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Long-term safety of methylphenidate in children and adolescents with ADHD: 2-year outcomes of the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study

THE LANCET. PSYCHIATRY

Volume 10 Fascicolo 5 pagg. 323 – 333 (2023)

The publisher's version is available at:

[https://dx.doi.org/10.1016/S2215-0366\(23\)00042-1](https://dx.doi.org/10.1016/S2215-0366(23)00042-1)

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1 **Title**

2 **Long-term safety of methylphenidate in children and adolescents**
3 **with ADHD: Results of a two-year naturalistic pharmacovigilance**
4 **study.**

5

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14 † We would like to dedicate this manuscript to our friend and colleague Alessandro Zuddas
15 who contributed greatly to the ADDUCE Consortium and who sadly passed away in July
16 2022.

17

18

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77

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79 **Abstract/summary:**

80 **Background:**

81 Methylphenidate is the most frequently prescribed medication for the treatment of attention-
82 deficit/hyperactivity disorder (ADHD) in children and adolescents in many countries. While
83 many randomised controlled trials support short-term efficacy, tolerability, and safety, data on
84 long-term safety and tolerability are limited. The aim of this study was to investigate the safety
85 of MPH over a two-year period in relation to growth and development, psychiatric health,
86 neurological health, and cardiovascular function in children and adolescents.

87 **Methods:**

88 As part of the European Attention-Deficit-Hyperactivity-Disorder-Drugs-Use-Chronic-Effects
89 (ADDUCE) research program, a two-year naturalistic, longitudinal, controlled study was
90 conducted to assess adverse effects of methylphenidate on growth and development,
91 psychiatric, neurological, and cardiovascular health outcomes. Three cohorts were recruited:
92 medication-naive ADHD patients who intended to start methylphenidate treatment (ADHD-
93 MPH), medication-naive ADHD patients who did not intend to start any ADHD medication
94 (ADHD-noMPH), and a control group without ADHD (noADHD).

95 **Findings:**

96 In total, n=1,410 participants were included (ADHD-MPH: n=756, ADHD-noMPH: n=391,
97 noADHD: n=263). 1,070 (76.3%) participants were males, 332 (23.7%) were females and 8
98 with unknown gender. The average age for the cohort was 9.28 years (S.D.=2.78), interquartile
99 range 7 to 11. 93.1% (n=1,312) of the participants were Caucasian. The ADHD-MPH and
100 ADHD-noMPH groups differed in ADHD symptom severity and other characteristics. After
101 controlling for the effects of these variables using propensity score, there was little evidence of
102 impact on growth or increased risk of psychiatric/neurological adverse events in the ADHD-
103 MPH compared to the ADHD-noMPH group. A statistically significant increase in pulse rate
104 and systolic and diastolic blood pressure was observed in the ADHD-MPH group compared to
105 the ADHD-noMPH group after 24 months of treatment.

106 **Interpretation:**

107 Overall, the results suggest that long-term treatment with methylphenidate for two years is safe.
108 There was no evidence to support the hypothesis that methylphenidate treatment leads to

109 reductions in growth. Methylphenidate-related pulse and blood pressure changes, although
110 relatively small do require regular monitoring.

111 **Funding:**

112 European Union's Seventh Framework Programme Grant agreement; ID:260576.

113

114 **Research in context**

115

116 **Evidence before this study**

117 As part of the European Union-funded Attention-Deficit-Hyperactivity-Disorder-Drugs-Use-
118 Chronic-Effects (ADDUCE) project (ID: 260576) we conducted and published three systematic
119 reviews of studies on long-term adverse effects of MPH/ADHD medication. These reviews
120 highlighted the relative lack of long-term data for cardiovascular, growth, neurological and
121 psychiatric effects. Of ten studies on cardiovascular safety only two were longer than one year.
122 Neither of these reported significant changes in blood pressure or heart rate. We identified
123 eighteen studies focussed on the long-term effects of MPH on growth. While MPH was
124 associated with statistically significant pre-post reductions in both height and weight, effect
125 sizes were small, inconsistent across studies, and the clinical impact judged to be minimal. Data
126 on potential long-term effects of MPH on neurological and psychiatric outcomes were spread
127 across forty-six publications of varying quality and design. While several studies suggested a
128 reduction in depression and suicidality the findings for tics, dyskinesia, and psychosis-like
129 symptoms were inconsistent. None of these studies across all outcome domains included a
130 comparison with unmedicated ADHD.

131

132 **Added value of this study**

133 This is the first naturalistic, prospective, longitudinal, controlled study to investigate safety of
134 MPH over a two-year period in relation to growth and development, psychiatric health,
135 neurological health, and cardiovascular function in children and adolescents. Data from 1,410
136 children and adolescents were analysed. Over this period, save an effect on weight velocity at
137 the six-month assessment, MPH was not associated with growth or psychiatric/neurological
138 symptoms. Long-term MPH treatment was associated with significant, albeit moderate on
139 average, increases in systolic and diastolic blood pressure and pulse rate.

