identified 5,389,519 adults born between 1941 and 1983, without pre-existing cardiovascular diseases, from Swedish registers. The study period was from January 1st, 2001 to December 31st, 2013. Incident cardiovascular disease events were identified according to International Classification of Diseases (ICD) codes. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazards regression models with ADHD as a time-varying exposure. Cumulative incidences were estimated by flexible parametric models and visualized by standardized survival curves. A total of 2,750,621 [51.04%] individuals were males. The mean age at study entry was 38.44 (range 18-60) years. After an average 11.8 years of follow-up, 38.05% of individuals with ADHD, vs 23.57% of the controls, had at least one diagnosis of cardiovascular disease. ADHD was significantly associated with increased risk of any cardiovascular disease (HR=2.05 [95% confidence interval [CI]=1.98-2.13]), after adjusting for sex and year of birth. Further adjustments for birth country, well-established risk factors for cardiovascular diseases, and psychiatric comorbidities, attenuated but could not fully explain the association (HR=1.65, 95%CI= 1.59-1.71). The strongest associations were found for cardiac arrest (HR=1.88, 95%CI=1.49-2.36) and peripheral vascular disease/arteriosclerosis (HR=1.71, 95%CI=1.47-1.99). Stronger associations were observed in males and younger adults, while comparable associations were found among individuals with or without psychotropic medications and family history of cardiovascular diseases.ADHD is a novel independent risk factor for a wide range of cardiovascular diseases. Our findings highlight the importance of carefully monitoring cardiovascular health, and developing age-appropriate and individualized strategies to reduce the cardiovascular risk in adults with ADHD.

**Background**

Attention-deficit/hyperactivity disorder (ADHD), characterized by pervasive and impairing inattention and/or hyperactivity-impulsivity, is one of the most common neurodevelopmental disorders, with a global prevalence of about 2-7% in children and 2.5% in adults.1-3 ADHD is comorbid with a number of psychiatric (e.g., anxiety and depression4) and physical (e.g., obesity5 and asthma6) disorders. Prospective studies have previously demonstrated that several psychiatric conditions (e.g., depression,7,8 schizophrenia,9 bipolar disorder,10 and anxiety disorder11) as well as neurodevelopmental disorders (e.g. autism,12,13 intellectual disabilities12 and conduct disorder12) are associated with higher risk of cardiovascular diseases, the leading cause of mortality worldwide.14 The mechanisms linking psychiatric illness to cardiovascular diseases are complex, but risky health behaviours (e.g., smoking, drinking alcohol, substance abuse and sedentary lifestyles),15 and prolonged use of psychotropic medications,16 have been proposed as potential contributors to the risk. Although accumulating evidence suggests a higher risk of cardiovascular diseases among individuals with some psychiatric disorders, little is known about the risks of overall and specific groups of cardiovascular diseases in ADHD.

In relation to ADHD, cardiovascular diseases have mainly been studied as potential adverse effects of ADHD pharmacological treatment,17,18 as ADHD medications have previously been reported to be associated with elevated blood pressure and heart rate, which may further increase the risk of severe cardiovascular events (e.g., stroke, myocardial infarction).19 However, only a few previous studies have reported association between ADHD and cardiovascular diseases. A small Dutch study20 with 231 older adults found no association between ADHD diagnoses and cardiovascular diseases, but elevated levels of ADHD symptoms were associated with increased risk of cardiovascular diseases. Recently, a Swedish register-based cohort study21 with 4,288,451 sibling pairs and 1,841,303 family clusters (age: 18-81 years) showed that adults with ADHD were at increased risk of a wide range of physical health conditions, including cardiovascular diseases, compared with adults without ADHD.

There are still several knowledge gaps on the relationship between ADHD and cardiovascular diseases. First, only broad measures of cardiovascular diseases, encompassing a wide range of circulatory system diseases, have been used in previous studies on ADHD.20,21 Thus, little is known about the risks of specific groups of cardiovascular diseases in ADHD. This is important to inform prevention and treatment strategies, which may vary substantially depending on which specific cardiovascular diseases are most strongly associated with ADHD. Second, no studies have explored the role of psychiatric comorbidities and use of psychotropic medications in the development of cardiovascular diseases in ADHD. This is an important limitation as adults with ADHD are frequently diagnosed and treated (e.g., psychotropic medication) for other psychiatric disorders (e.g., mood disorder and substance use disorder), which in turn may influence the risk of cardiovascular diseases.16 Third, the role of well-established risk factors for cardiovascular diseases, such as low educational attainment,22 smoking,23 sleep problems,24 metabolic conditions (e.g., obesity25, type 2 diabetes mellitus (T2DM),26 and dyslipidemia27), as well as cardiovascular family history24, have not been explored in the association between ADHD and cardiovascular diseases. These modifiable and non-modifiable risk factors have the potential to be included in screening tools to identify people who are at increased risk of cardivascular diseases.28 Finally, even though it is well-established that the prevalence rates of ADHD and cardiovascular diseases are higher in males than in females,29,30 and that the core symptoms of ADHD often decline with increasing age,31 while the incidence of cardiovascular disease increases substantially with advancing age32, it is currently unclear if these patterns translate into sex- and age-differences in the associations of ADHD with cardiovascular diseases. A better understanding of such sex- and age-specific associations is needed for risk stratification and individualized treatment recommendations for individuals with ADHD.

