Blood pressure, heart rate, and CNS stimulant medication use in children with and without ADHD: analysis of NHANES data

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It is estimated that 2–3% of children in the US have hypertension (HTN) and 8% of children ages 4–17 carry the diagnosis of attention-deficit hyperactivity disorder (ADHD). The prevalence of HTN and cardiovascular (CV) risk factors in children with ADHD on CNS stimulant treatment (stimulants) compared to no treatment and compared to their healthy counterparts is not well described. Using National Health and Nutrition Survey data, we examined demographic, blood pressure (BP) and CV risk factors of 4,907 children aged 12–18 years with and without the diagnosis of ADHD, and further examined the CV risk in a subgroup of ADHD patients on stimulants. Three hundred eighty-three (10.7%) children were reported to have ADHD, of whom 111 (3.4%) were on stimulants. Children with ADHD on stimulants were significantly younger, male, and white compared to those with ADHD not on medication and those without ADHD. Body mass index (BMI), eGFR, cholesterol, the prevalence of albuminuria, and poverty were not significantly different between the three groups. One hundred sixty (2.7%) had BP in the hypertensive and 637 (12.4%) in the pre-hypertensive range. The prevalence of elevated BP (HTN and/or pre-HTN range) was not different between children with ADHD on stimulants compared to ADHD without medication and those without ADHD. Heart rate (HR) was significantly higher in the ADHD group on stimulants vs. the groups ADHD on no stimulants and without ADHD. When the relationship between stimulants and the risk of abnormal BP was examined, there was a significant interaction between having BP in the HTN range and sex. After adjusting for BMI, race, and age, females with ADHD on stimulants tended to be older and had significantly more BP in the hypertensive range. On the other hand, males were more likely to be of a white race and older, but not hypertensive. Children with ADHD on stimulants have significantly higher HR than children with ADHD on no stimulants and children without ADHD. On the other hand, the prevalence of abnormal BP classification is comparable between the three groups.

Keywords: hypertension, heart rate, pediatrics, attention-deficit hyperactivity disorder, NHANES, central nervous system stimulants

INTRODUCTION

Hypertension (HTN) in children and adolescents has been associated with target organ damage. It has been reported that as many as 34–38% of young adults with mild blood pressure (BP) elevation demonstrate left ventricular hypertrophy, which is the most common manifestation of target organ damage in childhood and adolescent HTN. Other associated comorbidities include retinopathy, cognitive impairment, and decreased glomerular filtration rate (GFR) and atherosclerotic plaques in the aorta and carotid arteries (1–4).

Centers for Disease Control and Prevention (CDC) analysis of data from the 2007 National Survey of Children’s Health (NSCH) (5) found 9.5% of US children aged 4–17 years ever been diagnosed with attention-deficit hyperactivity disorder (ADHD), representing 5.4 million children in the US. Furthermore, ADHD diagnosis was two times more prevalent among males than females. Approximately 66.3% of children were reported to be taking medication for the disorder, with the highest prevalence of medication treatment among males aged 11–14 years. It should be noted that the prevalence of ADHD in children increased from 7.8% in 2003 to 9.8% in 2007 – a 21.8% increase in 4 years (5).

Stimulants are the mainstay of ADHD treatment. The effectiveness of stimulants in treating ADHD has been well documented. However, in 2006, because of concern over the cardiovascular...
The prevalence of HTN and other CV risk factors in children with ADHD on CNS stimulant medication compared to children with ADHD without CNS stimulant medication and children without ADHD is not well described. Using data from National Health and Nutrition Examination Survey (NHANES) 1999–2004, we examined demographic and CV risk factors in children with and without the self-reported diagnosis of ADHD. In addition, we examined CV risk factors in children with ADHD on CNS stimulant medications. Finally, since differences in prevalence of ADHD, medication treatment of ADHD, and abnormal BP have been reported by sex, we tested a hypothesis of an interaction between BP and sex among children with ADHD on CNS stimulants.