140

141 **Implications of all the available evidence**

142

143 Long-term safety data suggest that MPH used for the treatment of child and adolescent ADHD
144 is safe. Furthermore, long-term treatment with MPH appears to have beneficial effects not only
145 on the core symptoms of ADHD but also on several symptoms commonly associated with
146 ADHD. However, recommended follow-up examinations should be performed and, in
147 particular, pulse and blood pressure levels should be monitored.

Manuscript

148

149

150 **Introduction:**

151 Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder
152 characterised by the core symptoms of inattention, hyperactivity, and impulsivity, that is
153 associated with a wide range of psychiatric comorbidities and adverse health, academic, and
154 psychosocial outcomes ^{1,2}. The worldwide prevalence of ADHD is estimated to lie between 5-
155 7% in children and adolescents and 2-3% in adults, and the disorder is apparently more common
156 in males than in females ^{3,4}.

157 MPH, a central nervous system psychostimulant medication recommended by clinical
158 guidelines as a first-line treatment option for ADHD, is the most commonly prescribed
159 medication for the treatment of ADHD in children and adolescents globally ^{5,6}. MPH is known
160 to inhibit the reuptake of dopamine and norepinephrine into presynaptic neurons ⁷. It is assumed
161 that MPH increases the efficiency of prefrontal cortex activity and optimises executive and
162 attentional functions in patients with ADHD by improving dopaminergic and noradrenergic
163 modulation of cortical and subcortical circuits ⁸.

164 In recent decades, the use of MPH has increased considerably in many European countries as
165 well as in the United States, Asia, and Australia ⁶. While MPH is recommended as a first-line
166 treatment for ADHD in all current evidence-based ADHD clinical guidelines, it is not available
167 in all countries worldwide and has not yet been included in the World Health Organisation
168 (WHO) model list of essential medicines ^{9,10}. Indeed, two recent applications for inclusion in
169 this list were rejected by the committee, who stated that in their opinion, the benefit-to-harm
170 ratio of MPH remains uncertain for long-term use ¹⁰. Moreover, the committee also specifically
171 recommended that evidence on tolerability and safety of at least 52 weeks duration would be
172 informative for any future consideration for inclusion of MPH in the model list ¹⁰.

173 While short- and medium-term safety and tolerability of MPH have been extensively studied
174 ¹¹, we agree that long-term data are limited. This gap in knowledge was also highlighted by the
175 European Commission's Committee for Medicinal Products for Human Use (CHMP), which
176 specifically called for data describing the long-term (> 52 weeks) effects of MPH on (1) growth
177 and development, (2) neurological health, (3) psychiatric health, (4) sexual development and

178 fertility, and (5) cardiovascular responses in children and adolescents ¹². Here, we present data
179 from the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE)
180 research programme (ID: 260576). The ADDUCE consortium has conducted a programme of
181 research designed to fill the identified gaps in the current literature and to address the concerns
182 of the CHMP ¹³. ADDUCE has previously published a series of systematic reviews and
183 secondary analyses of existing datasets that describe the state of the art of the field ¹⁴⁻¹⁶. These
184 identified that a major gap in the field has been the failure to compare individuals routinely
185 taking ADHD medications in general clinical practice with individuals with ADHD who are
186 not on medication. The present paper addresses this gap and describes the findings from a two-
187 year (104 week) prospective cohort study designed to provide new data on long-term MPH
188 safety in children and adolescents with ADHD.

189 **Methods**

190 **Study design**

191 The ADDUCE study was a two-year (104 week) naturalistic prospective pharmacovigilance
192 multicentre study designed to investigate the long-term safety of MPH in children and
193 adolescents aged six to 17 years. The study was conducted in 27 European child and adolescent
194 mental health centres in the United Kingdom, Germany, Switzerland, Italy, and Hungary.
195 Ethical approval for the study was obtained from the East of Scotland Research Ethics Service
196 as the coordinating centre. In addition, ethical approvals were obtained for the other countries
197 and individual sites as necessary. Study participants were assessed five times over a two-year
198 follow-up period (see Figure 1). Three cohorts of children and adolescents were recruited:

199 ADHD-MPH group: children and adolescents with ADHD not previously medicated with any
200 ADHD medication who were about to start MPH treatment.

201 ADHD-noMPH group: children and adolescents with ADHD not previously medicated with
202 any ADHD medication, and who did not intend to start any ADHD medication.

203 noADHD group: an index group of children and adolescents without ADHD who screened
204 negative for ADHD at study enrolment.