In this register-based cohort study, we aimed to fill these knowledge gaps by investigating the prospective associations between ADHD and the risk of developing a broad range of cardiovascular diseases in adults. We also aimed to examine the extent to which any observed associations could be explained by common psychiatric comorbidities, well-established risk factors for cardiovascular diseases (e.g., low education level, smoking, sleep disorders, and metabolic conditions), psychotropic medications and cardiovascular family history. An additional exploratory aim was to assess the potential impact of sex and age.

**Methods**

This study was approved by the regional ethical review board in Stockholm, Sweden (reference number 2013/862-31/5). The informed consent is not required for pseudo anonymized register-based research according to Swedish law.

**Data sources and study cohort**

Data were obtained by linking multiple Swedish registries (Supplementary methods). The study cohort included all individuals born in Sweden between 1941 and 1983, who were alive and residing in Sweden in 2001 (n=5,448,328), from when outpatient data was available. We excluded individuals who had a history of any cardiovascular disease before/at baseline, and those who died or emigrated before being diagnosed with ADHD, leaving 5,389,519 individuals aged 18-60 years at the baseline. We followed them up from January 1st 2001 or the first diagnosis of ADHD (whichever came later), and until their first diagnosis of any cardiovascular disease, death, emigration, or December 31st, 2013 (whichever occurred first), with the oldest cohort member censored at 73 years of age.

**Measures**

***ADHD***

Individuals with ADHD were identified as those who had received their first ADHD diagnosis (ICD-9 or ICD-10: 314/F90) from the National Patient Register (NPR) at the age of 3 years or older, or first prescription of ADHD medication prescription (Anatomical Therapeutic Chemical, ATC codes: N06BA01/N06BA02/N06BA04/N06BA12 /N06BA09) from the Prescribed Drug Register (PDR), or both, before or during the follow-up period. This approach to identify individuals with ADHD has been validated and is widely used in Swedish register-based studies.21,33,34 In a sensitivity analysis, we only used diagnoses of ADHD from NPR for case identification, to reflect clinically diagnosed cases.

***Cardiovascular diseases***

Consistent with previous studies,35,36 incident cardiovascular disease events (including any cardiovascular diseases and specific diseases: ischemic heart disease, cerebrovascular disease, venous thromboembolism, hypertensive diseases, heart failure, arrhythmias, cardiac arrest and peripheral vascular disease/arteriosclerosis) were defined as the first diagnosis of cardiovascular disease from NPR or death from cardiovascular disease obtained from the Cause of Death Register. A complete list of all specific cardiovascular diseases, and corresponding ICD-8, ICD-9, and ICD-10 codes, is presented in **Table S1** in the Supplement.

***Covariates***

We collected information on year of birth, sex, and country of birth (Sweden, other Nordic country, and others) from TPR and highest educational level [elementary (⩽9 years), high school (10–12 years), postgraduate (>12 years)] from LISA as a proxy of socioeconomic status. T2DM, obesity, hyperlipidaemia, sleep disorders, heavy smoking (including tobacco abuse and nicotine dependence) and psychiatric comorbidities (including anxiety disorder, autism spectrum disorder, bipolar disorder, conduct disorder, depressive disorder, eating disorder, intellectual disability, personality disorder, schizophrenia and substance use disorder) diagnosed before the diagnosis of cardiovascular diseases were identified from NPR. ICD codes for all covariates are shown in **Table S1** in the Supplement. We further constructed a directed acyclic graph (DAG) to illustrate the potential pathways of the association between ADHD and cardiovascular diseases (Figure S1).

**Statistical analysis**

***Main analyses***

Cox proportional hazard regression model was used to estimate hazard ratios (HRs) with 95% confidence intervals (CI) expressing the rate/risk of cardiovascular diseases in individuals with ADHD, compared with individuals without ADHD, taking attained age as the underlying time scale. ADHD was modelled as a time-varying exposure, that is, individuals were assigned to the unexposed group before the diagnosis of ADHD, and were assigned to the exposed group from the first diagnosis or medication prescription of ADHD to the end of follow-up. The analysis was first conducted for ‘any cardiovascular disease’ as an outcome and then separately for six major categories and 17 individual cardiovascular diseases as described in **Table S1.** In addition to the underlying attained age, we adjusted for year of birth and sex in model 1. Model 2 further adjusted for education level, birth country, T2DM, obesity, dyslipidaemia, sleep problems and heavy smoking. We further adjusted for psychiatric comorbidities in model 3. Next, we conducted stratified analyses for ‘any cardiovascular disease’ by sex and age bands (18-30, 31-40, 41-50, 51-60 and 61-73 years) for models 1-3. The proportionality of hazards over underlying time scale was assessed using a Schoenfeld residuals-based test. There was no evidence of violation of the assumption.

Cumulative incidence of any cardiovascular disease among individuals with or without ADHD were estimated using flexible parametric models that adjusted for attained age, year of birth and sex, and were visualized by standardized survival curves.37 Cumulative incidence of any cardiovascular disease for each sex (adjusted for year of birth) and age bands (adjusted for sex and year of birth) was also estimated.

To further explore the specific contribution of each psychiatric comorbidity to the association between ADHD and any cardiovascular disease, given that the magnitude of their associated cardiovascular diseases risks is known to vary,12 model 1 and model 2 were repeated by comparing individuals without ADHD to individuals with ADHD only (without any psychiatric comorbidities), and those with ADHD plus each specific psychiatric comorbidity.