MATERIALS AND METHODS

STUDY POPULATION

Data from NHANES for the years 1999–2004 were analyzed. NHANES is an ongoing nationally representative cross-sectional survey of the civilian, non-institutionalized US population that uses a complex, stratified, and multistage probability design. The survey is performed by the National Center for Health Statistics at the CDC and released in 2-year increments. Survey participants underwent standardized interviews, physical examinations, and laboratory testing in their homes and at a mobile examination center (MEC). Height, weight, and BP measurements were obtained on all NHANES participants aged 12–18 years.

National Health and Nutrition Survey 1999–2004 was approved by the National Center for Health Statistics Institutional Review Board. All of the participants 18 years of age provided informed consent and for those participants under the age of 18 years, parents/guardians provided informed consent.

Participant use of CNS stimulants was obtained from self-report. A personal interview was conducted as part of NHANES protocol and participants were queried on use of prescription medication during a 1-month period prior to the survey date. Participants 16 years of age and younger had a proxy respond for them while those older than 16 years responded for themselves.

STUDY VARIABLES

Demographic variables included in the current study are age (years), sex, and self-reported race/ethnicity (categorized as Mexican-American, Black, White, and other). Poverty-income ratio (PIR) is a ratio of a family’s income to the poverty threshold as defined by the US Census Bureau. A PIR ≤1 was defined as below the poverty threshold by NHANES.

Physical examination measures were obtained in the MEC according to standardized protocol (7). Three systolic and diastolic BP measurements were obtained for each participant using a mercury sphygmomanometer. Based on the average of three BP measurements and using methods similar to those previously published (8, 9), we classified participants as having BP in the hypertensive range if BP was ≥95th percentile for age, sex, and height and BP in the pre-hypertensive range if BP was ≥90th percentile and <95th percentile for age, sex, and height. A 60 s pulse (heart rate [HR]) was calculated by multiplying the 30-s resting HR times two (1). Participants receiving antihypertensive medications were excluded from this study.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²). BMI z-scores were calculated based on 2000 CDC growth charts (10).

Laboratory procedures are described in detail in the NHANES General Information for Public Files and Laboratory Files (11, 12). High-sensitivity C-reactive protein (CRP) was measured by latex-enhanced nephelometry. Serum cholesterol levels were measured on the Beckman SynchroX L20 (Beckman Coulter, Brea, CA, USA). Urinary albumin levels were measured by using a solid-phase fluorescent immunoassay. Urinary creatinine levels were measured by using the Jaffe rate reaction with a CX3 analyzer (Beckman Astra, Brea, CA, USA). The urinary albumin/creatinine ratio (ACR) was calculated as urinary albumin divided by urinary creatinine. A 1:30 was used to define albuminuria. Serum creatinine was measured by means of the modified kinetic Jaffe reaction during the survey period. Because the Jaffe method is known to overestimate eGFR compared to current “gold standard,” glomerular filtration rate (eGFR) was estimated using the new Schwartz formula (13), which has a constant that on average estimates GFR to be lower by 20% compared to the old formula in the adolescent population. Also, the new Schwartz formula is close to the Cournahan–Barratt formula used in Europe to estimate GFR.

Attention-deficit hyperactivity disorder was ascertained through self-report among NHANES participants aged 12–18 years of age. Participants were asked whether or not they were ever told by a doctor or health professional that they had attention-deficit disorder.

STATISTICAL ANALYSIS

Continuous, normally distributed variables are presented as mean ± SD and categorical variables are presented as % (n). p-Values were calculated by weighted least squares or weighted logistic regression analyses. Continuous, abnormally distributed variables are presented as median (25th, 75th percentile). Given that the prevalence and use of medication for ADHD is more common among males, we tested the hypothesis that BP (systolic and diastolic percentile) was influenced by the sex of the ADHD child. An interaction term product of sex × BP percentile (systolic and diastolic separately) was entered into two regression models to represent the interaction. Statistical regression models adjusted for ADHD (with and without CNS stimulant use), age, BMI z-score, ethnicity (white vs. non-white), fasting glucose, total cholesterol, eGFR, CRP, HR, and poverty.

Standard errors for all estimates were obtained with the Taylor-linearized variance estimation. Six year sample weights were applied to account for the complex sampling design of NHANES. This includes unequal probabilities of selection, over-sampling, and non-response. All statistical tests used a two-tailed α of <0.05 and were run on Stata (SE 11.2; College Station, TX, USA).