205 Details of the study and of the study protocol have been published elsewhere ¹⁷.

206

207 **Participants**

208 To ensure that the study results could be generalised to typical ADHD populations in clinical
209 services throughout the EU the inclusion criteria were deliberately broad and the exclusion
210 criteria minimal. Eligible participants for the ADHD-MPH and ADHD-noMPH groups were
211 children and adolescents aged six to 17 years with ADHD diagnosed by a qualified clinician
212 according to the DSM-IV criteria. Participants eligible for the noADHD group were children
213 and adolescents within the same age range who scored less than 1.5 on average on the Swanson,
214 Nolan, and Pelham IV rating scale (SNAP-IV)¹⁸ for ADHD items, and whose hyperactivity
215 score on the parent-rated Strengths and Difficulties Questionnaire (SDQ)¹⁹ was within the
216 normal range (<6). Participants were excluded if they had previously taken any ADHD
217 medications but remained eligible if they had previously taken or were currently taking other
218 psychotropic drugs. Participants in the ADHD-MPH and ADHD-noMPH groups were recruited

219 from community-based child and adolescent mental health services at the four coordinating
220 centres in the UK, Germany, Italy, and Hungary and additionally in 23 satellite sites (n=6 in the
221 UK, n=4 in Italy, and n=13 in Germany and Switzerland). Children and adolescents in the
222 noADHD group were recruited through advertisements in the communities local to the clinical
223 sites. In accordance with country-specific regulations, required written informed consent/assent
224 was obtained from patients and their legal guardians prior to study participation.

225 **Outcomes**

226 The study outcomes were those highlighted by the European Medicines Agency (EMA) through
227 CHMP as needing additional research: growth, cardiovascular, psychiatric and neurological
228 health.

229 The **primary outcome** measure was height velocity, operationalised as height velocity standard
230 deviation score (SDS). This was estimated from at least two consecutive height measurements,
231 and normalized with reference to the mean and SD of a population of the same age and sex:

$$232 \text{ height velocity SDS} = \frac{v - \bar{v}}{\text{SD}}$$

233 The mean and SD height velocities for each country represented in the study were obtained
234 from the most recent standardized growth charts available for the respective countries.

235 Secondary growth outcomes were weight and body mass index (BMI). Cardiovascular health
236 was assessed through pulse rate and blood pressure, which were measured at each visit.
237 Outcomes for psychiatric health included: the Mood and Feelings Questionnaire (MFQ)²⁰ to
238 assess symptoms of depression; a shortened version of the Psychosis-Like Symptoms semi-
239 structured interview (PLiKSi)²¹ to assess delusions and hallucinations; and the Yale Global Tic
240 Severity Scale (YGTSS)²² to assess motor and phonic tics. The Columbia - Suicide Severity
241 Rating Scale (C-SSRS)²³ and the Substance Use Questionnaire (SUQ)²⁴ were used to assess
242 suicidality and substance use, respectively. Neurological outcomes regarding dyskinesia were
243 measured using the Abnormal Involuntary Movement Scale (AIMS)²⁵. The effectiveness of
244 MPH treatment on core ADHD and oppositional defiant disorder (ODD) symptoms was also
245 measured. Table S1 provides an overview of all outcome measures, and Table S2 presents the
246 schedule of visits and assessments.

247

248 **Statistical analyses**

249 Description at baseline

250 Characteristics of participants included in the study were presented for each group, and the
251 groups were compared using statistical tests (t-test, ANOVA, chi-square tests where
252 appropriate). The changes of time-varying factors throughout the study period are also
253 presented.

254 Within group changes over time were calculated using the crude scores for all three groups.
255 Due to the substantial difference between the groups with and without ADHD, it was not
256 possible to conduct propensity score analyses to account for baseline differences for all three
257 groups. Therefore, the longitudinal between-group analyses using adjusted estimates were only
258 conducted for comparisons between the ADHD-MPH and ADHD-noMPH groups (Table 2 and
259 Table 3).

260 Propensity score

261 We compared the outcome status between children in the ADHD-MPH group and the ADHD-
262 noMPH group. As children with severe symptoms may have a higher likelihood of being treated
263 with MPH, propensity score (PS) adjustment was applied to address potential differences in
264 patient characteristics between the medicated and the not medicated group²⁶. (Appendix 1)

265 Analysis for each outcome variable

266 Logistic regression models were used for dichotomous outcomes and generalized mixed models
267 were applied for continuous outcomes. The propensity scores were adjusted as a continuous
268 variable in all models. All continuous outcomes were log-transformed to ensure the model
269 assumptions are met for robust analyses^{27,28}.

270 We did not adjust p-values for multiple comparisons, as the primary hypothesis concerned the
271 effect of the 'group' variable. Moreover, in a pharmacovigilance study, statistical power is at
272 least as important as type one error.

273 Multiple imputation for missing data

274 Multiple imputations were conducted using a Gibbs sampler to address missing data. Only the
275 33 baseline factors that were included in the propensity score model were included in the
276 imputation. Both complete-case analyses and imputed analyses were conducted.

277 All analyses were conducted with SAS version 9.4.

278 **Role of funding**

279 The project received funding from the European Union's Seventh Framework Programme for
280 research, technological development and demonstration under grant agreement no. 324487.

281 The funder of the study had no role in study design, data collection, data analysis, data
282 interpretation, or writing of the report. However, the team worked with the European
283 Medicines Agency to ensure that the objectives of ADDUCE programme are addressing the
284 public health concerns raised by the CHMP.

