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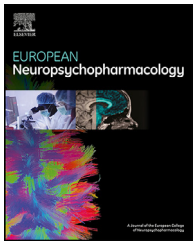

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# Long-term methylphenidate exposure and 24-hours blood pressure and left ventricular mass in adolescents and young adults with attention deficit hyperactivity disorder

J.K. Buitelaar[1,2,*], G.H.H. van de Loo-Neus[2], L. Hennissen[1], C.U. Greven[1,2], P.J. Hoekstra[3], P. Nagy[4,5], A. Ramos-Quiroga[6], E. Rosenthal[7], S. Kabir[7], K.K.C. Man[8,9,10], Wong IC[8,9,10], D. Coghill[11], ADDUCE consortium[#,†]

[1] *Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboudumc, Nijmegen, The Netherlands*
[2] *Karakter Child and Adolescent Psychiatry University Centre, Nijmegen, The Netherlands*
[3] *University of Groningen, University Medical Center Groningen, Department of Child and Adolescent Psychiatry & Accare Child Study Center, Groningen, Netherlands*
[4] *Vadaskert Child and Adolescent Psychiatric Hospital, Budapest, Hungary*
[5] *Bethesda Children's Hospital, Budapest, Hungary*
[6] *Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain*
[7] *Evelina London Children's Hospital, London, UK*
[8] *Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom*
[9] *Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong*
[10] *Laboratory of Data Discovery for Health, Hong Kong Science Park, Hong Kong Special Administrative Region, China*
[11] *Departments of Paediatrics and Psychiatry, University of Melbourne, Australia*

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* Correspondence to: Jan Buitelaar, Dept Cognitive Neuroscience (204), Radboudumc, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands
*E-mail address:* Jan.Buitelaar@radboudumc.nl (J.K. Buitelaar).
[#]ADDUCE consortium: other members are Alexander Häge, Tobias Banaschewski, Sarah K. Inglis, Sara Carucci, Marina Danckaerts, Ralf W. Dittmann, Bruno Falissard, Peter Garas, Chris Hollis, Kerstin Konrad, Hanna Kovshoff, Elizabeth Liddle, Suzanne McCarthy, Antje Neubert, Edmund J.S. Sonuga-Barke, and Alessandro Zuddas.
[†]Professor Zuddas has passed away July 2022.

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**Abstract**
Young people with attention deficit hyperactivity disorder (ADHD) are now being treated with psychostimulant medication for longer than was previously the case and are increasingly likely to remain on methylphenidate into adolescence and adulthood. This study was designed to determine whether the long-term use of methylphenidate (MPH, immediate release or extended release) increases blood pressure and left ventricular mass (LVM) identified by echocardiography in adolescents and young adults with ADHD aged 12-25 years. In a five-site cross-sectional design two groups were compared for 24- hour blood pressure and heart rate (HR) registrations and LVM: 1) adolescents and young adults with ADHD who had been treated with MPH for > 2 years (N=162, age mean (SD) 15.6 (3.0)), and 2) adolescents and young adults with ADHD who had never been treated with methylphenidate (N=71, age mean 17.4 (4.2)). The analyses were controlled for propensity scores derived from age, sex, height, weight, and 19 relevant background variables.
A blood pressure indicative of hypertension (>95$^{th}$ percentile) was observed in 12.2% (95% confidence interval 7.3 – 18.9%) of the participants in the MPH treated group and in 9.6% (95%CI 3.2 – 21.0%) of the MPH naïve group, with overlapping intervals. The 24-hour recorded systolic blood pressure (SBP) and HR were significantly higher during daytime in medicated individuals with ADHD than in those with unmedicated ADHD, but were similar in both groups during the night. 24-hour diastolic blood pressure (DBP) did not differ between both groups during either daytime or at night. LVM, corrected for body-surface area (LVMBSA), also did not differ between the two groups (p=0.20, controlling for confounders). Further, MPH daily dose and duration of treatment were unrelated to LVMBSA, SBP, and DBP.
Long-term MPH use in adolescents and young adults with ADHD is associated with small but significant increases of SBP and HR during daytime. Given the current sample size, the proportions of hypertension do not differ significantly between MPH treated and MPH-naïve individuals with ADHD. Future studies with larger samples, longer treatment duration, and/or with within-subject designs are necessary. The results do, however, further support recommendations that highlight the importance of monitoring blood pressure and HR during MPH treatment.


