Government of Western Australia
Department of Health

# Raine ADHD Study:

## Long-term outcomes associated with stimulant medication in the treatment of ADHD in children

This research study is a collaboration between the Ministerial Implementation Committee for Attention Deficit Hyperactivity Disorder in Western Australia (MICADHD) and the Telethon Institute for Child Health Research (TICHR), with funding provided by the Western Australian Department of Health (DOH)

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# 1. Executive Summary

## *1.1 Background*

The short term-benefits of methylphenidate and dexamphetamine in the management of Attention Deficit Hyperactivity Disorder (ADHD) symptoms are well described throughout the literature. Similarly, the short-term side-effects of these stimulant medications are well-documented. However, the long-term benefits and side-effects have been less well studied.

This project uses longitudinal data collected as part of the Western Australian Pregnancy Birth Cohort to examine the long-term social, emotional, school-based, growth, and cardiovascular outcomes associated with the use of stimulant medication in the treatment of ADHD. These outcomes are measured at the age of 14-years.

## *1.2 Summary of results*

### ADHD Diagnosis and Outcomes

- Children with a diagnosis of ADHD as reported by parents (regardless of medication use), perform significantly worse at age 14 years on measures of depression, self perception, social functioning, academic performance, school enjoyment and attention than those without a diagnosis.
- This is consistent with previous research and suggests that children diagnosed with ADHD have an underlying condition that impacts negatively on a range of long-term life skills.

### Outcomes Associated with Medication-Use for Children Diagnosed with ADHD

### Social/Emotional and School-Based outcomes

- No significant differences based on medication-use were noted for the following measures taken at 14 years of age: depression, self-perception, and social-functioning.
- Whilst no statistically significant results were noted, a trend toward slightly higher depression scores was noted with the use of medication.
- A trend toward slightly lower self-esteem and social functioning was also noted with medication use at one time point or two time points. However, consistent medication-use at all time points, including at 14 years, trended toward slightly improved self-perception and social functioning.

- It should be emphasised that where these trends were noted, the effect sizes were small and were not statistically significant

## School-Based outcomes

- In children with ADHD, ever receiving stimulant medication was found to increase the odds of being identified as performing below age-level by a classroom teacher by a factor of 10.5 times (compared to never receiving stimulant medication).
- Absenteeism and school enjoyment were not found to be significantly predicted by stimulant medication-use.
- It should be noted that analyses examining academic performance and absenteeism were limited due to low sample size and the lack of ability to examine differences based on the level of exposure to medication.

## Height and Weight

- Height: There was no significant difference in average height or weight (at 14 years of age) when comparing children who were consistently on medication to those who were never on medication.
- Non-significant trends indicated very little difference in growth measures between the 'consistently medicated' and 'never medicated' groups.
- This is inconsistent with previous research; however it is likely that the small sample sizes in the stimulant exposure categories may have prevented significant results from being identified.

## Cardiovascular Function

- Systolic Blood Pressure: no significant difference based on stimulant medication use was noted.
- Diastolic Blood Pressure: children who had consistently received stimulant medication at all time points had significantly greater diastolic blood pressure than children who had never received medication (10.79 mmHg higher).
- Children who had consistently received stimulant medication at all time points (including when cardiovascular health was measured) also had a significantly greater diastolic blood pressure than children who were currently receiving medication but had not in the past (7.05 mmHg higher).
    - These findings suggest that an elevation in diastolic blood pressure may not be due solely to the immediate short-term effects of stimulant medication on cardiovascular function.

- Resting Heart Rate: no significant difference based on stimulant medication use was noted. However a non-significant trend of higher resting heart rate in children receiving stimulant medication at all time points in the study was noted.

### Change in Key ADHD Symptoms

- On average, externalising behaviour and attentional problems did not appear to improve or worsen significantly between the ages of 5 and 14 in children with ADHD, regardless of medication use.
- Where an effect was noted, this was in the direction of symptoms worsening with the use of ADHD medication (however, this effect was small and not statistically significant).
- The results seem to indicate that there is little long-term benefit of stimulant medication in the core symptoms of ADHD. This is not unexpected, as medication is used for the temporary management of core ADHD symptoms rather than as a cure.
- Some concern may be raised over the apparent lack of effect with regard to children 'currently' on medication, as it would be expected that some short-term reduction in symptoms would be observed. However, the lack of a short-term effect may be explained by the fact that *parents* completed the assessments of core symptoms. Given that medication is taken mostly during school hours, the 'onboard' effects of medication may not be apparent to parents.

## *1.3 Conclusions*

The strength of the current study lies in its ability to provide a unique long-term view of a wide range of outcomes and their associations with the use of stimulant medication in the treatment of ADHD. Whilst limitations of the study prevent any strong causal relationships from being identified, some interesting results were observed that indicate rigorous research into the area is strongly warranted.

- The lack of significant improvements in long-term social, emotional and academic functioning associated with the use of stimulant medication suggests a purpose-designed, longitudinal research study should be conducted to better understand the suspected long-term social, emotional and educational benefits of stimulant medication in the treatment of ADHD.
- The results also indicated that between the age of 8 and 14 years there may be an effect of stimulant medication on diastolic blood pressure above and beyond the well-established immediate short-term effects on cardiovascular function. The finding that consistent use of medication was associated with an average elevation 10mmHg at 14-years of age indicates that the long-term cardiovascular implications of stimulant

medication-use need to take a high priority when determining directions for future research.