285 **Results**

286

287 Between February 2012 and January 2016, n=756 participants were recruited into the ADHD-
288 MPH group, n=391 into the ADHD-noMPH group, and n=263 into the noADHD group (see
289 also Table S3). Due to the differences in clinical practice across the four participating
290 countries, the proportions of participants in each group differed considerably between
291 countries. As was to be expected, the majority of participants with ADHD were male (male:
292 82.4%, n=622; female: 17.6%, n=133; unknown: n=1 in the ADHD-MPH group and male:
293 85.0%, n=329; female: 14.8%, n=58; unknown: n=4 in the ADHD-noMPH group), and the
294 sex ratio in the noADHD group was much more balanced (45.6%, n=119 male, 53.6%, n=141
295 female). The majority of subjects across all three groups were Caucasian (ADHD-MPH
296 group: 696, ADHD-noMPH group: 373, noADHD group: 243). There were statistically
297 significant differences in age between the three groups, with a mean age of 9.22 years in the
298 ADHD-MPH group, 8.74 years in the ADHD-noMPH group, and 10.25 years in the
299 noADHD group. Table 1 provides an overview of the baseline characteristics, shows the
300 corresponding group comparisons. As this was a non interventional observational study not all
301 participants attended every visit (see Table S3) reasons for non-attendance were not captured.
302 There was no substantial difference in baseline characteristics between the complete sample
303 (Table 1) and those participants included in the 24 month follow-up assessments (Table S4).
304 Few participants in the ADHD-MPH group who attended visit reported discontinuing MPH
305 since previous visit (Table S5).

306 **Baseline differences**

307 In accordance with the age differences between the groups, corresponding differences emerged
308 with respect to height and weight at baseline, but not with respect to BMI. There were no
309 differences between the groups with regard to diastolic blood pressure or pulse rate. However,
310 baseline mean systolic blood pressure was higher in the noADHD and the ADHD-MPH groups
311 compared to the ADHD-noMPH group, and these differences remained statistically significant
312 after adjusting for age and sex. In line with expectation, compared to the noADHD group, the
313 two ADHD groups had higher scores on the SNAP-IV Total score, the Inattention and
314 Hyperactivity/Impulsivity subscales, and the SNAP-IV ODD scale (all $p < 0.0001$). Moreover,
315 the ADHD-MPH group had higher SNAP-IV scores (Total, Inattention and
316 Hyperactivity/Impulsivity) than the ADHD-noMPH group (all $p < 0.0001$). Table 1 provides an
317 overview of all baseline scores and the corresponding group differences.

318 **Adverse events**

319 No serious adverse events were reported during the study. The results of the between group
320 analyses (ADHD-MPH and ADHD-noMPH) are detailed in Tables 2 and 3 (imputed analyses)
321 and Tables S7 and S8 (complete case analyses).

322 **Growth**

323 There was no difference between the ADHD-MPH and ADHD-noMPH groups on height
324 velocity, the primary outcome, at any time point. Weight velocity showed an initial slowing at
325 six months in the ADHD-MPH group ($p < 0.0001$), but no differences were seen after this point.
326 There were no group differences with respect to BMI at any time point (see Table 3).

327 We further investigated the percentage changes in the height and weight velocity for the 3
328 groups detailed in figures S1-4. There were few differences between the three groups on the
329 percentage changes in the height and weight velocity (figure S1 and S2). We looked in more
330 detail at the subgroup of participants who had a decreased weight velocity at 6-months ($n=366$
331 in the ADHD-MPH group, $n=116$ in the ADHD-noMPH group and $n=109$ in the noADHD
332 group). While no major difference is observed for this group on height velocity in this subgroup,
333 there was a trend for increasing weight velocity throughout the follow-up period (figure S3 and
334 S4). Although we cannot conduct further analyses due to the limited sample size, these results
335 do not suggest that, at a group level, the reduction in weight velocity seen at 6 months continued
336 and that there was no subsequent loss of height velocity for this group, but instead their weight
337 velocity improved throughout the follow-up period.

338 **Cardiovascular**

339 Within group analyses identified that mean systolic blood pressure increased significantly
340 between baseline and 24 months in the ADHD-MPH (from 108 to 113 mmHg, $p < 0.0001$) and
341 ADHD-noMPH (104 to 108 mmHg, $p < 0.0001$) groups but not in the noADHD group (109 to
342 111 mmHg, $p = 0.08$). In the ADHD-MPH group, diastolic blood pressure (65 to 67 mmHg,
343 $p = 0.02$) and pulse rate (80 to 83 bpm) also increased over this period, while this was not the
344 case for the other two groups (64 to 65 mmHg, 66 to 65 mmHg, 80 to 79 bpm, 78 to 79 bpm).
345 Between group statistical analyses confirmed a greater increase in systolic and diastolic blood
346 pressure in the ADHD-MPH group compared to the ADHD-noMPH group at six, 12, and 24
347 (but not 18) months post-baseline. Moreover, pulse rate increased more in the ADHD-MPH

348 group than in the ADHD-noMPH group at 12 and 24 months but not at six or 18 months (see
349 Table 3).

350 **Psychiatric and Neurological Symptoms**

351 Parent- and child-ratings of mood improved significantly across all three groups during the
352 study. Child self-rated and parent-rated mood improved significantly more in the ADHD-MPH
353 group than in the ADHD-noMPH group after 24 months of treatment ($p=0.01$, $p=0.02$) (see
354 Table 3).