## 1. Introduction

With a population prevalence of about 5% in children and adolescents, Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most common neuropsychiatric disorders (Polanczyk et al., 2015). ADHD is characterised by a pattern of inattentive and/or hyperactive and impulsive behaviours that significantly and negatively impact quality of life and social, academic, or occupational functioning (Faraone et al., 2021). Rather than being limited to childhood, ADHD often persists into adulthood. About 15% of individuals with ADHD still meet full ADHD diagnostic criteria in adulthood, and 40-60% remit only partially and continue to have ADHD symptoms as adults and/or impaired functioning (Faraone et al., 2006). Clinical guidelines and practice parameters describe the pivotal role of medication in the clinical management of ADHD (NICE 2018). These recommendations are based on numerous clinical trials that have shown both stimulant and non-stimulant medication to be highly efficacious in reducing ADHD symptoms, with moderate to large effect sizes and a percentage of clinical responders of 70% or higher (Cortese et al., 2018) (Storebø et al., 2015).

The most prescribed medications for ADHD are stimulant-class medications like methylphenidate (MPH) and amphetamines (Polanczyk et al., 2015). The mechanism by which stimulants act in reducing symptoms in ADHD is not completely clear, however, it is believed that they inhibit the reuptake of dopamine and noradrenaline into the presynaptic neuron and, in the case of amphetamines increase the release of dopamine into extraneuronal space (Quansah and Zetterström, 2019). Stimulant treatment has been associated with, on average, statistically significant but small increases in systolic blood pressure (SBP) for methylphenidate, and diastolic blood pressure (DBP), SBP, and heart rate (HR) for amphetamines (for review (Hennissen et al., 2017, Liang et al., 2018)). Although the mean increases are relatively small, a significant minority (5-15%) of individuals experience larger increases tipping them into clinically relevant hypertension (Hammerness et al., 2009). Sustained increases in blood pressure and heart rate are at the long term the most common causes of left ventricular hypertrophy and also increase the risk of myocardial infarction (Mancia and Grassi, 2008, Cramariuc and Gerdts, 2016). Investigation of cardiovascular function in relation to ADHD medication has been mostly limited to single blood pressure readings and electrocardiogram (ECG) registrations, but some recent studies have applied more advanced techniques to assess cardiovascular function. A prospective study in 73 children with ADHD did not find an association between stimulant treatment for one and two years and echocardiographic alterations, though the isovolumetric relaxation and deceleration times for diastolic function were significantly increased (García Ron et al., 2022). Another study assessed cardiac

function by echocardiography and tissue Doppler imaging in 58 stimulant-treated children with ADHD and another 58 treatment naïve children with ADHD and was unable to establish cardiac function impairments (Kara et al., 2018).

Children with ADHD are now being treated for longer than was previously the case and are increasingly likely to remain on methylphenidate treatment into adolescence and adulthood. (van de Loo-Neus, Rommelse, and Buitelaar, 2011) Furthermore, an increasing number of individuals are being diagnosed with ADHD in adulthood and methylphenidate is more frequently being started for the first time in adults who are already at greater risk of cardiovascular disorders than children (Elliott et al., 2020). Given the increasing and extended exposure to ADHD medication, the present study was designed to [1]investigate the association of long-term methylphenidate treatment and cardiac function by obtaining echocardiography and 24-hour blood pressure recordings, measures that are respectively more sensitive than ECG and single blood pressure recordings. The focus is on methylphenidate because it is the most often prescribed psychostimulant (Raman et al., 2018). A cross-sectional study design was used to differentiate between the cardiovascular risks associated with ADHD itself, and those associated with long-term methylphenidate treatment by comparing adolescents and young adults with ADHD, treated with methylphenidate for 2 years or longer, to a similar group of late adolescent and adult subjects with ADHD never treated with methylphenidate or other ADHD medications.

This study addressed the following specific questions: Is long-term use of methylphenidate in adolescent and young adults with ADHD associated with 1) increased 24-hour recordings of SBP and DBP, and 2) increased left ventricular mass as identified by echocardiography?

## 2. Methods

This cross-sectional observational study was part of the ADDUCE (Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects) project funded by the 7th framework programme of the European Commission.