## *1.4 Limitations*

There are a number of limitations associated with the current study that should be taken into account when interpreting the results:

- The relatively low sample size in the stimulant-use comparison groups may have reduced the chance of finding real differences where they may have existed.
- Whilst a number of steps were taken to reduce the possible biases between the comparison groups, particularly with regard to symptom severity, it is still possible that these may not be adequately controlled for, threatening the validity of some multivariable models.
- Measures used to document ADHD symptoms (CBCL 1991) may have been inadequate to document severity (though previous research has documented it to be useful in differentiating ADHD from non-ADHD cases). The version of the Achenbach scales used does not document ICD10/DSM IV criteria.
- Due to sample size issues, dextroamphetamine and methylphenidate use were combined into one composite group: ‘stimulant use’. This prevented the effects of the different medications on the various outcomes to be identified.
- Dosage and adherence to medication was not measured as part of the study. Medication usage at each of the time points was determined by the mother reporting that the medication had been used in the 6 months prior to completing the questionnaire.
- ADHD diagnosis by a medical professional was reported by the child’s parent and was not validated using diagnostic tools.
- The subtypes of ADHD were not able to be analysed separately (due to sample size).

# 2. Stimulant Medication in the treatment of ADHD

## *2.1 Introduction*

*ADHD*

Attention Deficit/Hyperactivity Disorder (ADHD) a disorder is typified by hyperactivity, impulsivity and/or attention difficulties that significantly impact upon social, academic, and/or occupational functioning (America Psychiatric Association, 2000). Children with ADHD have been identified as being at greater risk of experiencing poor academic performance, problems with social integration, and emotional difficulties during childhood and adolescence (Barkley, 1997; Edbom, Granlund, Lichtenstein, & Larsson, 2008; Gewirtz, Stanton-Chapman, & Reeve, 2009; Malhi & Singhi, 2001; Powers, Marks, Miller, Newcorn, & Halperin, 2008). The disorder also has long-term implications for development into adulthood, with ADHD being associated with greater risk for outcomes such as drug/alcohol abuse, poor relationship quality and imprisonment (Eakin et al., 2004; Rosler, Retz, Yaqoobi, Burg, & Retz-Junginger, 2009).

*Prevalence*

ADHD is currently the most commonly diagnosed psychiatric disorder in children. A recent review of the literature indicated that internationally, approximately 5.3% of children under the age of 18 years are diagnosed with ADHD (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). More locally, the proportion of Australian children meeting the diagnosis requirements for ADHD has been estimated at approximately 8% (AIHW, 2003).

*Treatment*

The current treatment of choice for ADHD in Western Australia (and worldwide in general) is the prescription of stimulant medication, either alone or in conjunction with cognitive/behavioural treatments (Taylor, O'Donoghue, & Houghton, 2006).

The two most commonly prescribed stimulants in WA are dextroamphetamine sulphide (dexamphetamine) and methylphenidate (short and long acting). The 2008 annual report released by the WA Stimulant Regulatory Scheme indicated that approximately 1.26% of *all children in the state* had received either dexamphetamine or methylphenidate in the treatment of ADHD during that year (Department of Health, 2008).

Given the significant rate of stimulant prescription in WA children, is it important to know whether this form of treatment is effective and safe for children with ADHD.

*Effectiveness of stimulant medication in treatment of ADHD*

Short-term to medium-term

There have been many randomised controlled trials indicating the effectiveness of both dexamphetamine and methylphenidate in the short-term treatment of core ADHD symptoms. The majority of these studies span between 2 weeks and approximately 6 months. Whilst the body of research is too large to cover comprehensively in this report, a number of reviews and meta-analyses summarising the results of the literature-base have been identified. These reviews and meta-analyses indicate that the use of both dexamphetamine and methylphenidate result in the clinically meaningful short-term reduction in the key symptoms of ADHD: attention, hyperactivity and impulsivity (Greenhill, Halperin, & Abikoff, 1999; Leonard, McCartan, White, & King, 2004; Schachter, Pham, King, Langford, & Moher, 2001; Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008).

Whilst the greater part of the literature provides consistent evidence for the effects of stimulant medication in the management of ADHD symptoms, it is noted that a strong 'publication bias' (i.e. the likelihood of positive findings being published over 'null' findings) is present within the ADHD treatment literature (Schachter et al., 2001). This may result in meta-analyses overestimating the effect of medication on certain domains. However despite this concern, the size of the body of research, along with the broadly consistent findings, has resulted in a general consensus amongst medical researchers that methylphenidate and dexamphetamine are effective in managing the short-term symptoms of ADHD.

Long-term

Whilst a consensus has been reached on the short-term benefits of stimulant medication in the management of ADHD symptoms, there is still debate as to whether these short-term effects translate to long-term benefits to a child's academic performance and/or social and emotional wellbeing. This debate exists due mainly to the lack of research examining specific long-term outcomes or the disparate findings amongst studies that do exist.

With regard to the long-term effects of stimulant medication on the social and emotional wellbeing during childhood and adolescence, the existing research is sparse. Of the few studies examining the relationship between stimulant medication-use and long-term social and emotional outcomes (such as peer relationship quality, depression and anxiety) no significant effects were observed (Gillberg et al., 1997; Hoza et al., 2005; M. T. A. Cooperative Group, 2004a). However, the overall lack of research into the area makes it difficult to reach any conclusions regarding the long-term effect of stimulant medication on social and emotional outcomes.

The long-term academic outcomes associated with stimulant medication have been better studied. However, to date, these research findings have been inconsistent. Some studies found long-term academic gains associated with the use stimulant medication (Barbaresi, Katusic, Colligan, Weaver, & Jacobsen, 2007; Powers et al., 2008), particularly with regard to mathematics skill (Scheffler et al., 2009). However, other research has indicated no effect of stimulant medication on the academic outcomes of children with ADHD (Carlson & Bunner, 1993; Charles & Schrain, 1981; Loe & Feldman, 2007); including a meta-analysis (Jadad, Boyle, Cunningham, Kim, & Schachar, 1999). Other studies have identified that that stimulant medication is associated with a significant academic improvement in the short-term, but that benefits are no longer present after three years (M. T. A. Cooperative Group, 2004a; J. M. Swanson et al., 2007).