RESULTS

Table 1 presents the characteristics of the 4,907 children aged 12–18 years in NHANES 1999–2004 meeting the study inclusion criteria.
Table 1 | Demographic and bio-clinical characteristics of study population.

| BP classification range | ADHD on CNS stimulants | ADHD not on CNS stimulants | No ADHD | Total |
|--------------------------|------------------------|----------------------------|---------|-------|
| Normotensive             | 82.64 (91)             | 84.19 (228)                | 85.12 (2791) | 84.96 (4110) |
| Pre-hypertensive         | 13.79 (16)             | 13.24 (37)                 | 12.19 (584) | 12.36 (637) |
| Hypertensive             | 3.57 (4)               | 2.06 (7)                   | 2.69 (149)  | 2.57 (160)  |
| Systolic BP percentile   | 40.87 (31.93)          | 37.53 (30.70)              | 38.46 (3752) | 38.48 (36.89) |
| Diastolic BP percentile  | 38.78 (33.94)          | 38.68 (33.02)              | 41.54 (3763) | 41.23 (3728) |
| Pulse (beats/min)        | 81.72 (170.03)         | 76.33 (15.62)              | 76.76 (1757) | 76.90 (1754) |

*Continuous variables presented as mean ± SD and categorical variables presented as % (n). p-Values calculated by weighted chi-square analysis or weighted least squares with no ADHD as the reference.

*p < 0.05 for comparison between ADHD on CNS stimulants and no ADHD.

*p < 0.05 for comparison between ADHD not on CNS stimulants and no ADHD.

*p < 0.05 for chi-square analysis between ADHD with and without CNS stimulants and no ADHD.

criteria. Since this was a representative sample of the US population, these children represent nearly 23 million non-institutionalized US children between the ages of 12–18 years in the US. Among these, 10.8% (n = 383) had self-reported diagnosis of ADHD; 7.3% (n = 272) were not on ADHD CNS stimulant medications; and 3.4% (n = 111) were on CNS stimulant medications. Mean age was 15 years (SD 2.8). Children with ADHD on CNS stimulant medication were significantly younger, male, and white (p < 0.05) compared to those with ADHD not on medication and those without ADHD. HR was significantly higher in children with ADHD on CNS stimulant medication compared to children with ADHD and not on stimulants (76.33 beats/min) and children with no ADHD (76.76 beats/min) (Table 1). BMI z-score, eGFR, cholesterol, the prevalence of albuminuria, and poverty were not significantly different between the three groups.

Among the study sample, 2.7% (n = 160) children had a mean BP in the hypertensive and/or pre-hypertensive range. The prevalence of abnormal BP (hypertensive and/or pre-hypertensive range) was not significantly different between children with ADHD on CNS stimulant medication compared to children with ADHD without medication and those without ADHD. Systolic and diastolic BP percentiles were also not significantly different between the three groups (Table 1).

In linear regression models with systolic and diastolic BP percentile (BP percentile for age, sex, and height) as the outcome, we tested the hypothesis that BP may be influenced by the sex of the child with ADHD on CNS stimulants. A product interaction term of sex × systolic and diastolic BP percentile was entered into two separate regression models along with the lower level terms. The interaction terms (sex × systolic BP percentile) and (sex × diastolic BP percentile) were statistically significant (p < 0.01) in models that included both main effect terms along with ADHD (with and without CNS stimulant use), age, BMI z-score, ethnicity (white vs. non-white), fasting glucose, total cholesterol, eGFR, CRP, HR, and poverty.

Table 2 presents the study population characteristics by sex. Females with ADHD and on CNS stimulants were significantly older, shorter in stature, and had a lower ACR than those without ADHD. Conversely, males with ADHD and on CNS stimulants were significantly younger, and had a higher CRP and HR compared to those without ADHD.