### 2.1. Participants

Participants aged between 12 and 25 years with a clinical diagnosis of any type of ADHD according to DSM-IV-TR criteria were recruited from ADHD clinics at 5 sites in Europe (Nijmegen, Budapest, Groningen, Barcelona, Dundee). Any comorbidity and co-medication (except treatment with dexamphetamine or atomoxetine) were allowed. Participants had been clinically diagnosed with ADHD and were either continuously treated with methylphenidate (IR or ER preparations) for 2 years or longer or were ADHD-medication naïve and had never been treated with methylphenidate or other ADHD-medication at any time. The study was conducted from March 2014 to October 2015. The project was approved by all local ethics committees, and written informed consent was obtained from all participants.

### 2.2. Procedures

All participants were first seen at a screening visit to inform them about the study and obtain written informed consent. Next, at the baseline visit, comprehensive face-to-face assessments to collect clinical measures (see below) were conducted. A general physical examination, including extended cardiac examination with inspection, palpation and auscultation, was conducted by a trained and qualified physician. Either at the baseline or at the last visit, an echocardiography and an ambulatory 24- hours blood pressure measurements were obtained.

#### 2.2.1. Demographic and clinical measures

Information on dose and duration of treatment with MPH was obtained by parent and/or self-report. Daily doses of extended-release MPH were recalculated to those of immediate-release MPH. Information on demographics, medical and psychiatric history, physical health, developmental history, psychiatric and non-psychiatric medication(s) prescribed or continued during the procedure was obtained at the screening and baseline interview.

Psychiatric interview. The ADHD clinical diagnosis was confirmed by a (semi)-structured interview conducted by a trained researcher or clinician. If <18 years, the ADHD module of the K-SADS was used (Kaufman et al., 1997); if >=18 years the CAADID (Conners Adult ADHD Diagnostic Interview for DSM-IV (Epstein and Kollins, 2006), www.mhs.com/) or DIVA (Diagnostic Interview for Adult ADHD (Kooij, 2010)) was used depending on local procedures.

Rating scales. To assess the severity of ADHD symptoms, the ADHD rating scale (ADHD-RS DSM-IV) was completed (DuPaul et al., 1998). This scale includes the 18 DSM-IV items on inattentive and hyperactive-impulsive symptoms, each to be scored on a four-point Likert scale, ranging from 0=never to 3 = always. Severity of the disorder was assessed by the Clinical Global Impression-Severity (CGI-S) for adults (Busner and Targum, 2007) and by the Children's Global Assessment Scale (CGAS) for adolescents (Shaffer et al., 1983, Molina et al., 2013). The CGI-S is a 7-point scale with scores from 1=normal to 7= most severe. The CGAS score ranges from 'extremely impaired' (1-10) to 'doing very well' (91-100). The Substance Use Questionnaire (SUQ) was used to assess substance use (Molina et al., 2013)· It assesses the use of alcohol in detail and other substances (tobacco, marijuana, amphetamines/other stimulants, barbiturates/other sedatives, opioids/other narcotics, inhalants, hallucinogenics/psychedelics, cocaine) in less detail. Participants responded to questions about lifetime use ("ever"), age of first use, and recent frequency of use for alcohol, marijuana, cigarettes, and a range of illicit and prescription drugs. All rating scales listed above were completed by a healthcare professional or research assistant who interviewed the participant or, when participants were younger than 18 years, interviewed their parent/carer.

To assess comorbid behaviour problems, participants in both groups completed the Youth Self Report (YSR) (adolescents), or the Adult Self report (ASR) (adults). The YSR and the ASR are both part of the Achenbach system of empirically based assessment (ASEBA) (Achenbach, 2009) and capture a range of mental health problems such as anxiety-depression, withdrawal depression, somatic complaints, thought problems, social problems, rule-breaking behaviour, aggression, and attention problems. The above syndromes were coalesced to form internalising (anxiety-depression, withdrawal depression and somatic complaints) and externalising problems (rule-breaking and aggressive behaviour) (Achenbach, 2009).