***Sensitivity analyses***

First, we only used the diagnosis from NPR, without information on ADHD medications, to identify individuals with ADHD. Second, because treatment with stimulants (ATC codes: N06BA01, N06BA02, N06BA04, N06BA12), antipsychotics (ATC codes: N05A), anxiolytics, hypnotics and sedatives (ATC codes: N05B, N05C), and antidepressants (ATC codes: N06A) are known to be associated with cardiovascular diseases16,38, we excluded individuals with ADHD and ever treated with stimulants or other psychotropic medications during the follow-up period, to rule out the potential impact of medication treatment on the studied associations. Third, to control for the familial susceptibility of cardiovascular diseases, we excluded those with family history of cardiovascular diseases, which was defined as any cardiovascular event among any first-degree relatives (biological parents and full siblings). Finally, we used ADHD as time-invariant exposure (i.e. individuals with diagnosis of ADHD were considered as exposed from the baseline to the end of the follow-up, regardless of the timing of the ADHD diagnosis) to further test the robustness of the results.

Data management was performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA), data analyses were performed with R, version 4.0.5 (R Foundation for Statistical Computing) and Stata (version 15.0; Stata Corp LP, College Station, TX).

**Results**

**Cohort Description**

We followed 5,389,519 individuals for a total of 64,084,464 person-years. Among these, 2,750,621 [51.04%] were males and 2,638,898 [48.96%] were females, with a mean (SD) age at study entry of 38.44 (12.32) years and a mean (SD) follow-up of 11.80 (2.85) years. A total of 37,027 (0.68%) individuals (20,475 [55.30%] male and 16,552 [44.70%] female) had a diagnosis of ADHD or an ADHD medication prescription (**Table 1**). During the follow-up, 746,572 individuals was newly diagnosed with cardiovascular diseases. The overall incidence rate of cardiovascular diseases within the study period was 1.65 per 100 person-years. In addition, individuals with ADHD were more likely to have a lower education attainment and to be diagnosed with obesity, sleep disorder, heavy smoking and all type of psychiatric comorbidities, compared with people without ADHD.

**Main analyses**

At the end of the follow-up, the cumulative incidence of any cardiovascular disease was 38.05% (95% CI, 34.87%–41.52%) for individuals with ADHD and 23.57% (95% CI, 23.47%–23.67%) for those without ADHD (**Figure 1**). As shown in **Figure 2,** adults with ADHD had a more than two-fold increased risk of any cardiovascular disease (HR=2.05, 95% CI=1.98-2.13), compared with those without ADHD, after adjusting for sex and year of birth. The associations attenuated, but remained significant, when adjusted for sociodemographic characteristics and well-established risk factors for cardiovascular diseases in model 2 (HR=1.84, 95%CI=1.77-1.91). Further adjustments for psychiatric comorbidities (model 3) attenuated but did not fully explain the associations (HR=1.65, 95%CI= 1.59-1.71). Positive associations were additionally observed for all studied specific cardiovascular diseases across all adjusted models in individuals with ADHD compared with those without ADHD. The highest adjusted hazard ratios were observed for cardiac arrest (HR=2.28, 95% CI=1.81-2.87), hemorrhagic stroke (HR=2.16, 95% CI=1.68-2.77) and peripheral vascular disease/arteriosclerosis (HR=2.05, 95% CI=1.76-2.38) in model 2. When further adjusting for psychiatric comorbidities, most of the relative risks (20 out of 22 specific cardiovascular diseases) were slightly attenuated but remained statistically significant.

**Subgroup analyses**

The associations between ADHD and cardiovascular diseases were stronger across all levels of adjustments in males (HR=1.70, 95% CI=1.62-1.79 in Model 3) compared to females (HR=1.58, 95% CI=1.49-1.68). . Accordingly, higher cumulative incidence of cardiovascular diseases over time was found in males compared to females. When stratified by age bands, the highest adjusted HR was observed in the youngest adults (18-31 years, HR=2.49, 95% CI=2.17-2.87), while the lowest association was found in the oldest adults (60-73 years, HR=1.22, 95% CI=1.08-1.37). However, the cumulative incidence of events was lowest among young adults, and then increased substantially with age. For example, at the end of the follow-up, the prevalence of cardiovascular diseases was 5.89% among the youngest adults with ADHD (vs. 2.87% for non-ADHD group), while the number was increased to 94.26% among the oldest adults with ADHD (vs 73.55% for non-ADHD group). P-values for sex and age differences <0.001. See **Table 2 and Figure 1**.

Using individuals without ADHD as a reference group, we found the relative risk of cardiovascular diseases was slightly higher among individuals with ADHD plus any psychiatric comorbidity (HR=1.87, 95% CI=1.79-1.95), compared with ADHD only (HR=1.72, 95% CI=1.59-1.86). Specifically, additional increase in the risk of cardiovascular diseases were found among those with comorbid depression, personality disorder, anxiety disorder, substance use disorder or eating disorder, compared with ADHD only. The strongest associations were found for eating disorder (HR=2.21, 95%CI=1.72-2.85) and substance use disorder (HR=2.20, 95%CI=2.08-2.32) (**Figure 3 and Table S2**).