Tables 3 and 4 present results for regression analyses with systolic and diastolic BP percentile as the outcome stratified by sex. In each of these models, children with ADHD (with and without the use of CNS stimulants) are compared to those without ADHD (the reference group). For females, only poverty and eGFR...
Table 2 | Demographic and bio-clinical characteristics of study population among (A) females ($n = 2,463$) and (B) males ($n = 2,444$).

|                          | ADHD on CNS stimulants | ADHD not on CNS stimulants | No ADHD | Total |
|--------------------------|------------------------|---------------------------|---------|-------|
| **(A) FEMALES**          |                        |                           |         |       |
| $n$                      | 26                     | 76                        | 2361    | 2,463 |
| Age (years)$^b$          | 14.95 (2.82)           | 14.83 (2.40)              | 13.77 (2.23) | 14.93 (2.80) |
| Race                     |                        |                           |         |       |
| White                    | 1.19 (12)              | 2.92 (28)                 | 57.32 (594) | 61.62 (634) |
| Black                    | 0.52 (26)              | 13.55 (706)               | 14.13 (735) | 13.55 (203) |
| Mexican-American         | 0.21 (15)              | 10.53 (868)               | 10.90 (891) | 10.90 (891) |
| Other                    | 0.36 (7)               | 12.94 (193)               | 13.55 (203) | 13.55 (203) |
| Poverty (yes)            | 31.85 (7)              | 48.75 (1417)              | 46.56 (1468) | 46.56 (1468) |
| **(B) MALES**            |                        |                           |         |       |
| $n$                      | 85                     | 196                       | 2163    | 2,444 |
| Age (years)$^b$          | 14.06 (2.01)           | 14.94 (2.32)              | 15.03 (2.85) | 14.97 (2.77) |
| Race$^d$                 |                        |                           |         |       |
| White                    | 76.55 (37)             | 76.98 (85)                | 59.49 (507) | 62.22 (629) |
| Black                    | 9.08 (26)              | 10.64 (63)                | 14.31 (677) | 13.65 (766) |
| Mexican-American         | 4.12 (13)              | 4.66 (34)                 | 11.85 (809) | 10.69 (856) |
| Other                    | 10.25 (9)              | 7.71 (14)                 | 14.36 (170) | 13.44 (193) |
| Poverty (yes)            | 39.08 (40)             | 4728 (110)                | 43.61 (1,279) | 43.77 (1,299) |
| **BP classification range**$^d$ |                      |                           |         |       |
| Normotensive             | 75.43 (31)             | 94.13 (100)               | 91.04 (3039) | 90.9 (3170) |
| Pre-hypertensive         | 11.45 (2)              | 5.65 (6)                  | 6.21 (214) | 6.27 (222) |
| Hypertensive             | 13.11 (3)              | 2.76 (104)                | 2.83 (108) | 2.83 (108) |
| Systolic BP percentile   | 46.92 (34.56)          | 38.71 (29.99)             | 37.85 (38.08) | 38.03 (35.91) |
| Diastolic BP percentile  | 44.47 (34.90)          | 43.99 (31.78)             | 44.48 (36.66) | 44.46 (36.49) |
| Pulse (beats/min)        | 82.17 (1721)           | 82.78 (1650)              | 79.04 (1713) | 79.24 (170) |
| **Continuous variables presented as mean $\pm$ SD and categorical variables presented as % (n). p-Values calculated by weighted chi-square analysis or weighted least squares with no ADHD as the reference.**

$^b$p $< 0.05$ for comparison between ADHD on CNS stimulants and no ADHD.

$^c$p $< 0.05$ for comparison between ADHD not on CNS stimulants and no ADHD.

$^d$p $< 0.05$ for chi-square analysis between ADHD with and without CNS stimulants and no ADHD.
Table 3 | Systolic blood pressure percentile linear regression models by sex.