The current state of evidence indicates a clear need for more longitudinal research examining the relationship between the use of stimulant medication and long-term social, emotional, and academic outcomes.

*Side-effects of stimulant medication*

Given the number of children currently receiving stimulant medication, a large amount of research has been conducted into the side-effects of stimulant medications. The two most consistent findings of this research are the effect of stimulant medication on growth (weight and height) and cardiovascular function.

Effects of stimulant medication on growth measures have been found in many longitudinal studies. Methylphenidate and dexamphetamine have both been associated with a 'less than

expected' growth trajectory for both height and weight during childhood and adolescence (Charach, Figueroa, Chen, Ickowicz, & Schachar, 2006; Faraone & Giefer, 2007; M. T. A. Cooperative Group, 2004b; Mattes & Gittelman, 1983; Poulton, 2005). A review conducted in 2005 indicated that, in general, studies examining the effect of stimulant medication on growth measures show an initial impact upon height and weight, but that this effect is followed by resumption of growth within the first few years of treatment (Poulton, 2005). However, the review notes that children on medication remain at lower height and weight when compared to peers.

Whilst caution is advised to clinicians to carefully monitor each individual child's growth when receiving stimulant medication, the effect is found to be small and is often interpreted as no clinically meaningful effect (Faraone & Giefer, 2007; Poulton, 2005). However, some researchers indicate that whilst the effect on height and weight themselves may not be clinically significant, the process by which stimulant medication impacts upon physical growth, and whether this results in other potential side-effects, needs to be better understood (Poulton, 2006).

With regard to cardiovascular effects of stimulant medication; there is a large body of literature examining the short-term effects of stimulant medication on cardiovascular function in children with ADHD (Findling, Short, & Manos, 2001; Samuels, Franco, Wan, & Sorof, 2006; Volkow et al., 2001). Based on the findings of this research, it is now well accepted that both methylphenidate and dexamphetamine result in statistically significant increases in blood pressure and heart rate. On average, these studies find that stimulant medication raises blood pressure (systolic, diastolic or both) by approximately three to four mmHg and heart rate by approximately five beats per minute. These differences are deemed to be small enough to represent no clinically meaningful effect (Volkow et al., 2001) and this research is often stated as evidence for the minimal side-effects of stimulant medication.

However, it should be noted that the vast majority of the research examining the cardiovascular effects of stimulant medication span from just hours to weeks (the rare study will examine effects over 12 months); and the long-term implications of the cardiovascular effects of stimulant medication-use over a number of years have not yet been adequately explored.

Current Research Project

Given the number of children receiving stimulant medication in Western Australia, and world-wide, the lack of long-term research examining the benefits and side-effects of stimulant medication in the treatment of ADHD is concerning. The need for more longitudinal research is clearly indicated.

The comprehensive collection of rich child- and family-related information as part of the longitudinal Western Australian Pregnancy Birth Cohort (Raine) Study provides a unique opportunity to explore a number of the long-term outcomes associated with the use of stimulant medication in the treatment of ADHD.

The current study aims to use longitudinal data from the Raine Study to examine the long-term associations between stimulant medication-use during childhood and adolescence and a number of outcomes for children with ADHD. These outcomes, measured at 14 years of age, include: Social, Emotional, Educational, Physical, and Cardiovascular.

# 3. Raine Study and Sample

The Western Australian Pregnancy Birth Cohort (Raine) Study is an ongoing longitudinal study following 2,868 children. The study began in 1989 as a pregnancy cohort of women enrolled at or before the 18th week of gestation from the public antenatal clinic at the principal obstetric hospital in Perth, Western Australia or nearby private practices. Since 1989, data has been collected from the participants (both the mother and her child) at regular intervals including when the child turned 1, 2, 3, 5, 8, 10, 14 and 17 years old.

A large range of information covering sociodemographic, academic, and health and wellbeing indicators for the child and their family is collected at each of the follow-ups. This information is collected via interview, and self-report questionnaire completed by the parent and child, and direct physical examination of the child. Information is also collected through questionnaires completed by the child's teacher and principal.

The longitudinal and comprehensive nature of the Raine study provides a unique opportunity to examine the long-term outcomes associated with the use of stimulant medication during childhood.

At the time of writing this report, data was available up to the 14-year follow up.

## *3.1 Sample*

Two samples were used in the current study. The first is made up of all children in the Raine study sample for whom 14-year follow-up data were available (n = 1785). The second is a sub sample of Raine study children who had been diagnosed with ADHD for whom data was available at the 14 year follow-up (n = 131). All children in both samples were aged 13 yrs or 14 yrs. Children diagnosed with an intellectual disability were not included the current study (due to the confounding effect on a number of outcome measures).

## *3.2 Measures*

ADHD Diagnosis

Parents were asked to complete the following two items at the 5-year, 8-year, 10-year and 14-year follow-ups:

*1) Does your child now, or has your child had in the past, have any of the following **health professional diagnosed** medical conditions or health problems?*

A number of medical conditions were outlined, including both *Attentional Problems* and *Behavioural Problems*.

*2) If you answered 'Yes' to any of the above, please describe the condition or problem below in more detail (e.g. is longsighted - wears glasses for reading; diagnosed with Attention Deficit Disorder; asthma requiring occasional medication; spina bifida)*

If parents indicated a diagnosis of ADD/ADHD, they were called by a Raine researcher to verify that the diagnosis had been made by an appropriate health professional.

Whilst information was available to further classify children as falling into the three subtypes of ADHD (primarily inattentive, hyperactive/impulsive, combined), these groups were not able to be analysed separately due to the low levels of power associated with reducing the sample size of the groups.

Use of Stimulant Medication

Parents were asked to complete the following item:

*In the past six months has your child taken/used any prescription medication(s)?*

The parent was then asked to provide a description of the type of medication. If the parent reported the use of dextroamphetamine or methylphenidate, the child was coded as having used stimulant medication at that particular follow-up point.