**Sensitivity analyses**

Results from sensitivity analyses are presented in **Table 3**. First, when ADHD was only defined by diagnosis from the NPR, the cardiovascular risks were similar to those of the main analysis, but with a stronger association (HR=1.76, 95% CI=1.68-1.84) after adjusting for all covariates. Second, the estimates were similar when excluding individuals with ADHD diagnosis and treated with stimulants (HR=1.77, 95% CI=1.69-1.85), or other psychiatric medications (including antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants) (HR=1.83, 95% CI=1.74-1.91). Third, when restricting our main analyses to individuals without family history of cardiovascular diseases, the risk estimates for cardiovascular diseases remained largely similar (HR=1.65, 95% CI=1.59-1.71). Finally, we generally found the same results across all levels of adjustment when using ADHD as time-invariant exposure (HR=1.64, 95% CI=1.58-1.70).

**Discussion**

In this large-scale, register-based cohort study, we found that adults with ADHD were more than twice as likely to develop at least one cardiovascular disease, compared with those without ADHD, independently from treatment with psychotropic medications. The increased risks were present across all types of cardiovascular diseases, but the strength of the associations was strongest for cardiac arrest, hemorrhagic stroke and peripheral vascular disease/arteriosclerosis. Well-established risk factors for cardiovascular diseases and psychiatric comorbidities could not fully explain the associations, indicating that ADHD is an important, independent risk factor for a wide range of cardiovascular diseases. This finding is consistent with a recent two-sample Mendelian randomization study reporting a direct causal effect of ADHD on coronary artery disease.39 Although the underlying mechanisms remain unclear, plausible biological mechanisms could explain the observed association between ADHD and cardiovascular diseases, including immune system abnormalities,40,41 neuromodulator dysregulation,42,43 and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis.44,45 Alternatively, the observed associations could also be partly explained by shared etiological components, as suggested in a previous genetically-informed study based on sibling pairs.21 Future studies are needed to fully understand the underlying mechanisms linking ADHD with cardiovascular diseases.

By the end of the follow-up, when the oldest participants were 73 years old, 73.55% of the population without ADHD developed at least one cardiovascular disease, which is in line with the American Heart Association (AHA), reporting that the prevalence of cardiovascular diseases in adults is ~75% from 60–79 years.32 However, the corresponding number in those with ADHD was substantially higher (94.26%). Our findings were consistent with the few available studies on this topic.20,21 The observed strength of associations between ADHD and cardiovascular diseases were largely comparable to estimates of associations between cardiovascular diseases and schizophrenia,9 depression8 and bipolar disorders10, but stronger than associations with anxiety,11 obsessive-compulsive disorder36 and stress-related disorders.35 In contrast to the available evidence base for other psychiatric disorders,46 the associations between ADHD and cardiovascular diseases has been substantially understudied. Our findings call for enhanced clinical awareness of cardiovascular risk among adults with ADHD.

 We note that the finding of stronger risk in younger (i.e., 18-30 years) compared to older adults is likely due to a healthier reference group for younger adults. Sex differences in ADHD29 and cardiovascular diseases30 are well-established, with higher prevalence estimates in males than in females for both conditions, but our study extends this knowledge base by showing that the associations between ADHD and cardiovascular diseases is stronger in males than in females. The present study point to the potential value of screening for cardiovascular risk factors in ADHD, particularly targeting young adulthood and males, even though more evidence is needed to evaluate the cost-effectiveness of screening strategies before recommending systematic screening in this group.

The findings from this study suggests that the presence of established risk factors for cardiovascular diseases and psychiatric comorbidities could not fully explain the observed associations. However, comorbid eating disorder or substance use disorder significantly increased the risk of cardiovascular diseases among individuals with ADHD. As suggested in previous studies, around 80% of patients with an eating disorder are affected by a cardiac complication,47 and prolonged heavy use of certain substances (e.g., drugs, alcohol, tobacco and/or heroin) substantially increases the risk of several serious cardiovascular problems, including hypertension, stroke, heart attack and cardiac arrest.48 Therefore, appropriate identification and treatment of psychiatric comorbidity (in particular eating disorder and substance use disorder) and appropriate life-style interventions to modify well-established risk factors of cardiovascular diseases are necessary to successfully impact cardiovascular health among adults with ADHD.

 Finally, our findings also suggest that the observed associations between ADHD and cardiovascular diseases are independent from the use of stimulants and other psychotropic medications, even though a slightly stronger association was found among individuals with ADHD not treated with antipsychotics, anxiolytics, hypnotics and sedatives and antidepressants. A seemingly protective effect of psychotropic medication for the risk of cardiometabolic conditions and mortality has also been found in other neuropsychiatric disorders.49-51 However, we are cautious to attribute our finding of a risk reductions to psychotropic medication alone, because confounding by indication needs to be carefully considered using other study designs (e.g., within-individuals comparisons). Therefore, our results should not be interpreted as that psychotropic medication are free from cardiovascular adverse effects, and they should continue to be used with caution in adults with ADHD.