| Systolic percentile | Coefficient | 95% Confidence interval | p-value |
|---------------------|-------------|-------------------------|--------|
| **FEMALES**         |             |                         |        |
| ADHD not on CNS stimulant | −0.57       | −8.23 to 7.10           | 0.88   |
| ADHD on CNS stimulant  | 6.76        | −8.33 to 21.85          | 0.37   |
| Age (years)         | −0.27       | −1.07 to 0.53           | 0.51   |
| BMI z-score         | 6.64        | 5.18 to 8.10            | <0.001 |
| White (yes)         | −1.42       | −4.38 to 1.54           | 0.34   |
| Glucose (mg/dl)     | 0.02        | −0.18 to 0.18           | 0.99   |
| eGFR (ml/min/1.73m²) | 0.02        | 0.00 to 0.04            | 0.03   |
| Poverty (yes)       | 3.93        | 0.75 to 7.12            | 0.02   |
| Total cholesterol   | −0.01       | −0.05 to 0.04           | 0.76   |
| Pulse (beats/min)   | 0.23        | 0.11 to 0.35            | <0.001 |
| **MALES**           |             |                         |        |
| ADHD not on CNS stimulant | −1.17       | −5.49 to 3.15           | 0.59   |
| ADHD on CNS stimulant  | 2.61        | −4.40 to 9.61           | 0.46   |
| Age (years)         | −1.23       | −1.89 to −0.57          | <0.001 |
| BMI z-score         | 7.19        | 5.81 to 8.56            | <0.001 |
| White (yes)         | −5.00       | −8.72 to −1.30          | <0.01  |
| Glucose (mg/dl)     | 0.10        | 0.00 to 0.20            | 0.05   |
| eGFR (ml/min/1.73m²) | −0.01       | −0.03 to 0.02           | 0.66   |
| CRP (mg/dl)         | −1.30       | −4.90 to 2.30           | 0.47   |
| Poverty (yes)       | −0.08       | −3.73 to 3.56           | 0.96   |
| Total cholesterol   | 0.07        | 0.03 to 0.12            | <0.01  |
| Pulse (beats/min)   | −0.01       | −0.13 to 0.12           | 0.94   |

Table 4 | Diastolic blood pressure percentile linear regression models by sex.

| Diastolic percentile | Coefficient | 95% Confidence interval | p-value |
|----------------------|-------------|-------------------------|--------|
| **FEMALES**          |             |                         |        |
| ADHD not on CNS stimulant | −0.63       | −7.30 to 6.04           | 0.85   |
| ADHD on CNS stimulant  | 0.07        | −1.39 to 14.03          | 0.99   |
| Age (years)          | 1.32        | 0.48 to 2.15            | <0.01  |
| BMI z-score          | −1.54       | −3.01 to −0.07          | 0.04   |
| White (yes)          | 1.82        | −1.21 to 4.86           | 0.23   |
| Glucose (mg/dl)      | 0.05        | −0.09 to 0.19           | 0.50   |
| eGFR (ml/min/1.73m²) | 0.06        | 0.03 to 0.08            | <0.001 |
| CRP (mg/dl)          | −1.46       | −3.21 to 0.30           | 0.10   |
| Poverty (yes)        | 2.80        | −0.78 to 6.39           | 0.12   |
| Total cholesterol    | 0.02        | −0.03 to 0.07           | 0.42   |
| Pulse (beats/min)    | 0.24        | 0.13 to 0.35            | <0.001 |
| **MALES**            |             |                         |        |
| ADHD not on CNS stimulant | −1.84       | −5.73 to 2.35           | 0.52   |
| ADHD on CNS stimulant  | −4.03       | −9.94 to 1.87           | 0.18   |
| Age (years)          | 0.05        | −0.80 to 0.90           | 0.91   |
| BMI z-score          | −2.35       | −3.57 to −1.13          | <0.001 |
| White (yes)          | −0.36       | −3.21 to 2.48           | 0.80   |
| Glucose (mg/dl)      | 0.01        | −0.09 to 0.11           | 0.86   |
| eGFR (ml/min/1.73m²) | 0.06        | 0.03 to 0.08            | <0.001 |
| CRP (mg/dl)          | −1.07       | −5.05 to 2.91           | 0.59   |
| Poverty (yes)        | −0.16       | −3.07 to 2.75           | 0.91   |
| Total cholesterol    | 0.02        | −0.03 to 0.06           | 0.47   |
| Pulse (beats/min)    | 0.27        | 0.11 to 0.42            | <0.01  |

are significant predictors of systolic BP percentile while adjusting for other covariates. Among males, age, BMI percentile, ethnicity (white), and total cholesterol are significant predictors of systolic BP percentile while adjusting for other covariates. It is worth noting that the SBP coefficient for females with ADHD on CNS stimulants on medications is 2.5 times greater than for males (n = 85); 6.76 compared to 2.61.