A number of 'medication use' measures were developed to examine the effect of stimulant medication on different outcomes. These were as follows:

- Stimulant Exposure
    - Categories: Received no medication; Received medication at one follow-up point; Received medication at 2 follow-up points; Received medication at 3 follow-up points
- Any Use

    - Categories: Never received medication; Ever received medication
- Recent Use
    - Categories: Received no medication; Received medication in the past; Currently receiving medication (not used at all time points in the past); Consistent use of medication at all time points

The measure of 'medication use' used for each of the outcome measures is outlined and justified in the results section.

Performance Intelligence

Performance Intelligence was measured using the Block Design subtest of the Weschler Intelligence Scale for Children - Third Edition (Weschler, 1991).

The Block Design is a task that requires a child to reproduce a visual pattern using a number of red and white blocks. Children are given a raw score based on their speed and accuracy. This raw score is then compared to age-normative data and converted to a scaled score.

Puberty

Puberty was measured using the Tanner Stages of physical development. This scale asks participants to rate their development based on a number of physical sexual characteristics, such as development of breasts, genitalia and development of pubic hair. There are five stages from childhood and adulthood that are represented on the scale, ranging from 1 (prepubertal) to 5 (fully developed).

For the current study, children whose Tanner stage of development was rated as 3 or 4 were classified as mature and those with a rating of 1 or 2 were classified as immature (no children reported a Tanner stage of 5).

Sociodemographic Measures

A number of sociodemographic items were collected at the time of birth: those used in the current project were:

- Mother's Age
    - 14 - 20yrs; 21 - 27yrs; 28 - 34yrs; 35 - 46yrs
- Family Structure
    - Biological father living with mother; Biological father living away from mother
- Family Income
    - <$12,000; $12,000 - $35,000; >$35,000
- Mother's Education
    - Lower School; Upper School; Trade Certificate/Diploma; University/College Degree

Externalising Behaviour and Attentional Problems

Externalising behaviour and attentional problems were measured using the Externalising Behaviour Subscale (CBCL-Externalising) and the Attentional Problems (CBCL-Attention) from the Achenbach Child Behaviour Checklist (CBCL) (Achenbach, 1991).

The version of the CBCL used in the Raine study contains a total of 140 items that are modified to suit the age group being tested. The parents are asked to rate their child on a scale of 1 to 5 on each of these items. Of these, 24 items are summed to produce a raw score of Externalising Behaviour and 14 items are summed to provide a raw score of Attentional Problems. These raw score are then converted to t-scores based on normative-referenced data.

CBCL-Externalising and CBCL-Attention measured at the 5-year follow-up and 14-year follow up were used in the current study.

Depression

Depression was measured using the Beck Youth Depression Inventory (BDI-Y) (Beck, Steer, & Brown, 1996). The BDI-Y is a 20-item questionnaire filled out by the child. Each item is designed to assess an aspect of mood/affect and have a 4 point response scale that allowing the intensity of the feeling to be quantified.

Responses on the 20 items are summed and these raw score are converted to normative-referenced t-scores; providing an indication of the child's level of depression in comparison to his or her peers. Higher scores indicate a greater degree of depression.

Self-Perception

The Harter Adolescent Self-Perception Scale (ASPP) (Harter, 1986) was used to measure a child's self-perception. This scale contains 45 items asking the child to rate their feelings toward themselves in reference to a number of domains: Scholastic Competence, Social Acceptance, Athletic Competence, Physical Appearance, Behavioural Conduct, and Global Self Worth.

The responses to these items (scored as 1 - 4) are summed to form a scale quantifying the child's feelings of global self-worth. The scale ranges from 45 to 180, with higher scores indicating more positive feelings of self-worth.

Social Functioning

The Harter Adolescent - Social Acceptance (ASPP-S) (Harter, 1986) was used to measure a child's social functioning. This scale contains six items asking the child to rate themselves with regard to their friendships and social interactions (on a scale of 1 to 5).

The responses to these items are summed to form a scale of social functioning ranging from 5 to 30, with higher score indicating more positive functioning.

Teacher-rated Academic Performance

In the current study, academic performance was measured by a 5-point item asking the teacher to rate the child's academic performance (ranging from 'below average' to 'well above average'. Due to the distribution of the item it was converted into a dichotomous measure with two categories: "Child is performing below average", and "child is performing at or above average".

Absenteeism

The measure used to examine absenteeism was computed by dividing the number of days absent from school by the number of days that had passed in the school year. Those children who were absent for 10% or more of the available days were labelled as "high absenteeism", those who had less were classified as "low/average absenteeism" (cut-offs were determined using distributional methods).

Enjoyment of School

This measure was based on the summed total of 16 items designed to assess a child's enjoyment of various aspects of school (on a scale of 1 to 5). The responses to all items were summed to generate an overall scale of school enjoyment (ranging from 16 - 80). Higher scores indicate greater enjoyment at school.

Height and Weight

At each follow-up of the Raine study, a child undergoes a comprehensive physical examination. The current study uses measurements of height and weight taken at the 5-year follow-up and the 14-year follow-up.

Raw height and weight measurements corrected for gender and age by calculating z-scores. Z-scores are calculated by subtracting a participant's height (or weight) from the mean height (or weight) for children of their age and gender. This is then divided by the standard deviation of the height (or weight) measurement for their age/gender sub-population. This provides an age and gender-standardised height (or weight) score with a mean score of 0 and a standard deviation of 1. Z-scores are considered the most valid method for assessing growth variability in samples of children/adolescents (Chinchilli, McEnery, & Chan, 1990)

"Growth" scores were then calculated by calculating the difference between z-score at age 14 and at age 5.