The studies have several limitations. First, the national registers mainly capture the most severe cases, which might lead to an underestimation of the number of patients with milder symptoms of ADHD or less severe cardiovascular diseases. In addition, the potential detection bias (i.e., individuals with ADHD and psychiatric comorbidities being more likely to be diagnosed with CVDs as they have more frequent contact with the health care system compared with those without ADHD) cannot be ruled out in current study. However, the risk of cardiovascular diseases among individuals with severe ADHD (combined with other psychiatric comorbidities) were not consistently higher than those with ADHD only, which indicated that the potential detection bias cannot fully explain the observed association between ADHD and CVDs. Second, the administrative prevalence of ADHD increase over calendar time, reflecting changes in the psychiatric health care system and diagnostic practices across time, and the late inclusion of outpatient specialist care records in the NPR (from 2001) and information on medication in PDR (from 2005), might have led to a possible loss of early diagnoses for ADHD in our cohort, particularly for older adults. As a consequence, the average age of cohort entry and cardiovascular disease diagnosis among individuals with ADHD was younger than among those without ADHD. Delayed diagnosis (mean age at ADHD diagnosis was 21.91 [13.94] years) may have resulted in misclassification from exposed to unexposed person-time, which would be most likely to bias estimates towards the null. Third, as the median age of the study population at the end of the follow-up was 50.49 (range 31-73) years, we might have mostly captured early onset cases of cardiovascular diseases. Even though we had enough power to explore the associations among adults aged 60-73 years in the age-stratified analysis, the prevalence of ADHD might have been substantially underestimated in the oldest generation. Therefore, future studies with more recent data would be necessary to explore the association of ADHD with later onset cardiovascular diseases among older adults. Finally, we had no data on lifestyle related factors (such as dietary intake and physical activities) that may contribute to the observed association as confounders or mediators. Our results suggested that heavy smoking and sleep problems could explain only a small portion of the associations, but tobacco use and sleep disorders identified from registers might only reflect the most severe cases. Thus, further studies with detailed information on lifestyle are warranted to clarify the impact of these factors on the association of interest.

In this large-scale, register-based cohort study, we found that ADHD is a novel risk factor for a wide range of cardiovascular diseases, independent from well-established risk cardiovascular risk factors, psychiatric comorbidity, and psychotropic medication treatment. The findings underscore the importance of carefully monitoring cardiovascular health in adults with ADHD, and highlight a critical need for development of age-appropriate and individualized strategies to reduce the risk of cardiovascular morbidity in adult ADHD. Additional studies are needed to confirm our findings and to further explore the mechanisms underlying the association between ADHD and cardiovascular diseases.

**Contributors**

LL, ZC and HL conceived and designed the study. LL analysed the data and drafted the manuscript. JWS and MGA assisted with data analysis. All authors assisted with the methods, and contributed to the interpretation of results and writing of the final manuscript. LL is the guarantor and attests that all listed authors meet authorship criteria and that no other individuals meeting the criteria have been omitted. LL and HL had full access to all the data in the study, and all authors had final responsibility for the decision to submit for publication.

**Declaration of interests**

HL has served as a speaker for Medice, Evolan Pharma and Shire/Takeda and has received research grants from Shire/Takeda; all outside the submitted work. EDR has served as a speaker for Shire Sweden AB outside the submitted work. MS received honoraria/has been a consultant for Angelini, Lundbeck. No other disclosures were reported.

**Acknowledgment**

The project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No. 667302 and 965381. HL acknowledge financial support from the Swedish Research Council (2018-02599) and the Swedish Brain Foundation (FO2021-0115). ZC was supported by grants from the Swedish Council for Health, Working Life and Welfare (2019-00176), MD has received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 754285. EDR was supported by grant 2019-01172 from the Swedish Research Council for Health, Working Life, and Welfare (FORTE), grant PD20-0036 from the Swedish Society for Medical Research (SSMF), and Funds from the Strategic Research Program in Epidemiology at Karolinska Institutet.

 **References**

1. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers* 2015; **1**: 15020.

2. Davidson MA. Literature Review: ADHD in Adults: A Review of the Literature. *Journal of Attention Disorders* 2007; **11**(6): 628-41.

3. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. *Lancet Psychiatry* 2018; **5**(2): 175-86.

4. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry* 2006; **163**(4): 716-23.

5. Cortese S, Moreira-Maia CR, St Fleur D, Morcillo-Peñalver C, Rohde LA, Faraone SV. Association Between ADHD and Obesity: A Systematic Review and Meta-Analysis. *The American journal of psychiatry* 2016; **173**(1): 34-43.

6. Cortese S, Sun S, Zhang J, et al. Association between attention deficit hyperactivity disorder and asthma: a systematic review and meta-analysis and a Swedish population-based study. *Lancet Psychiatry* 2018; **5**(9): 717-26.

7. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J* 2006; **27**(23): 2763-74.

8. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *European Heart Journal* 2014; **35**(21): 1365-72.

9. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *The American heart journal* 2005; **150**(6): 1115-21.

10. Swartz HA, Fagiolini A. Cardiovascular Disease and Bipolar Disorder: Risk and Clinical Implications. *The Journal of clinical psychiatry* 2012; **73**(12): 1563-5.

11. Tully PJ, Harrison NJ, Cheung P, Cosh S. Anxiety and Cardiovascular Disease Risk: a Review. *Current Cardiology Reports* 2016; **18**(12): 120.

12. Momen NC, Plana-Ripoll O, Agerbo E, et al. Association between mental disorders and subsequent medical conditions. *New England Journal of Medicine* 2020; **382**(18): 1721-31.

13. Sun X, Chen L, Wang Z, et al. Association of Autism Spectrum Disorder, Neuroticism, and Subjective Well-Being With Cardiovascular Diseases: A Two-Sample Mendelian Randomization Study. *Frontiers in Cardiovascular Medicine* 2021; **8**: 566.

14. Mc Namara K, Alzubaidi H, Jackson JK. Cardiovascular disease as a leading cause of death: how are pharmacists getting involved? *Integr Pharm Res Pract* 2019; **8**: 1-11.