For both males and females BMI z-score, eGFR, and HR were significant predictors of diastolic BP percentile while adjusting for other covariates. Among females only age was a significant predictor of diastolic BP percentile.

**DISCUSSION**

To our knowledge, this is the largest study to examine the effect of CNS stimulant medication use on BP classification in a study population representative of the US children and adolescents. In this study, we report comparable prevalence of elevated BP (prehypertensive and hypertensive range) between patients with self-reported ADHD vs. no ADHD diagnosis. Also, we report comparable prevalence of elevated BP between the ADHD patients on stimulant medications vs. no medications. HR was significantly higher in the group on CNS stimulant medications compared to children with ADHD on no stimulants and no ADHD.

It is important to point out that children with self-reported ADHD on stimulant medications had a slightly higher systolic BP percentile, which was not significantly different between the groups and did not change BP classification. We also report a significant difference in BP classification by sex; females with ADHD are significantly more hypertensive, while males with ADHD on CNS stimulants had a significantly higher HR.

Ten percent of this nationally representative sample of 4,907 children had ADHD. One-third of children with ADHD were on medications, 90% of whom were on CNS stimulants. Methylphenidate and amphetamine−dextroamphetamine were the two most commonly used medications.

Our findings are consistent with a meta-analysis of adult studies examining the relative change in various CV parameters associated with ADHD treatment modalities, Mick et al. reported that subjects randomized to CNS stimulant treatment demonstrated a statistically significant increased resting HR [+5.7 bpm (95% CI: 3.6, 7.8), p < 0.001] and systolic BP findings [+2.0 mmHg (95% CI: 0.8, 3.2), p = 0.005] compared with subjects randomized to placebo (14). Samuels and colleagues examined the effect of stimulants on 24-h ambulatory BP in children with ADHD, in a double-blind, randomized, cross-over trial they reported elevations in most hemodynamic parameters derived from ABPM during the active treatment period; overall diastolic BP (69.7 vs. 65.8 mmHg, p = 0.02) and waking diastolic BP (75.5 vs. 72.3 mmHg, p = 0.03) were significantly higher during active treatment. Total HR was also significantly higher during active treatment (85.5 vs. 79.9 beats/min, p = 0.004) (15). In a systematic review by Westover and colleagues examining the
relationship between stimulant medications and CV events, 10 population-based observational studies were reviewed. Six out of seven studies in children and adolescents did not show an association between stimulant use and adverse CV outcomes. In contrast, two out of three studies in adults found an association. The authors concluded that findings of an association between prescription stimulant use and adverse CV outcomes are mixed. Studies of children and adolescents suggest that statistical power is limited in available study populations, and the absolute risk of an event is low (16).

The duration of CNS stimulant medication effects on CV parameters is not well understood, it is possible that these effects are less prominent with time. Hammerness and colleagues examined the effects of high doses of extended-release methylphenidate (OROS MPH) on CV variables in 114 adolescents with ADHD, they reported small but statistically significant changes in DBP and HR at 6 weeks, without further increases up to 6 months follow-up. A small but not statistically significant increase in SBP was observed at 6 weeks, this increase was statistically significant at 6 months of follow-up (17). It is important to point out that male and female participant data were combined and analyzed together in this study, the study did not classify BP or present BP percentiles and did not comment on change in BP classification with increased BP. On the other hand, this study demonstrated a significant increase in HR in the first 6 weeks, which was sustained until the end of the follow-up period; one patient had to stop the treatment due to intermittent palpitations. Among the 1758 youth enrolled in the Italian ADHD National Registry, statistically significant increases were observed in CV measures: in the atomoxetine group after 6 months in diastolic pressure (methylphenidate group after 6 months in HR (tistically significant increases were observed in CV measures: in the atomoxetine group after 6 months in diastolic pressure (methylphenidate group after 6 months in HR (with the help of renal auto regulation, GFR is maintained relatively stable over a wide range of BP in healthy individuals; it is unclear how CNS stimulants and increased sympathetic outflow affect this relationship.