The reference data used to calculate z-scores were the Centres for Disease Control and Prevention clinical Growth Charts for the United States (Kuczmarski et al., 2002). No reliable Australian growth data are available.

Cardiovascular Function

Cardiovascular function was measured at the 14-year follow up using DINAMAP machines. These provide accurate automated measurements of systolic blood pressure, diastolic blood pressure, and resting heart rate.

Cuffs were applied to the participant's right arm by a trained research assistant. After 5 minutes of rest, measurements were automatically taken at 2-minute intervals for 10 minutes. The measures of cardiovascular function used in the current project are the average values of the first two readings.

# 4. Part A: Analytical Methods

A number of approaches in identifying the independent effect of stimulant medication on the long-term social, emotional, school-related, and physical outcomes of children with ADHD were used in the current study.

Multivariable Modelling

The first approach was to conduct multivariable models to identify the relationships between stimulant medication and child outcomes at 14 years whilst controlling for a number of covariates.

Where outcome measures were continuous, general linear models (GLM), controlling for propensity for medication (see section 4.1 for more detail on propensity score), symptom severity and other child and family measures, were conducted to determine the independent relationship between stimulant medication and each outcome of interest. Differences were assessed based on estimated marginal means (using Least Squares Difference) at a significance level of 0.05.

Where outcomes were non-normally distributed (e.g. heavily skewed/truncated), the appropriate distributions were used in the multivariable models (e.g. Poisson log linear).

Where outcomes were dichotomous (i.e. had two possible response categories; such as “yes” and “no”, or “low” and “high”), binary logistic regression models (controlling for the same measures) were conducted and adjusted odds ratios were calculated.

Change in normative-referenced measures

The second analytical approach was to compare normative referenced measures that were taken at two time points: prior to medication-commencement (at five years); and at 14 years of age.

The relative changes from time-point one to time-point two for CBCL-E and CBCL-A were calculated (referred to as ‘Change Scores’).

A positive change score reflects an increase/elevation in the symptom, whereas a negative change score indicates and improvement.

Generalised Linear Models, controlling for propensity score and sociodemographic measures, were conducted to identify the association between medication use and change in symptom severity over time.

## *4.1 Controlling for potential systematic differences between medication groups*

Given the naturalistic design of the current study, there is a risk that any differences between the control (no medication) and comparison groups (use of medication) may be due to the systematic differences between the groups rather than the effect of the medication itself.

For example, the most severely affected children may have a greater likelihood of being treated with medication, thus being more likely to experience negative outcomes independent of medication use (J. M. Swanson et al., 2007). Thus, if severity isn't controlled for, results may spuriously indicate that medication is associated with poorer outcomes.

Three methods have been employed in an attempt to reduce the potential effect of bias: 1) controlling for symptom severity, 2) controlling for sociodemographic measures, and 3) calculating a 'propensity score'.

Symptom Severity

The measures that were used to control for symptom severity were two subscales from the Child Behaviour Checklist (CBCL) that were conducted when the child was aged five years. These measures were Attention Problems (CBCL-A), and Externalising Behaviour (CBCL-E).

The optimal method for adjusting for symptom severity would use estimates of severity at each follow-up. However, due to the fact that the immediate effects of medication (being taken at the time of the follow-up) would influence the ratings of symptom severity in the current study, this was not possible. An estimate for symptom severity that was recorded *before commencement* of medication needed to be identified for the current study.

The age of five years was chosen as none of the current sample had commenced medication at this age. The next follow-up age (8 years) saw approximately 40% of the sample commence medication.

*Limitations of "Symptom Severity Control"*

- The CBCL is parent-rated and subjective
- The version of the CBCL used in the Raine study was prior to the 2001 revision. As such, the measure is not well-designed to detect attentional problems (Heubeck, 2000)
- Behaviour and attention at five years of age may not necessarily be good predictors of behaviour and attention at later ages

The limitations associated with the measures used to control for symptom severity need to be carefully considered when interpreting the results of the multivariable models presented in the report.

Sociodemographic Measures

The following sociodemographic measures were adjusted for in all multivariable models: Income of Family, Family Structure, Mother's Age, and Gender of the Child.

Propensity Score

To reduce the bias due to systematic differences between test groups 'propensity scores' were created. This method uses a number of sociodemographic and symptom severity measures to classify a child as having a 'high' or 'low' likelihood of being given stimulant medication.

The inclusion of the propensity score in the multivariable analyses reduces the risk of effects mistakenly being attributed to medication when it may be factors associated with the *propensity* to receive medication that influenced the outcome.

For example, as mentioned above, symptom severity may increase the likelihood of a child receiving medication. Without controlling for this, it may appear that medication was a determining factor in social, emotional, or physical outcomes when it was in fact the severity of the ADHD that predicted both the outcome and the likelihood of medication.

The advantage of the propensity score is that it allows a composite measure to be constructed based on many potential predictors. This value can then be included in the same models as the individual covariates themselves, more completely adjusting for systematic differences between test groups.

For information on the construction of the propensity score, see Appendix A

Propensity scores were converted to a binary measure ('high' and 'low' likelihood of receiving medication) and this was included as a covariate in the multivariable models.

# 5. Results: ADHD and use of stimulant medication

## *5.1 Diagnosis of ADHD and demographic makeup of sample*

Of the 1785 adolescents in the sample, 131 (7.3%) had received a diagnosis of ADHD by the 14-year follow-up.

Of the sample that had received a diagnosis of ADHD, 75.6% (n = 99) were male; compared to 48.9% non-ADHD-diagnosed sub sample (n = 808).

Twenty-two percent (n = 27) were born into 'lower income' families (<$12,000); compared to 12.0% of the non-ADHD diagnosed sub sample (n = 181).