15. Escobar DF, Noll PR, Jesus TF, Noll M. Assessing the Mental Health of Brazilian Students Involved in Risky Behaviors. *International Journal of Environmental Research and Public Health* 2020; **17**(10).

16. Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World psychiatry : official journal of the World Psychiatric Association (WPA)* 2015; **14**(3): 339-47.

17. Mick E, McManus DD, Goldberg RJ. Meta-analysis of increased heart rate and blood pressure associated with CNS stimulant treatment of ADHD in adults. *European Neuropsychopharmacology* 2013; **23**(6): 534-41.

18. Cortese S. Pharmacologic Treatment of Attention Deficit-Hyperactivity Disorder. *The New England journal of medicine* 2020; **383**(11): 1050-6.

19. Liu H, Feng W, Zhang D. Association of ADHD medications with the risk of cardiovascular diseases: a meta-analysis. *European child & adolescent psychiatry* 2019; **28**(10): 1283-93.

20. Semeijn EJ, Kooij JJ, Comijs HC, Michielsen M, Deeg DJ, Beekman AT. Attention-deficit/hyperactivity disorder, physical health, and lifestyle in older adults. *Journal of the American Geriatrics Society* 2013; **61**(6): 882-7.

21. Du Rietz E, Brikell I, Butwicka A, et al. Mapping phenotypic and aetiological associations between ADHD and physical conditions in adulthood in Sweden: a genetically informed register study. *Lancet Psychiatry* 2021; **8**(9): 774-83.

22. Kubota Y, Heiss G, MacLehose RF, Roetker NS, Folsom AR. Association of Educational Attainment With Lifetime Risk of Cardiovascular Disease: The Atherosclerosis Risk in Communities Study. *JAMA internal medicine* 2017; **177**(8): 1165-72.

23. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *Journal of the American college of cardiology* 2004; **43**(10): 1731-7.

24. Fan M, Sun D, Zhou T, et al. Sleep patterns, genetic susceptibility, and incident cardiovascular disease: a prospective study of 385 292 UK biobank participants. *European Heart Journal* 2019; **41**(11): 1182-9.

25. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2021; **143**(21): e984-e1010.

26. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovascular Diabetology* 2018; **17**(1): 83.

27. Hedayatnia M, Asadi Z, Zare-Feyzabadi R, et al. Dyslipidemia and cardiovascular disease risk among the MASHAD study population. *Lipids in Health and Disease* 2020; **19**(1): 42.

28. Imes CC, Lewis FM. Family history of cardiovascular disease, perceived cardiovascular disease risk, and health-related behavior: a review of the literature. *The Journal of cardiovascular nursing* 2014; **29**(2): 108-29.

29. Rucklidge JJ. Gender differences in attention-deficit/hyperactivity disorder. *Psychiatr Clin North Am* 2010; **33**(2): 357-73.

30. Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. *BMJ Global Health* 2017; **2**(2): e000298.

31. Simon V, Czobor P, Balint S, Meszaros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry* 2009; **194**(3): 204-11.

32. Yazdanyar A, Newman AB. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. *Clinics in geriatric medicine* 2009; **25**(4): 563.

33. Larsson H, Ryden E, Boman M, Långström N, Lichtenstein P, Landen M. Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. *The British Journal of Psychiatry* 2013; **203**(2): 103-6.

34. Sun S, Kuja-Halkola R, Faraone SV, et al. Association of Psychiatric Comorbidity With the Risk of Premature Death Among Children and Adults With Attention-Deficit/Hyperactivity Disorder. *JAMA Psychiatry* 2019; **76**(11): 1141-9.

35. Song H, Fang F, Arnberg FK, et al. Stress related disorders and risk of cardiovascular disease: population based, sibling controlled cohort study. *BMJ (Clinical research ed)* 2019; **365**: l1255.

36. Isomura K, Sidorchuk A, Brander G, et al. Risk of specific cardiovascular diseases in obsessive-compulsive disorder. *Journal of psychiatric research* 2021; **135**: 189-96.

37. Hinchliffe SR, Lambert PC. Flexible parametric modelling of cause-specific hazards to estimate cumulative incidence functions. *BMC Medical Research Methodology* 2013; **13**(1): 13.

38. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World psychiatry : official journal of the World Psychiatric Association (WPA)* 2015; **14**(2): 119-36.

39. Leppert B, Riglin L, Wootton RE, et al. The Effect of Attention Deficit/Hyperactivity Disorder on Physical Health Outcomes: A 2-Sample Mendelian Randomization Study. *American journal of epidemiology* 2020; **190**(6): 1047-55.

40. Fernández-Ruiz I. Immune system and cardiovascular disease. *Nature Reviews Cardiology* 2016; **13**(9): 503-.

41. Hoekstra PJ. Attention-deficit/hyperactivity disorder: is there a connection with the immune system? *European child & adolescent psychiatry* 2019; **28**(5): 601-2.

42. Ahmad Banday A, Lokhandwala MF. Defective renal dopamine D1 receptor function contributes to hyperinsulinemia-mediated hypertension. *Clinical and experimental hypertension* 2006; **28**(8): 695-705.

43. Misener V, Luca P, Azeke O, et al. Linkage of the dopamine receptor D1 gene to attention-deficit/hyperactivity disorder. *Molecular psychiatry* 2004; **9**(5): 500-9.