355 The prevalence of both broad and narrowly defined psychotic-like symptoms decreased for all
356 three groups. The numbers at baseline were too small to allow for a meaningful statistical
357 analysis. However, when adjusting for baseline differences, there were no significant
358 differences between the changes for the ADHD-MPH and ADHD-noMPH groups between
359 baseline and 24 months (see Table 2).

360 Tic prevalence decreased in all three groups ($p<0.0001$ for both ADHD groups and $p=0.02$ in
361 the noADHD group). After adjusting for baseline differences, the two ADHD groups did not
362 significantly differ regarding tic reduction at six months. However, at 12 months, the tic
363 reduction was significantly greater in the ADHD-noMPH group than in the ADHD-MPH group
364 (odds ratio 4.71, $p=0.041$). At 24 months, the prevalence of tics in the ADHD-MPH group was
365 still 2.4% but it was not possible to calculate an odds ratio between the two groups at this time
366 point because the prevalence in the ADHD-noMPH group was zero (see Table 2).

367 The prevalence of suicidal ideation and behaviour decreased steadily for all three groups across
368 the study. At 24 months, the prevalence lay at 3.17% in the ADHD-MPH group, 0.77% in the
369 ADHD-noMPH group, and 0.76% in the noADHD group. After adjusting for baseline
370 differences, there were no significant group differences between the ADHD-MPH and ADHD-
371 noMPH groups at the six-, 12-, and 24-month follow-ups. The results were unchanged when
372 suicidal ideation and suicidal behaviour were considered separately (see Table 2).

373 Prevalence rates for reported smoking were low at baseline in all three groups (ADHD-MPH:
374 4.9%, ADHD-noMPH: 2.8%, noADHD: 3.0%), remained low in all groups over the entire 24-
375 month observation period with rates at 24 months of 2.1%, 1.5% and 2.7% respectively, and
376 decreased over this period in the ADHD-MPH group. Alcohol use was significantly less
377 prevalent in both ADHD groups than in the noADHD group at baseline (0.5% in both ADHD

378 groups vs 2·3% in the controls) and remained below the level of the control group during the
379 observation period (ADHD-MPH: 0·9%, ADHD-noMPH: 0%, noADHD: 4·9%). Marijuana
380 use was also uncommon at baseline in all three groups and remained low throughout the
381 observation period (always less than 1% in all groups). After adjusting for baseline differences,
382 we found no evidence for negative effects of MPH on smoking, alcohol use, or marijuana use
383 (see Table 2).

384 Scores on the AIMS, indicating abnormal movements, decreased (with lower scores reflecting
385 greater improvement) for all three groups during the 24-month period. After adjusting for
386 baseline differences, we found a larger AIMS score reduction during treatment in the ADHD-
387 MPH group than in the ADHD-noMPH group at six ($p<0\cdot0001$) and 12 ($p<0\cdot0016$) but not 24
388 ($p=0\cdot09$) months (see Table 3).

389 Results on ADHD core symptoms are summarised in Table 3 and Appendix 2.

390 **Discussion**

391 Using a naturalistic, prospective, longitudinal, controlled design, the ADDUCE study was the
392 first to collect comprehensive data on the safety of MPH in previously stimulant naïve children
393 and adolescents with ADHD over a two-year period in terms of growth, cardiovascular
394 function, and psychiatric and neurological health and compared these with participants with
395 ADHD not treated with MPH and a non-ADHD comparison group.

396 Due to concerns that a reduction in growth may be a particularly common adverse effect of
397 long-term administration of MPH for ADHD, we chose height velocity as the primary outcome
398 measure for this study. Our findings did not reveal any differences in height velocity between
399 the groups with and without MPH treatment at any of the follow-up time points. These findings
400 conflict with the conclusions of our recent systematic review and meta-analysis on the impact
401 of long-term stimulant treatment on growth by Carucci and colleagues¹⁴. There we reported that
402 MPH might be associated with a slight growth deficit, especially with respect to height, but that
403 these reductions were judged to have a minimal clinical impact and to generally remit in
404 adulthood. In that review the pre-post standardized mean difference for the effects of 24-month
405 treatment with a stimulant medication (either MPH or amphetamine) was small (SMD 0·27,
406 95% CI 0·22-0·31), and interestingly, only half (6/12) of the included studies reported pre-post
407 differences in height¹⁴.

408 With respect to weight, the only differences between medicated and unmedicated individuals
409 with ADHD in our sample were identified six months after starting medication, and there were
410 no between-group differences at 12, 18, or 24 months. These findings are in line with the results
411 of the meta-analysis by Carucci and colleagues¹⁴, who reported small but significant reductions
412 in weight gain associated with MPH as a monotherapy (SMD 0·24, 95% CI 0·14-0·35), which
413 is equivalent to a reduction in weight gain of around 1·43 kg over a 2-year period for a ten-
414 year-old boy. Similar to the findings of our current study, several authors have reported that the
415 effects of psychostimulants on weight are time-limited and subsequently normalize²⁹⁻³¹.