#### 2.2.2. Cardiovascular measures

24-hour blood pressure was measured using a Spacelabs ambulatory blood pressure recorder, and automatically analysed with the accompanying software (https://www.spacelabshealthcare.com/products/diagnostic-cardiology/abp-monitoring/). The recorder was placed on the subjects by a trained research-assistant or nurse blinded to treatment status and result of the echocardiogram. Hypertension in those aged 18-25 years (adults) was defined using the average of 24-hour blood pressure measures of SBP and/or DBP with a positive z value $\geq$ 1.65 (equivalent to the 95th percentile of the normal distribution) (Mancia et al., 2013). Hypertension in children

(below 18 years of age) was evaluated using a similar approach of using a z value $\geq$ 1.65 (to define the 95th percentile) which additionally depend on age, sex and height (Lurbe et al., 2009). The binary variable clinical hypertension was the primary dependent variable. The average SBP, DBP and mean blood pressure, pulse pressure and HR over the 24-hour period and separately during the day and night were recorded in each individual and were the secondary endpoints for analysis.

Echocardiograms. Experienced cardiac physiologists acquired the echocardiograms using Philips 7500 or IE33 ultrasound systems (Philips Inc, Andover, Mass, USA). All data were stored digitally and analysed by a single cardiac physiologist at a reference centre (SK at Evelina London Children's Hospital, London, UK) who was blind to the treatment status and blood pressure data. Left ventricular mass (LVM) was calculated using 2D-guided M-mode echocardiography in either a parasternal long axis or short axis view of the left ventricle, as recommended by the American Society of Echocardiography (Lang et al., 2005). The continuous variable LVM calculated according to the formula of Devereux (Devereux et al., 1986) and corrected for body-surface area (BSA), was used as the primary dependent variable.

### 2.3. Statistical approach

Descriptive and clinical characteristics of the subjects of the two groups were compared by analysis of variance (ANOVA) or non-parametric tests, as appropriate. A logistic regression model was built with group (MPH treated versus MPH-naïve) as independent variable and the binary variable hypertension (hypertension vs normal) as the dependent variable, and age and sex as covariates. Linear regression analyses were run on the continuous scores of SBP, DBP and mean blood pressure, pulse pressure and HR with group as independent variable. A linear regression analysis was also run with the LVM corrected for BSA as the dependent variable and group as the independent variable.

To limit the biases related to the allocation of methylphenidate treatment for the analysis of observational data, a propensity score was calculated (D'Agostino, 1998, Austin et al., 2007). In the initial comparative analysis, 28 variables were found to be different between the stimulant treated and the control group. To specifically determine the variables that must be included in the propensity scores, an association analysis of these 28 variables was made according to the blood pressure level (hypertension vs normal). Given the low power due to the sample size, we decided to take into account variables that were associated with hypertension at the p $<$0.250 level. At this stage, 19 variables were selected to compute the propensity scores using a logistic regression model. The propensity score was estimated after a multiple imputation of missing data using a Markov Chain Monte Carlo method. The quality of the propensity score was appreciated with standardized differences. The convergence criteria were met, and the validity indices were good. For details on the variables incorporated in the propensity analysis, see the supplementary materials Tables S2 and S3. The propensity score and potential confounders that were considered of major importance (because of their clinical relevance or because of the bivariate analysis) were incorporated in all analyses.

#### 2.3.1. Sample size calculation

We planned to include methylphenidate-treated ADHD patients and never-medicated ADHD controls in a ratio of 2:1. A sample size of 736 patients and 368 controls (total 1104) has 80% power (alpha = .05) to detect an increased relative risk of 2 (10% versus 5% negative cardiovascular outcomes (hypertension and abnormal echocardiogram) in treated patients and controls.

## 3. Results

Due to recruitment difficulties and exclusions, only 233 participants (162 in the methylphenidate and 71 in the control group) were enrolled. Blood pressure measures were available from 191 participants because these measures were considered unreliable in 42 participants because they did switch off the equipment during parts of the day and/or night.

### 3.1. Descriptive and clinical data

The daily dose of MPH ranged from 10 to 90 mg, with a mean of 34.5 mg (SD 14.4), the daily dose by weight ranged from 0.14 to 1.28 mg/kg (mean 0.61, SD 0.27). The duration of MPH treatment ranged from 24 months to 120 months (mean 60.1, SD 25.0). The MPH treated group, compared to the MPH naïve group, was on average 1.8 year younger, had less severe ADHD symptoms (while being on treatment), had more often a combined ADHD type, were diagnosed at an earlier age, and had lower weight and body mass index (BMI) (see Table 1). The MPH treated group had less often a positive family history for mental disorders (particularly autism and intellectual disability) and used marijuana less often (Table 1). Family history of cardiovascular disease and chronic physical disease was similar in both groups, as was SBP and DBP at study entry. In adolescent participants, co-occurring internalizing behaviour problems were less frequent in the treated group, whereas co-occurring externalizing problems and CGAS scores were similar in both groups (See Table S1 in the supplementary materials). In young adult participants, the treated group had lower total scores for co-occurring behaviour problems and a higher GAF score compared to the treatment-naïve group (Table S1). The physical and cardiovascular examinations did not reveal abnormalities and any differences between the two groups.