44. Corominas M, Ramos-Quiroga J, Ferrer M, et al. Cortisol responses in children and adults with attention deficit hyperactivity disorder (ADHD): a possible marker of inhibition deficits. *ADHD Attention Deficit and Hyperactivity Disorders* 2012; **4**(2): 63-75.

45. Jokinen J, Nordström P. HPA axis hyperactivity and cardiovascular mortality in mood disorder inpatients. *Journal of affective disorders* 2009; **116**(1-2): 88-92.

46. Nielsen RE, Banner J, Jensen SE. Cardiovascular disease in patients with severe mental illness. *Nature Reviews Cardiology* 2021; **18**(2): 136-45.

47. Casiero D, Frishman WH. Cardiovascular Complications of Eating Disorders. *Cardiology in Review* 2006; **14**(5).

48. Schulte MT, Hser Y-I. Substance use and associated health conditions throughout the lifespan. *Public health reviews* 2013; **35**(2): 3.

49. Brander G, Isomura K, Chang Z, et al. Association of Tourette syndrome and chronic tic disorder with metabolic and cardiovascular disorders. *JAMA neurology* 2019; **76**(4): 454-61.

50. Isomura K, Brander G, Chang Z, et al. Metabolic and cardiovascular complications in obsessive-compulsive disorder: a total population, sibling comparison study with long-term follow-up. *Biological psychiatry* 2018; **84**(5): 324-31.

51. Tiihonen J, Mittendorfer-Rutz E, Torniainen M, Alexanderson K, Tanskanen A. Mortality and cumulative exposure to antipsychotics, antidepressants, and benzodiazepines in patients with schizophrenia: an observational follow-up study. *American Journal of Psychiatry* 2016; **173**(6): 600-6.

**TABLES**

**Table 1.** Descriptive characteristics of individuals with and without ADHD

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Total****N=** 5,389,519 | **Individuals with ADHD** **N=** **37,027** | **Individuals without ADHD** **N=** **5,352,492** |
|  | **N (%)** | **N (%)** | **N (%)** |
| **Mean age at baseline** | 38.43 (12.32) | 30.34 (9.25) | 38.49 (12.32) |
| **Mean age of first CVD diagnosis** | 56.41 (10.25) | 47.13 (10.50) | 56.45 (10.23) |
| **Incidence rate of CVD** | 1.65% | 1.79% | 1.16% |
| **Year of birth** |  |  |  |
| 1941-1950 | 1207438 (22.40) | 1084 (2.93) | 1206354 (22.54) |
| 1951-1960 | 1165832 (21.63) | 4532 (12.24) | 1161300 (21.70) |
| 1961-1971 | 1320673 (24.50) | 10696 (28.89) | 1309977 (24.47) |
| 1977-1983 | 1695576 (31.46) | 20715 (55.94) | 1674861 (31.29) |
| **Sex** |  |  |  |
| Male  | 2750621 (51.04) | 20477 (55.30) | 2730144 (51.01) |
| Female | 2638898 (48.96) | 16550 (44.70) | 2622348 (48.99) |
| **Country of birth** |  |  |  |
| Sweden | 4254357 (78.94) | 33193 (89.64) | 4221164 (78.86) |
| Denmark, Finland, Norway or Iceland | 198791 (3.69) | 867 (2.34) | 197924 (3.70) |
| Other | 936371 (17.37) | 2967 (8.01) | 933404 (17.44) |
| **Educational attainment\*** |  |  |  |
| Primary and lower secondary | 801454 (14.87) | 9578 (25.87) | 791876 (14.79) |
| Upper secondary | 2246375 (41.68) | 17657 (47.69) | 2228718 (41.64) |
| Postsecondary | 1799447 (33.39) | 8080 (21.82) | 1791367 (33.47) |
| Postgraduate | 65325 (1.21) | 161 (0.43) | 65164 (1.22) |
| **Well-established risk factors for CVD** |  |  |
| Type 2 diabetes | 157982 (2.93) | 969 (2.62) | 157013 (2.93) |
| Obesity  | 117795 (2.19) | 2279 (6.15) | 115516 (2.16) |
| Dyslipidemia | 109839 (2.04) | 426 (1.15) | 109413 (2.04) |
| Sleep problems | 145189 (2.69) | 4146 (11.20) | 141043 (2.64) |
| Heavy smoking  | 50768 (0.94) | 1046 (2.82) | 49722 (0.93) |
| **Psychiatric Comorbidities**  |  |  |
| Anxiety Disorder  | 205125 (3.81) | 15394 (41.58) | 189731 (3.54) |
| Autism spectrum disorder | 13412 (0.25) | 4123 (11.14) | 9289 (0.17) |
| Bipolar disorder | 45530 (0.84) | 5201 (14.05) | 40329 (0.75) |
| Conduct disorder  | 1908 (0.04) | 451 (1.22) | 1457 (0.03) |
| Depressive disorder | 267240 (4.96) | 15977 (43.15) | 251263 (4.69) |
| Eating disorder | 11716 (0.22) | 1033 (2.79) | 10683 (0.20) |
| Intellectual disability | 20480 (0.38) | 1218 (3.29) | 19269 (0.36) |
| Personality disorder | 66408 (1.23) | 7984 (21.56) | 58424 (1.09) |
| Schizophrenia | 29901 (0.55) | 885 (2.39) | 29016 (0.54) |
| Substance use disorder | 220295 (4.09) | 13996 (37.80) | 206299 (3.85) |