Our study is limited by its cross-sectional design and the inability to draw any causal relationships. All three BP measures were taken at one sitting 5 min apart. As such, none of the children included in the study can be diagnosed truly hypertensive or pre-hypertensive based on the fourth report recommendations. Rather, the average of three BP measures here serve as a proxy for BP status similar to many other published studies (8, 9). Another limitation of the study is our use of the modified Schwartz formula to estimate GFR, while the formula has not been validated in healthy children and adolescents, a modified formula uses a constant that yields an eGFR that is lower by almost 20–30% compared to the original formula, this allowed correcting for the use of the Jaffe method to measure serum creatinine that was used during the survey period. Although patients were queried about medication usage, being a cross-sectional study, we neither know the duration of CNS stimulant use nor do we know compliance of use. There is also a possibility that study subjects have not answered questions honestly with respect to diagnosis of ADHD. However, since NHANES is not a survey about ADHD, there should be no reason for an individual to bias results and not be truthful about this history. Nonetheless, there is a possibility that some may have over- or under-reported. Similarly, some may have over- or under-reported taking medication for ADHD. However, NHANES asks that survey participants bring all medication to the mobile examination and examiners record the medications directly from the containers brought in from the patient. This would reduce the likelihood of bias. It is also possible that a child was on a medication break and this was not reported. After stratifying by sex, the number of children on CNS stimulant medications with BP in the hypertensive and pre-hypertensive range was relatively small.

On the other hand, this study has a number of strengths in that it examines a large pediatric cohort, representative of the US population. Also, in this study, we classified each patient’s BP based on the average of three measurements obtained during the survey exam and adjusted for height and sex: normal BP, hypertensive, or pre-hypertensive range. In this study, we were able to compare a subgroup of self-reported ADHD patients on CNS stimulants to a larger group of self-reported ADHD patients on no medications as well as to healthy counterparts.
CONCLUSION

Overall, children on CNS stimulants tend to have higher HRs and slightly higher BP percentiles. The difference in BP percentiles did not translate into a difference in the prevalence of BP in the hypertensive and/or pre-hypertensive ranges between children with ADHD on stimulant treatment vs. no treatment and was comparable to children without ADHD. Sex differences in BP classification may exist in children on CNS stimulant treatment. These findings as well as the higher CRP levels in males on CNS stimulants need to be confirmed by future studies. Prescribers of CNS stimulant medication need to be aware of the potential long-term adverse effects of these medications and need to weigh the risk and benefits when starting stimulant treatment.