### 3.2. 24-hour blood pressure recording

The analysis of our primary dependent variable showed that a hypertension (blood pressure ($>95^{th}$ percentile) was observed in 12.2% (95% confidence interval 7.3 - 18.9%) of the participants in the MPH treated group and in 9.6% (95%CI 3.2 - 21.0%) of the treatment-naïve group with overlapping intervals (see Table 2). This result of a non-significant difference in the rate of hypertension in the MPH treated group was confirmed in the multivariate logistic regression analysis that also included age, sex and the propensity score (see Table 3). The 24-hour recorded SBP was significantly higher through day time in medicated ADHD than in unmedicated ADHD, but was similar in both groups through the night (see Table 2). 24-hour DBP did not differ between both groups during either daytime or through the night. HR was also significantly higher during daytime in medicated individuals with ADHD than in those with unmedicated ADHD, with no differences in HR during night time (Table 2).

**Table 1** Descriptive and clinical data

| | MPH treated ADHD (N= 162) | Medication naïve ADHD (N= 71) | Statistics |
|---|---|---|---|
| Gender n(%) | | | |
| Male | 132 (81.5) | 55 (77.5) | P=0.48 |
| Female | 30 (18.5) | 16 (22.5) | |
| Age mean(SD) | 15.6 (3.0) | 17.4 (4.2) | P < 0.0001 |
| 12-17 year n(%) | 136 (83.9) | 42 (59.2) | P < 0.0001 |
| 18-26 year n(%) | 26 (16.1) | 29 (40.8) | |
| Height (m) mean (SD) | 1.70 (0.12) | 1.7 (0.10) | P=0.19 |
| Weight (kg) mean (SD) | 58.6 (16.8) | 67.2 (19.1) | P=0.0008 |
| BMI mean (SD) | 20.5 (4.5) | 23.0 (5.4) | P=0.0006 |
| ADHD-DSM-IV Rating scale | | | |
| Total mean (SD) | 25.4 (12.0) | 30.5 (10.0) | P= 0.002 |
| Inattention mean (SD) | 14.1 (5.9) | 18.0 (5.4) | P < 0.0001 |
| Hyper/Impuls mean (SD) | 11.2 (7.1) | 12.6 (7.0) | P=0.20 |
| Age at ADHD diagnosis | | | |
| mean (SD) | 9.1(3.2) | 14.3(4.3) | P<0.001 |
| ADHD presentation type n(%) | | | |
| Inattentive | 31(19.4) | 27(38.6) | P=0.008 |
| Hyperactive/impulsive | 32(20.0) | 8(11.4) | |
| Combined | 97(60.6) | 35(50.0) | |
| Dosage methylphenidate | | | |
| mg/day mean (SD) | 34.5 (14.4) | n.a. | |
| mg/kg/day mean (SD) | 0.61 (0.27) | n.a. | |
| Duration of treatment | | | |
| Months mean (SD) | 60.1 (25.0) | n.a. | |
| Systolic BP mean (SD) | 119.5 (12.8) | 120 (12.5) | P=0.89 |
| Diastolic BP mean (SD) | 72.4 (9.1) | 72.9 (8.6) | P=0.78 |
| Employed n(%) | 30 (18.7) | 14 (19.7) | P=0.91 |
| Caucasian n(%) | 151 (96.8) | 68 (98.5) | P=0.27 |
| Education n(%) | | | |
| Secondary school | 82(50.9) | 35(49.3) | P=0.14 |
| Higher education | 15(9.3) | 13(18.3) | |
| Sport n(%) | 103(64.0) | 44(62.0) | P=0.77 |
| If yes: hours/week mean(SD) | 5.4(5.0) | 4.6(2.3) | P=0.20 |
| Cigarette smoking n(%) | 46(28.6) | 27(38.6) | P=0.17 |
| Use of alcohol n(%) | 102(63.4) | 50(71.4) | P=0.23 |
| Marijuana n(%) | 11(11.2) | 23(32.9) | P<0.001 |
| | | | |
| Mental disorder in family n(%) | 53(33.5) | 34(49.3) | P=0.027 |
| If yes: autism n(%) | 9(5.6) | 10(14.1) | P=0.025 |
| Intellectual disability n(%) | 2(1.2) | 5(7.0) | P=0.029 |
| Cardiovascular disease in family n(%) | 86(55.1) | 42(60.9) | P=0.42 |
| Chronic physical disease in family n(%) | 68(43.6) | 30(43.5) | P=0.99 |