416 The finding of an increased systolic blood pressure in our sample is consistent with a recent
417 systematic review and meta-analysis by Hennissen and colleagues¹⁵, who found a small but
418 statistically significant increase associated with MPH treatment (SMD 0·25, 95% CI 0·08–0·42,
419 $p < 0·01$) when pooling the results of ten trials. However, unlike the latter review, we here also
420 found statistically significant increases in both diastolic blood pressure and pulse rate in the

421 medicated vs. unmedicated ADHD group. Results of another study of the ADDUCE consortium
422 showed that long-term use of MPH in adolescents and young adults with ADHD (aged 12 to 25
423 years) was associated with a small but statistically significant increase in systolic blood pressure
424 and heart rate compared to controls (=ADHD patients without MPH treatment), whereas
425 diastolic blood pressure did not differ between the two groups³². Overall, current data suggest
426 that long-term treatment with MPH affects cardiovascular parameters, although these effects
427 appear to be mostly without clinical significance.

428 Depression scores in our sample, as measured by the MFQ, were higher (worse) at baseline in
429 patients with ADHD than in controls but decreased in the ADHD-MPH group over the 24
430 months of the study. This corresponds to findings from several other studies providing evidence
431 that long-term MPH treatment is associated with a favourable outcome regarding mood and
432 depression^{16,33,34}. A nationwide longitudinal cohort study using the Swedish national registers
433 found that ADHD medication was associated with a reduced long-term risk (i.e., three years
434 later) for depression, and this risk was lower for longer duration of ADHD medication³⁵.
435 Moreover, a within-individual analysis suggested that depression was 20% less common during
436 periods when patients received ADHD medication compared to periods when they did not
437 receive medication³⁵.

438 We found no evidence that long-term treatment with MPH increased the risk of psychosis-like
439 symptoms. This finding is consistent with several previous studies. An analysis of population-
440 based electronic medical records in Hong Kong, based on Clinical Data Analysis and Reporting
441 System (CDARS) data from 2001 to 2014, found no evidence for increased risk of psychosis
442 during MPH-exposed compared with non-exposed periods³⁶. Furthermore, a Swedish cohort
443 study using population-based observational data from three population-based registries also
444 found no increase in psychotic events during MPH treatment³⁷. Two other comparative studies
445 also provided evidence that MPH reduces the risk of psychosis-like symptoms^{38,39} and one
446 study found that MPH treatment reduced the risk of hospitalization for psychosis³⁴. However,
447 as we pointed out in our own review, there is also some, albeit limited, evidence that psychosis
448 may result from MPH treatment in individual cases¹⁶.

449 Our findings also suggest that long-term MPH use is generally safe in patients with ADHD and
450 comorbid tics. This is in line with several studies showing that, in most cases, stimulants do not
451 worsen tics in patients with ADHD and coexisting tic disorder⁴⁰. However, clinicians should

452 continue to exercise caution when using MPH in individuals prone to tics, as it may still
453 exacerbate existing tics in individual cases.

454 The higher reported rates of suicidal behaviour and/or suicidal ideation in the ADHD-MPH
455 group before treatment may reflect the severity of the psychiatric symptoms that prompted the
456 decision to assess for ADHD in the first place. Similarly, the higher rates in the ADHD-MPH
457 group compared to the ADHD-noMPH group may also be reflected in the clinical decision to
458 initiate medication treatment due to greater severity. Our finding that MPH treatment was not
459 associated with an increased incidence of suicidal ideation, and may in fact be associated with
460 a reduction in risk, is in line with several other studies¹⁶. Chen and colleagues reported a 20%
461 within-patient reduction in the rate of suicide-related events during periods on stimulant
462 medication⁴¹. Using a self-controlled case series design based on data from the Hong Kong
463 CDARS registry, Man and colleagues reported that the incidence of suicide attempts was higher
464 in the 90-day period immediately before the start of MPH treatment and returned to baseline
465 levels during continuation of MPH treatment⁴². In a Taiwanese nationwide population-based
466 cohort study, Liang and colleagues observed a 72% risk reduction in those prescribed MPH for
467 more than 180 days⁴³. Moreover, in a large cohort of patients with ADHD, within-individual
468 analyses demonstrated that stimulant medication was associated with a 28% reduced risk of
469 suicide attempts⁴⁴.

470 Potentially due to the relatively young age of our sample, we found a very low prevalence of
471 reported substance use in the two ADHD groups, which were even lower than those in the
472 noADHD control group. Notwithstanding the low prevalence of reported substance use at
473 baseline, there was no indication that MPH treatment increased the risk for smoking, alcohol or
474 marijuana use. This is in line with findings from previous studies. For instance, Humphreys and
475 colleagues found comparable outcomes between children with ADHD - with and without a
476 history of medication treatment - for any substance use as well as for abuse or dependence
477 outcomes across all substance types⁴⁵. Likewise, Chang and colleagues found no increased risk
478 of substance abuse among individuals prescribed with stimulant ADHD medication⁴⁶.
479 Furthermore, Schoenfelder and colleagues reported that consistent stimulant treatment of
480 ADHD may reduce smoking risk and that this effect was larger in samples with more severe
481 psychopathology⁴⁷.