\* 476918 (8.85%) with missing values on educational attainment; CVD: cardiovascular diseases

**Table 2.** Association between ADHD and cardiovascular diseases as hazard ratios (HR) with 95% confidence intervals (CI) adjusted for covariates

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | No. of cases/person years | Model 1 | Model 2  | Model 3 |
|  | ADHD | Non-ADHD |
| **Overall**  | **2748/152790** | **743824/63895674** | **2.05 (1.98-2.13)** | **1.84 (1.77-1.91)** | **1.65 (1.59-1.71)** |
| **Sex a,b** |  |  |  |  |  |
| Male | 1702/87987 | 421961/32276606 | 2.10 (2.00-2.20) | 1.89 (1.80-1.98) | 1.70 (1.62-1.79) |
| Female | 1046/64803 | 321863/31619068 | 2.00 (1.88-2.13) | 1.76 (1.65-1.87) | 1.58 (1.49-1.68) |
| **Age b**  |  |  |  |  |
| 18-30  | 208/37481 | 19837/12752749 | 2.78 (2.42-3.19) | 2.43 (2.12-2.79) | 2.49 (2.17-2.87) |
| 31-40  | 623/56004 | 52297/16122195 | 2.74 (2.53-2.96) | 2.36 (2.18-2.55) | 2.14 (1.97-2.32) |
| 41-50 | 988/40109 | 126418/15078010 | 2.32 (2.18-2.47) | 2.05 (1.93-2.19) | 1.82 (1.71-1.94) |
| 51-60  | 657/15603 | 269821/13909517 | 1.67 (1.54-1.80) | 1.54 (1.43-1.66) | 1.43 (1.32-1.54) |
| 61-73 | 274/3440 | 275292/5904282 | 1.50 (1.33-1.69) | 1.33 (1.18-1.50) | 1.22 (1.08-1.37) |

Model 1: Adjusted for sex and year of birth;

Model 2: Adjusted for sex, year of birth, education level, birth country, T2DM, obesity, dyslipidemia, sleep problems and heavy smoking.

Model 3: Adjusted for sex, year of birth, education level, birth country, T2DM, obesity, dyslipidemia, sleep problems, heavy smoking and psychiatric comorbidities.

a. Sex was not included as covariates in the models stratified by sex.

b. P-value for sex and age difference <0.001

**Table 3.** Summary of results from sensitivity analyses on associations between ADHD and cardiovascular diseases

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | No. of cases/person years | Model 1 | Model 2 | Model 3 |
|  | ADHD | Non-ADHD |
| ADHD diagnosis onlya |  |  |  |  |  |
|  |  2135/120138  | 744780/63930662 | 2.22 (2.13-2.32) | 1.99 (1.90-2.07) | 1.76 (1.68-1.84) |
| Excluding those treated with stimulantsa,b |  |  |  |  |
|  | 1959/107828 | 744780/63930662 | 2.25 (2.16-2.36) | 2.01 (1.92-2.10) | 1.77 (1.69-1.85) |
| Excluding those treated with other psychiatric medicationsa,b |  |  |  |
|  | 1871/94970 | 744780/63930662 | 2.29 (2.19-2.40) | 2.06 (1.97-2.16) | 1.83 (1.74-1.91) |
| Exclude those with family history of cardiovascular diseases |  |  |  |
|  | 2748/152550  | 743743/63599718 | 2.06 (1.98-2.14) | 1.84 (1.77-1.91) | 1.65 (1.59-1.71) |
| ADHD as time-invariant exposure |  |  |  |  |
|  | 2748/152790 | 743824/63579929 | 2.05 (1.97-2.13) | 1.83 (1.77-1.90) | 1.64 (1.58-1.70) |

a In theses sensitivity analyses, ADHD was defined only based on ICD codes;

b Detailed information on all dispensed drugs in Sweden was available since 1 July 2005.

Model 1: Adjusted for sex and year of birth;

Model 2: Adjusted for sex, year of birth, education level, birth country, T2DM, obesity, dyslipidemia, sleep problems and heavy smoking.

Model 3: Adjusted for sex, year of birth, education level, birth country, T2DM, obesity, dyslipidemia, sleep problems, heavy smoking and psychiatric comorbidities.

**FIGURES**

**Figure 1** Overall, sex- and age-specific cumulative incidence of cardiovascular diseases (cardiovascular disease) estimated by standardized survival curve (Shaded areas indicate 95% confidence intervals), adjusted for sex and year of birth, in individuals with ADHD (solid line) and those without ADHD (dotted line).

**Figure 2** Hazard ratio with 95% CIs of developing different types of cardiovascular diseases among adults with ADHD, compared with those without ADHD. In model 1, sex and year of birth were adjusted. In model 2, sex, year of birth, education level, birth country, T2DM, obesity, dyslipidemia, sleep problems and heavy smoking were adjusted. In model 3, sex, year of birth, education level, birth country, T2DM, obesity, dyslipidemia, sleep problems, heavy smoking and psychiatric comorbidities were adjusted. Attained age was used as underlying time scale.

**Figure 3.** Hazard ratio with 95% CIs of cardiovascular diseases among individuals with ADHD only and ADHD plus each specific psychiatric comorbidity, compared with those without ADHD. Cox models were adjusted for year of birth, sex, educational level, education level, birth country, obesity, T2DM, dyslipidemia, sleep problems, heavy smoking. Attained age was used as underlying time scale.