MPH methylphenidate; BP blood pressure; n.a. not applicable

### 3.3. Left ventricular Mass

LVM and body-surface area (BSA) means were significantly higher in treatment-naïve than in medicated ADHD participants, but no significant group difference was found for the LVMBSA (Table 2). This latter result was confirmed in a multivariate regression model that incorporated age, sex, height, weight, and the propensity score (Table 4).

### 3.4. Post-hoc analyses in the ADHD treated group

Regression models were built with SBP, DBP and LVMBSA as dependent measures and daily dose of MPH, duration of MPH treatment, sex, and age as predictors. In none of the models, daily dose and duration of treatment were significantly related to the cardiovascular measures.

**Table 2** Dependent measures: 24 h blood pressure and hear rate, and left ventricular mass

| | MPH treated ADHD (N=139) | Medication naïve ADHD (N=52) | statistics |
|---|---|---|---|
| High-normal blood pressure n(%) | 17 (12.2)_ | 5 (9.6) | P=0.80 |
| 24h blood pressure mmHG mean (SD) Systolic BP | | | |
| Day | 122.8 (8.5) | 119.0 (12.2) | P=0.017 |
| Night | 107.1 (9.0) | 107.0 (10.0) | P=0.922 |
| 24h blood pressure Diastolic BP) | | | |
| Day | 72.3 (5.5) | 71.7 (6.3) | P=0.58 |
| Night | 58.2 (5.4) | 58.9 (5.9) | P=0.45 |
| 24h heart rate (bpm) mean (SD) | | | |
| Day | 84.1 (10.6) | 79.7 (10.3) | P=0.011 |
| Night | 68.0 (9.0) | 68.2 (12.5) | P=0.89 |
| | MPH treated ADHD (N=162) | Medication naïve ADHD (N=71) | statistics |
| Left ventricular mass mean (SD) | 113.3 (29.3) | 125.1 (31.6) | P=0.013 |
| BSA mean (SD) | 1.67 (0.3) | 1.80 (0.3) | P=0.002 |
| LVMBSA | 67.7 (12.8) | 69.9 (13.1) | P=0.277 |

**Table 3** Multivariate logistic regression model for high blood pressure

| High Blood Pressure | Odds Ratio | 95% Wald Confidence Limits | P (Chi-2) |
|---|---|---|---|
| Group (MPH treated versus treatment-naïve) | 1.69 | 0.49 - 5.86 | 0.4077 |
| Age | 1.00 | 0.86 - 1.17 | 0.9615 |
| Gender | 2.34 | 0.86 - 6.39 | **0.0975** |
| Propensity Score | 0.59 | 0.05 - 7.31 | 0.6818 |

**Table 4** Multivariate regression model for Left ventricular mass

| Parameter Estimate | | Standard error | P [t] |
|---|---|---|---|
| Group (MPH treated versus treatment-naïve) | -3.152 | 2.421 | 0.195 |
| Age | 0.2818 | 0.393 | 0.475 |
| Gender | -12.583 | 3.236 | **<.0001** |
| Height | -15.916 | 10.698 | 0.139 |
| Weight | 0.253 | 0.108 | **0.0206** |
| Propensity Score | 4.599 | 5.385 | 0.394 |

## 4. Discussion

This cross-sectional study compared adolescents and young adults with ADHD treated with MPH for at least 2 years with medication-naïve adolescents and young adults with ADHD on 24-hours recordings of blood pressure and on left ventricular mass corrected for body surface area. Our findings indicate that long-term exposure to MPH in individuals with ADHD was associated with a higher percentage of hypertension compared to stimulant-naïve participants with ADHD (12.2% versus 9.6%) but with overlapping confidence intervals. Furthermore, MPH exposure was associated with a small but statistically significant elevation of continuous measures of SBP and HR, but only during day time and not through the night. There were no differences between the two ADHD groups in DBP or left ventricular mass (LVM) corrected for body-surface area (BSA). All analyses were adjusted for a propensity score to limit biases arising from factors that may contribute to the decision to start MPH treatment.