482 In the present study, we found no evidence of an increased risk of MPH-induced dyskinesia.
483 Rather, the results suggest that treatment with stimulants may, at least initially, reduce the

484 abnormal involuntary movements as measured by the AIMS. This may be mediated by reduced
485 hyperactivity and improved motor control.

486 The present findings need to be interpreted in the context of some limitations. First, the study
487 focussed on long-term safety rather than tolerability so we cannot comment on long-term
488 tolerability. Second, in common with all long-term observational studies and clinical trials, we
489 experienced a high loss-to-follow up over the 2 years follow-up period with 53.5% (n=755)
490 attended the visit at 24-month. Our participants were all stimulant naive at entry into the study
491 and it is likely that tolerability estimates are going to be lower in this type of sample than seen
492 in industry-sponsored studies that almost include those previously treated. While it is important
493 to highlight this limitation and note that the interpretations of our findings should be with
494 caution it is also important to recognise that longer term safety outcomes are only relevant to
495 those individuals that continue a treatment. Third, the observation period of the study was two
496 years, but, in routine care, many children and adolescents with ADHD will be treated with MPH
497 for a longer period. Fourth, despite the large sample size for a prospective study, the sample
498 size is still too small to rule out the possibility that long-term MPH treatment might result in
499 extremely rare but serious adverse events; however, previous retrospective studies with very
500 large samples have not yielded significant safety concern^{35-37,41,42,44,46,48-51}. Fifth, of relevance
501 for the interpretation of the results, a lack of mean change in growth (and in other aspects) does
502 not mean that clinically relevant changes cannot occur in individual cases. Accordingly, control
503 examinations for height and weight progression, as recommended by clinical guidelines remain
504 indicated even if there were no changes on average for the study population as a whole. Sixth,
505 as most of the participants are males and Caucasian, we are not able to perform gender-specific
506 or ethnicity-specific analyses due to the limited diversity in the study cohort. Seventh, this is an
507 observational study, we allowed the clinicians to choose the most appropriate treatment for the
508 individual patient in their own clinic and therefore did not restrict the treatment form in any
509 preparation, formulation, and dose. In addition, dose was recorded using a free-text entry and
510 adherence to treatment was not assessed. Eighth, similar to all observational studies, we could
511 not exclude the possibility of unmeasured confounding due to the naturalistic and observational
512 nature of this study. Additionally, the application of propensity score adjustment is one of the
513 few propensity-score-based analytic methods where the extent to which covariates were
514 successfully balanced between treated and comparator groups is difficult to investigate and to
515 demonstrate empirically²⁶. Ninth, as participants were recruited from 27 sites across four
516 countries it was not possible to compare findings across the different sites as the sample size

517 will not allow meaningful comparison. Finally, the study investigated long-term effects of MPH
518 only. To compare the safety profile of MPH with other approved ADHD medications, further
519 comparable prospective studies would be desirable.

520 In summary, the results of this study suggest that safety profile of long-term treatment with
521 MPH for two years is acceptable. The data do not support the hypothesis that long-term MPH
522 treatment is associated with impairments in growth. Pulse and blood pressure changes, although
523 minor on average, require regular monitoring. Moreover, long-term MPH treatment in children
524 with ADHD appears to have rather beneficial effects on some co-existing psychiatric
525 symptoms.

526

527 **Contributors**

528 ICKW, DC and TB were responsible for the study concept. All authors were responsible for
529 the study design. DC, AH, TB, SI, JB, SC, RWD, PG, and PN responsible for subject
530 recruitment. DC, TB, KM and ICKW verified the underlying data, BF and KM did the
531 statistical analyses. All authors were involved in the interpretation of data. KKCM, AH, DC,
532 TB and ICKW drafted the manuscript. All authors critically revised the manuscript for
533 important intellectual content. DC and ICKW were responsible for resource acquisition.

534 All authors had full access to all the data in the study, contributed to drafting the report, and
535 all take final responsibility for its content and for the decision to submit for publication.

536

537 **Declaration of interests**

538 KKCM reports grants from the CW Maplethorpe Fellowship, the National Institute for Health
539 Research, United Kingdom; the European Union Horizon 2020 Framework, Hong Kong
540 Research Grant Council and personal fees from IQVIA Holdings, Inc., unrelated to this work.

541 AH has received compensation for serving as consultant or speaker for Shire/Takeda and
542 Medice. The present work is unrelated to the above grants and relationships.

543 TB served in an advisory or consultancy role for Eyelevel, Infectopharm, Lundbeck, Medice,
544 Neurim Pharmaceuticals, Oberberg GmbH, Roche and Takeda. He received conference
545 support or speaker's fee by Jansen, Medice, and Takeda. He received royalties from Hogrefe,
546 Kohlhammer, CIP Medien, Oxford University Press; the present work is unrelated to these
547 relationships.