Mother's education at time of birth was similar across the sub samples, with 29.2% (n = 38) of ADHD-diagnosed children's mothers and 29.5% (n = 464) of non-diagnosed children's mothers having a university or college degree. Proportions of mothers who did not experience upper school were also similar (ADHD-diagnosed = 28.5%; non-ADHD-diagnosed = 24.3%).

Of children diagnosed with ADHD, 14.6% (n = 19) were born to mothers under the age of 20 years. Of the non-diagnosed children, 8.8% (n = 138) were born to mothers under the age of 20 years.

Eighteen percent (n = 23) of ADHD diagnosed children did not have their biological father living in the same house at the time of birth. This is compared to 9.4% (n = 147) of children who never received a diagnosis of ADHD.

Note: due to missing data, the values above do no reflect the percentage of the complete sample of 131 children falling within the each of the categories. These indicate the percentage of *valid* cases.

## *5.2 Use of Stimulant Medication in Children Diagnosed with ADHD*

Ever received medication

Of the 131 children in the ADHD-diagnosed sub sample, 21 (16.0%) reported the use of stimulant medication at all three follow-up points (8, 10, 14 years), 42 (32.1%) at two follow-up points, and 39 (29.8%) at one of the follow-up points. 29 (22.1%) reported no use of stimulant medication at any of the follow-up points.

Current use of medication

Of the ADHD sub sample, 21 (16.0%) were using medication at age 14 and had used it consistently since being diagnosed with ADHD; 40 (30.5%) were using medication at 14, but had not consistently used it in the past; 41 (31.3%) had used medication in the past be were not using it at age 14, and; 29 (22.1%) had not reported using stimulant medication.

Type of medication

The majority of children on medication had taken dextroamphetamine only (n=63, 61.7%) 22 (21.6%) had received methylphenidate only; and 17 (16.7%) had received a combination of the two types of medication at differing follow-ups.

Only four children (3.9%) reported using atomoxetine, a non-stimulant pharmacological treatment for ADHD. This reflected that Atomoxetine was not widely available at the time of the study and was not on the PBS schedule.

# 6. Results: Social and Emotional Outcomes

Children with ADHD have been found to have a greater risk of developing later social and emotional problems such as poor relationships with peers (Gewirtz et al., 2009), depression (Williams et al., 2008) and low self-esteem (Edbom et al., 2008; Malhi & Singhi, 2001).

ADHD can affect social functioning due to the fact that effective interpersonal interaction requires cue-identification and self-regulation, both of which are commonly affected in children with ADHD (Gewirtz et al., 2009; Matthys, Cuperus, & Van Engeland, 1999). Additionally, some evidence exists that indicates that ADHD diagnosed adolescents are less capable at interpreting emotional expression (Williams et al., 2008). These symptoms can result in problems with social integration and poor relationships with peers (Herman, Lambert, Ialongo, & Ostrander, 2007).

ADHD is has been theorised to impact upon feelings of self-worth and depressive thoughts through the cumulative effect of continued negative experiences (social and academic) due to ADHD symptoms (Herman et al., 2007).

To determine whether stimulant medication ameliorated the effect of ADHD on the long-term social and emotional outcomes of children, a number of outcomes were examined in regard to the relationship between stimulant medication and a) depression, b) social functioning, and c) self-perception.

All multivariable models are restricted to children with a diagnosis of ADHD and adjust for symptom severity at five years of age, sociodemographic characteristics and propensity score.

Note: For the unadjusted means of each outcome measure by ADHD-diagnosis and medication-use, see Appendix B: Unadjusted means for outcomes measures.

## *6.1 Depression*

Depression was measured using the Beck Depression Inventory (BDI). Higher scores indicate a higher level of depressive affect. The mean BDI t-score for ADHD-diagnosed children at the 14-year follow up (n = 117) was 43.75 (SD = 8.21). The mean score for the sample without an ADHD diagnosis (n = 1420) was 42.02 (SD = 8.21). This difference of 1.73 was statistically significant ($t$ (1535) = 2.19, $p$ <.05), indicating a higher level of depressive affect in children diagnosed with ADHD.

*Model Results*

After adjusting for all covariates, the results of Generalised Linear Model (using negative binomial with log link distribution due to a high skew; n = 100) indicated no significant effect of Stimulant Exposure on BDI score (Wald chi-square = .82 (3), *p* = .84). The estimated marginal means are provided in table 1.

**Table 1. Estimated marginal means for BDI by stimulant medication exposure (adjusting for gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 20 | 42.76 | 2.00 | 38.85 - 46.67 |
| 1 time point | 25 | 44.84 | 2.14 | 40.64 - 49.04 |
| 2 time points | 37 | 43.42 | 1.92 | 39.67 - 47.18 |
| 3 time points | 18 | 44.57 | 2.56 | 39.55 - 49.60 |

## *6.2 Self Perception*

Self perception was measured using the Harter Adolescent Self-Perception Profile (ASPP). Higher scores indicate a more positive self-perception. The mean ASPP score for children with ADHD (n = 116) was 125.99 (SD = 16.61). The mean score for children without a diagnosis of ADHD (n = 1419) was 128.98 (SD = 13.36). The difference of 2.99 was statistically significant (*t* (1533) = 2.00, *p* <.05) indicating a poorer self-perception in children diagnosed with ADHD.

*Model Results*

After adjusting for all covariates, the results of Generalised Linear Model (n = 98) indicated no significant effect of Stimulant Exposure on ASPP score: *F*(3, 84) = .831, *p* = 0.48. Estimated marginal means are provided in table 2.