The finding of an increase in SBP and HR associated with exposure to MPH is in line with previous reviews and meta-analyses (Hennissen et al., 2017, Liang et al., 2018). What our 24-hour blood pressure registration adds to previous studies is that this increase of SBP and HR is seen only during daytime and not maintained through the night. This means that the cardiovascular system can recover through the night, which will lower the risks of more persistent long-term adverse effects on the cardiovascular system. The absence of stimulant-associated changes in the DBP is also a reassuring finding. However, the percentage of hypertension was 25% higher in stimulant treated compared to treatment-naïve participants. Though not statistically significant with the current sample size, this finding is in line with previous studies that suggest that relatively small group-level changes in blood pressure may mask clinically significant blood pressure increases in a significant number of individuals. These findings support the recommendations in clinical guidelines to carefully monitor blood pressure and HR during treatment with psychostimulants (NICE 2018).

The present study used echocardiography to assess the left ventricular mass in stimulant treated and untreated participants with ADHD. We did not observe group differences in the left ventricular mass corrected for body surface area, while using a multivariate model that incorporated age, sex, height, weight and the propensity score. Left ventricular mass is particularly sensitive to an elevation of DBP, and thus this finding fits with the absence of increases in DBP.

The prescribed daily dose of MPH varied substantially from 10 to 90 mg, with an average dose of 34.5 mg. Given that the participants were adolescents and young adults this may be considered to be somewhat low compared with the doses recommended in guidelines, or those prescribed in prospective clinical studies. For example, in the Multimodal Treatment of ADHD (MTA) study, the daily doses of MPH for children 7-10 years old were on average between 30 and 41 mg (The MTA Cooperative Group 1999). However, the prescribed daily dose in this study reflects clinical practice in care-as-usual in five sites across Europe. Dose of MPH and treatment duration were not related to the cardiovascular parameters, which is with regard to dose in accordance with an earlier meta-analysis (Faraone et al., 2021). It should be noted that we were unable to collect information on medication adherence and assess the possible impact of drug holidays.

### 4.1. Strengths and limitations

This was the first study to implement gold standard and sensitive measures such as 24-hour blood pressure recordings and echocardiography to examine the potential associations between long-term exposure to methylphenidate and key parameters of the cardiovascular system. Given the relatively small number of patients included in the study due to recruitment problems and exclusions, the power of the analysis was reduced. The high percentage (18%, 42/233) of exclusions for the 24-hour blood pressure recordings, due to switching off the equipment and/or movement artefacts, is a reflection of the burden this study posed to the participants. Any interpretation of the results should take this limitation into consideration. Since the target and control groups did differ on a range of background variables and an observational design was used, we adjusted our analyses for a propensity score of variables that may be associated with the cardiovascular parameters and might bias the results. Nonetheless, there might still be differences between the two ADHD groups that we did not assess and may have confounded the analyses.

## 5. Conclusion

Long-term use of methylphenidate in adolescents and young adults with ADHD is associated with small but significant increases of SBP and HR during daytime. Proportions of hypertension do not differ significantly between MPH-treated and MPH-naïve individuals with ADHD. Future studies with larger samples, longer duration of treatment, and/or with within-subject designs are necessary. The results do, however, further support recommendations that highlight the importance of monitoring blood pressure and HR during MPH treatment (Cortese et al., 2013).

## Declaration of Interest

Jan K Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda, Medice, Angelini, and Servier, for work that is unrelated to the present paper. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents or royalties.

Gigi HH van de Loo-Neus has been in the past 3 years a speaker for Takeda and Medice without getting a fee, for work that is unrelated to the present paper. She is not an employee of any of these companies, and not a stock shareholder of any of these companies. She has no other financial or material support, including expert testimony, patents or royalties.

Peter Nagy has been in the past 3 years a consultant to and/or speaker for Medice, Servier, and Egis Pharmaceuticals for work that is unrelated to the present paper. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents or royalties.

David Coghill has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda, Medice, Novartis, and Servier, for work that is unrelated to the present paper. He has received royalties from Cambridge University Press and Oxford University Press. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, or royalties.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.09.001.

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