548 SI has no conflict of interest.

549 JB has been in the past 3 years a consultant to / member of advisory board of / and/or speaker
550 for Takeda/Shire, Roche, Medice, Angelini, Janssen, and Servier. He is not an employee of
551 any of these companies, and not a stock shareholder of any of these companies. He has no
552 other financial or material support, including expert testimony, patents, royalties.

553 SC had collaborations within projects from the European Union (7th Framework Program)
554 and in sponsored clinical trials by Shire Pharmaceutical Company, Lundbeck, Otsuka,
555 Janssen-Cilag and Angelini.

556 MD has received research funding outside this study from Takeda/Shire.

557 RWD has received compensation for serving as consultant or speaker, or he or the institution
558 he works for have received research support or royalties from the organizations or companies
559 indicated: EU (FP7 Programme), US National Institute of Mental Health (NIMH), German
560 Federal Ministry of Health/Regulatory Agency (BMG/BfArM), German Federal Ministry of
561 Education and Research (BMBF), German Research Foundation (DFG), Volkswagen
562 Foundation; Boehringer Ingelheim, Ferring, Janssen-Cilag, Lilly, Lundbeck, Otsuka, Servier,
563 Shire, Sunovion/Takeda and Theravance. He was a former employee in clinical CNS research
564 of Eli Lilly until Aug 2008, and owns Eli Lilly stock (small part of the respective annual
565 salary). Since then, he has fully been affiliated with the Department of CAP, CIMH, Med
566 Faculty Mannheim, University of Heidelberg, Germany.

567 BF has been a consultant to and/o speaker for Abbvie, Actelion, Allergan, Ammirall, Alnylam,
568 Amgen, Astellas, Astrazeneca, Bayer, Biogen, Biopeps, Bioproject, Biotronik, BMS,
569 Boehringer, Celgène, Daiichi-Sankyo, Ethypharm, Forestlab, Genevrier, Genzyme, Gilead,
570 Grünenthal, GSK, Idorsia, IMS, Indivior, IQVIA, JNJ, Léo, Lilly, Lundbeck, Menarini, MSD,
571 Novartis, Novonordisk, Otsuka, Pfizer, Pierre-Fratre, Recordati, Roche, SANOFI, Servier,
572 Takeda, UCB, ViiV and Wellmera.

573 PG has no conflict of interest.

574 CH receives research funding from the National Institute of Health Research (NIHR)
575 including the Health Technology Assessment (HTA) SATURN trial (Grant ref: NIHR128472)
576 comparing methylphenidate with guanfacine for children and young people with ADHD and
577 tics. CH was chair of the NICE Guideline (CG155) for psychosis and schizophrenia in
578 children and young people; member of the NICE ADHD Guideline Update committee
579 (NG87) and is a member of Eunethydis and the European ADHD Guideline Group.

580 KK has no conflict of interest.

581 HK has no conflict of interest.

582 EL has no conflict of interest.

583 SM has received speaker's fee, travel support and research support from Shire outside the
584 submitted work.

585 AN received research funding from the European Commission, the German Ministry of
586 Health and the German Federal Joint Committee outside the submitted work.

587 PN has been a consultant to and/or speaker for Medice, Servier, and Egis Pharmaceuticals for
588 work that is unrelated to the present paper.

589 ER received speaker's fee and travel support support from Shire outside the submitted work.

590 ESB has received in the last 3 years speakers fees from Takeda and Medice and research
591 support from QBTech.

592 AZ served in an advisory or consultancy role for Angelini, EduPharma, Servier. He received
593 conference support or speaker's fee by Angelini and Janssen. He has been involved in clinical
594 trials conducted by Angelini, Janssen, Lundbeck, Otsuka, Roche, Sevier, and Shire. He
595 received royalties from Giunti OS, Oxford University Press.

596 ICKW reports research and educational funding outside the submitted work from Amgen,
597 Bristol Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, Takeda, the Hong Kong
598 Research Grants Council, the Hong Kong Health and Medical Research Fund, the Hong Kong
599 Innovation and Technology Commission, the NIHR, the European Commission, and the
600 Australian National Health and Medical Research Council, and has also received expert
601 testimony payment from the Hong Kong Court of Final Appeal

602 DC has been in the past 3 years a consultant to / member of advisory board of / and/or speaker
603 for Takeda/Shire, Medice, Novartis, and Servier. He has received royalties from Oxford
604 University press and Cambridge University press. He is not an employee of any of these
605 companies, and not a stock shareholder of any of these companies. He has received research
606 support during this period from the Australian National Health and Medical Research Council
607 and the Royal Children's Hospital Foundation and funding for the current study from the
608 European Commission

609

610 **Data sharing**

611 The anonymised datasets generated during and/or analysed during the current study are
612 available from the corresponding author on reasonable request subjected to IRB approval of
613 the requestor's institution and review of investigators of ADDUCE Consortium.

614

615 **Acknowledgments**

616 This project has received funding from the European Union's Seventh Framework Programme
617 for research, technological development and demonstration under grant agreement no.
618 324487. The authors wish to thank the children and adolescents who took part in the study,
619 and their families.

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