**Table 2. Estimated marginal means for ASPP by stimulant medication exposure (adjusting for gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 20 | 128.9 | 4.97 | 119.0 - 138.8 |
| 1 time point | 24 | 123.9 | 5.16 | 113.7 - 134.2 |
| 2 time points | 37 | 126.7 | 4.68 | 117.0 - 136.0 |
| 3 time points | 17 | 132.6 | 6.22 | 120.3 - 145.0 |

## *6.3 Social Functioning*

Social Functioning was measured using the Harter Adolescent Self-Perception Profile - Social Functioning subscale (ASPP-S). Higher scores indicate better social functioning. The mean ASPP-S scale for ADHD-diagnosed children (n = 119) was 30.08 (SD = 7.35). The mean

score for non-ADHD-diagnosed children (n = 1426) was 32.42 (SD = 5.45). The difference of 2.35 was statistically significant (*t* (1543) = 4.38, *p* <.001) indicating a lower level of social function within children diagnosed with ADHD.

*Model Results*

After adjusting for all covariates, the results of Generalised Linear Model (n = 98) indicated no significant effect of Stimulant Exposure on ASPP score: *F*(3, 87) = .55, *p* = 0.65. Estimated marginal means are provided in table 3.

**Table 3. Estimated marginal means for ASPP-S by stimulant medication exposure (adjusting for gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 20 | 30.32 | 2.25 | 25.85 - 37.78 |
| 1 time point | 25 | 29.41 | 2.36 | 24.73 - 34.10 |
| 2 time points | 38 | 28.60 | 2.09 | 24.46 - 32.75 |
| 3 time points | 18 | 31.46 | 2.85 | 25.80 - 37.13 |

## *6.4 Summary*

For children diagnosed with ADHD, the use of stimulant medication appeared to have no significant relationship with depressive affect, self-perception, and social functioning at age 14. There was a non-significant trend of poorer self-perception and social functioning associated with having received medication at one or two time points (as compared to receiving no medication or consistently being medicated) with consistent (including current) medication trending toward improved self-perception. However, where these differences were noted, the effect sizes were small and not found to be statistically significant.

The measure of social functioning used in the above analyses was an assessment of the child's perception of their social interactions. As such, this measure did not provide an objective indication of the child's functioning.

It should be noted that the low sample size present in each of the comparison groups may have prevented the detection of significant differences across the groups. Despite this limitation, the lack of significant findings in conjunction with the small effects between comparison groups on outcome measures suggests that the use of stimulant medication may not be associated with long-term gains to social or emotional functioning as rated by the child. However, the limitations associated with the current study (see section 11. Limitations) prevent any strong conclusions from being made.

These findings indicate that more research needs to be conducted into determining whether the use of stimulant medication results in long-term social and emotional benefits for children

with ADHD. The differing outcomes associated with the consistency of medication use indicate that special attention will need to be given to differences in outcome according to continuous usage versus episodic usage.

# 7. Results: School-Related Outcomes

One of the biggest concerns with regard to ADHD is the impact it can have on academic functioning and other school-related outcomes. It is very well documented that children with ADHD have increased risk of poor academic performance (Barkley, 1997; Powers et al., 2008) and poor school attendance (Barbaresi et al., 2007).

Studies into the short-term effects of stimulant medications indicate that immediate management of ADHD symptoms allows children to function more effectively within a classroom, (Abikoff et al., 2007; Carlson & Bunner, 1993; Loe & Feldman, 2007). It is hypothesised that this makes children more available for learning and allows children to learn skills and concepts which are necessary to function well within a classroom in the future. Thus, children who have received stimulant medication at any time point should observe some long-term school-related benefits as a result (Carlson & Bunner, 1993).

However, the research examining the long-term academic outcomes associated with stimulant medication-use is far from conclusive, with some studies indicating a long-term benefit (Barbaresi et al., 2007; Powers et al., 2008; Scheffler et al., 2009) and others indicating no significant effect (Carlson & Bunner, 1993; Charles & Schrain, 1981; Jadad et al., 1999; Loe & Feldman, 2007; M. T. A. Cooperative Group, 2004a).

To further explore the long-term academic outcomes associated with the use of stimulant medication, the following section examines the independent relationship between stimulant medication-use and: Teacher-rated academic performance; attendance; and school enjoyment.

All multivariable models adjust for child's performance intelligence, symptom severity at five years of age, sociodemographic characteristics and propensity score.

Note: due to low response rate on teacher-completed questionnaires (58 children in the ADHD-diagnosed sample had available teacher-completed questionnaires), to maintain high enough numbers for multivariable analysis the 'Any Use' measure of stimulant exposure was used in the models predicting teacher-rated academic performance and school attendance.

Note: For the unadjusted means and proportions of each outcome measure by ADHD-diagnosis and medication-use, see Appendix B: Unadjusted means and proportions for outcomes measures.

## 7.1 Academic Performance

Academic performance was measured through the teacher-reported item assessing the child's academic performance. The two categories used in the analysis are 'below average', and 'average/above average'. Of the ADHD-diagnosed sub sample (n = 77), 49.4% were classified by their teacher as performing below age level. Of the sample without a diagnosis of ADHD (n = 964), 16.5% were classified as performing below age level. This difference was statistically significant ($\chi^2(1, N = 1041) = 50.17$, $p > .001$.

*Model Results*

The logistic regression analysis (n = 64) adjusting for child's intelligence, symptom severity, propensity, and sociodemographic measures indicated that stimulant medication significantly predicted teacher-rated academic performance.

The adjusted odds ratio for the use of stimulant medication in predicting "below average" classroom performance was 10.47 (95% CI: 1.12 - 97.49) (odds ratios are statistically significant if the 95% confidence interval does not include the number 1).

This result indicated that having received stimulant medication for the treatment of ADHD increased the odds of being identified as performing below age-level by a classroom teacher by a factor of 10.5 times. However, the large 95% confidence interval indicates some uncertainty as to where the exact value lies.

## 7.2 Absenteeism

Absenteeism was measured using the percentage of days a child was absent from school. "High" absenteeism was defined by being absent for 10% or more of possible school days. Of the ADHD-diagnosed sample (n = 80), 28.8% were classified as having "High" absenteeism. Of the non-ADHD-diagnosed sample (n = 924), 17.3% were classified as having "High" absenteeism. This difference was not significantly different $\chi^2(1, N = 1004) = 1.85$, $p = .17$.