AUTHOR CONTRIBUTIONS

Authors (Susan M. Hailpern, Brent M. Egan, Kimberly D. Lewis, Ghassan F. Shattat, Doaa I. Al Qaoud, and Ibrahim F. Shatat) had substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and all authors contributed to drafting the work or revising it critically for important intellectual content; and the final version was approved by all authors. All authors agree to accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics (2004) 114(2 Suppl): 555–76. doi:10.1542/peds.114.2.S2.555
2. Kappettas N, Nasothimiu E, Kollias A, Vazeou A, Stergiou GS. Ambulatory and home blood pressure monitoring in children and adolescents: diagnosis of hypertension and assessment of target-organ damage. Hypertens Res (2013) 36(4):285–92. doi:10.1080/hr.2012.220
3. Berenson GS, Srivanas SR, Bao W, Newman WP III, Tracy RE, Wathenwy GA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med (1998) 338(23):1650–6. doi:10.1056/NEJM199804133382302
4. Lande MB, Kaczorowski JM, Auinger P, Schwartz GL, Weitzman M. Elevated blood pressure and decreased cognitive function among school-age children and adolescents in the United States. J Pediatr (2003) 143(6):720–4. doi:10.1067/mpd.2003.300412
5. Centers for Disease Control and Prevention (CDC). Increasing prevalence of parent-reported attention-deficit/hyperactivity disorder among children – United States, 2003 and 2007. MMWR Morb Mortal Wkly Rep (2010) 59(44):1439–43.
6. Nissen SE. ADHD drugs and cardiovascular risk. N Engl J Med (2006) 354(14):1445–6. doi:10.1056/NEJM20060819.
7. National Health and Nutrition Examination Survey: Physician Examination Procedures Manual. Atlanta: Centers for Disease Control and Prevention (2003). Available from: http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/PE.pdf
8. Munter P, He J, Cutler JA, Wildman RP, Whelton PK. Trends in blood pressure among children and adolescents. JAMA (2004) 291(17):2107–13. doi:10.1001/jama.291.17.2107
9. Rosner B, Cook NR, Daniels S, Falkner B. Childhood blood pressure trends and risk factors for high blood pressure: the NHANES experience 1988-2000. Hypertension (2013) 62(2):247–54. doi:10.1161/HYPERTENSIONAHA.113.02128
10. Kuczmaszki RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC growth charts for the United States: methods and development. Vital Health Stat 11 (2002) 2461–190.
11. Schelleman H, Bilker WB, Strom BL, Kimmel SE, Newcomb C, Guevara JP, et al. Cardiovascular events and death in children exposed and unexposed to ADHD agents. Pediatrics (2011) 127(6):1102–10. doi:10.1542/peds.2010-3371
12. National Health and Nutrition Examination Survey: General Information for the Public Files of the 2007-2008 Laboratory Data. Atlanta: Centers for Disease Control and Prevention (2010). Available from: http://www.cdc.gov/nchs/nhanes/nhanes2007-2008/labdoc_e.htm
13. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskell F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol (2009) 20(3):629–37. doi:10.1681/ASN.2008030287
14. Mick E, McManus DD, Goldberg RJ. Meta-analysis of increased heart rate and blood pressure associated with CNS stimulant treatment of ADHD in adults. Eur Neuropsychopharmacol (2013) 23(6):534–41. doi:10.1016/j.euroneuro.2012.06.011
15. Samuels JA, Franco K, Wan E, Sorof JM. Effect of stimulants on 24-h ambulatory blood pressure in children with ADHD: a double-blind, randomized, cross-over trial. Pediatr Nephrol (2006) 21(1):92–5. doi:10.1007/s00467-005-2051-1
16. Westover AN, Halm EA. Do prescription stimulants increase the risk of adverse cardiovascular events? A systematic review. BMC Cardiovasc Disord (2012) 12:41. doi:10.1186/1471-2261-12-41
17. Hammerness P, Wilens T, Mick E, Spencer T, Doyle R, McCreary M, et al. Cardiovascular effects of longer-term, high-dose OROS methylphenidate in adolescents with attention deficit hyperactivity disorder. J Pediatr (2009) 155(1):84–9. doi:10.1016/j.jpeds.2009.02.008
18. Arcieri R, Germinario EA, Bonati M, Masi G, Zuddas A, Vella S, et al. Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. J Child Adolesc Psychopharmacol (2012) 22(6):423–31. doi:10.1097/CAP.2012.00114
19. Tjugen TB, Flaa A, Kjeldsen SE. High heart rate as predictor of essential hypertension: the kinetic state, evidence of prediction of hypertension, and hemodynamic transition to full hypertension. Prog Cardiovasc Dis (2009) 52(1):20–5. doi:10.1016/j.pcad.2009.05.008
20. Tjugen TB, Flaa A, Kjeldsen SE. The prognostic significance of heart rate for cardiovascular disease and hypertension. Curr Hypertens Rep (2010) 12(3):162–9. doi:10.1007/s11920-010-0014-8
21. Safer D, Allen R, Barr E. Depression of growth in hyperactive children on stimulant drugs. N Engl J Med (1972) 287(5):217–20. doi:10.1056/NEJM197208032870503
22. Goldman W, Seltzer R, Reuman P. Association between treatment with central nervous system stimulants and Raynaud’s syndrome in children: a retrospective case-control study of rheumatology patients. Arthritis Rheum (2008) 58(2):563–6. doi:10.1002/art.23301
23. Syed RH, Moore TL. Methylphenidate and dextroamphetamine-induced peripheral vasculopathy. J Clin Rheumatol (2008) 14(1):30–3. doi:10.1097/RHU.0b013e3181639aa
24. Yu ZL, Parker-Kotler C, Tran K, Weller RA, Weller EB. Peripheral vasculopathy associated with psychostimulant treatment in children with attention-deficit/hyperactivity disorder. Curr Psychiatry Rep (2010) 12(2):111–5. doi:10.1007/s11920-010-0093-7

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