*Model Results*

The logistic regression analysis (n = 67) adjusting for child's intelligence, symptom severity, propensity, and sociodemographic measures indicated that use of stimulant medication did not significantly predict absenteeism.

The adjusted odds ratio for the use of stimulant medication in predicting "high absenteeism" was 1.40 (95% CI: .17 - 11.78).

## *7.3 Enjoyment of School*

This measure was based on the summed total of 16 items designed to assess school enjoyment; possible scores range from 16 to 80, with higher scores indicating greater enjoyment of school. The mean Enjoyment of School score for children with ADHD (n = 114) was 32.35 (SD = 7.81). The mean Enjoyment of School score for non-ADHD-diagnosed children (n = 1383) was 33.84 (SD = 6.75). The difference of 1.49 was statistically significant ($t$ (1495) = 2.24, $p < .05$), indicating less school enjoyment in children diagnosed with ADHD.

*Model Results*

After adjusting for all covariates, the results of Generalised Linear Model (n = 96) indicated no significant effect of Stimulant Exposure on Enjoyment of School score: $F(3, 82) = .19$, $p = 0.90$. Estimated marginal means are provided in table 4.

**Table 4. Estimated marginal means for Enjoyment of School by stimulant medication use (adjusting for gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 20 | 33.03 | 2.60 | 27.87 - 38.20 |
| 1 time point | 23 | 34.58 | 2.72 | 29.18 - 39.98 |
| 2 time points | 35 | 34.02 | 2.45 | 29.14 - 38.89 |
| 3 time points | 18 | 35.73 | 3.25 | 29.27 - 42.20 |

## *7.4 Summary*

With regard to academic performance, it was found that stimulant medication use was associated with increased odds (10 times) of being classified as performing 'below age level' by a classroom teacher.

Whilst sample size issues did not allow the effect of exposure to stimulant medication to be examined (i.e. the analysis simply compared children who had ever used stimulant medication in the past to those who had never received stimulant medication), it would be expected that *any* stimulant medication-use would reduce short-term attentional and behavioural problems for the period in which it was used, thus allowing a child to learn the necessary information on which new information can be built upon in the future (Carlson & Bunner, 1993). The finding that stimulant medication-use increased the odds of *below-age-level* academic achievement by a factor of 10 times is in direct contrast to this hypothesis; indicating that 'any' use of stimulant medication is not associated with *improved* academic performance. However, the wide confidence interval makes it difficult to determine the exact size of the effect.

The finding that stimulant medication-use increased the odds of below-age-level academic achievement by a factor of 10 times strongly suggests that medication may not result in any long-term academic gains (as rated by a classroom teacher). And, at worst, may result in poorer teacher-rated academic performance. An alternative interpretation is that those children with poorer academic performance may have been more likely to have been medicated (independent of the ADHD severity). That is to say the degree of school failure/difficulty may have been used by the child's clinician to determine functional impact of their core ADHD symptoms, and may influence the course of treatment for a child.

More research that accounts for educational performance prior to medication commencement is required to allow the results gained in this study to be suitably interpreted.

Additionally, as mentioned, between-group comparisons based on the exposure to medication were not possible. This makes it impossible to determine whether there were different academic outcomes based on medication-use (e.g. increasing exposure predicting lower

performance; consistent adherence to medication predicting better performance than early cessation of medication). Future research should allow the comparison between medication-use groups to determine whether there are differences in academic gain/decline based on sub-categories of medication-use.

It should also be noted that no objective measures of classroom performance (e.g. test performance) were available at the time of preparing the current report. The measure "teacher-rated academic performance" is highly subjective and may not be a valid indicator of *actual* academic performance. Future studies examining outcomes in the Raine cohort may wish to examine the relationship between medication and performance on the WA Literacy and Numeracy Test while controlling for cognitive or intellectual ability.

The use of stimulant medication was found to have no significant associations with absenteeism or a child's enjoyment of school.

# 8. Results: Physical Side Effects

A number of physical outcomes have been shown to be associated with the use of stimulant medication. Those identified most often are measures of growth (height and weight) and measures of cardiovascular function (diastolic blood pressure, systolic blood pressure, and resting heart rate).

Longitudinal research has indicated that the use of both methylphenidate and dexamphetamine is associated with 'less than expected' growth trajectory (Charach et al., 2006; M. T. A. Cooperative Group, 2004b; Poulton, 2005). A review of the literature indicated that growth trajectory is most strongly affected within the first few years of medication-use and that normal growth trajectory resumes after this initial period of medication-use (Poulton, 2005). However, these children remain at significantly lower height and weight compared to children who never received medication.

Studies of the short-term effects have indicated that dexamphetamine and methylphenidate can both result in statistically significant changes in cardiovascular function. These studies show statistically significant elevation in blood pressure and heart rate (Biederman et al., 2006; Findling et al., 2001; Samuels et al., 2006; Wilens et al., 2004). However, these effects are small (usually < 5mmHg for blood pressure and <10bpm for heart rate) and are deemed to fall within clinically acceptable ranges for populations without serious cardiac problems (Volkow et al., 2001).

Whilst these short-term effects are well established, there is lack of published research examining the long-term effects of stimulant medication on cardiovascular function.

To further explore the long-term outcomes associated with stimulant medication-use, the following section examined the relationship between stimulant-use and height weight, systolic and diastolic blood pressures, and resting heart rate.

Due to the potential short-term effect of the current use of medication on cardiovascular function (and to a lesser extent, weight), the 'Recent Use' version of the medication use measures has been used in the following analyses (apart from height, where short-term effects of medication use would be minimal).

The following models control for symptom severity, demographic measures, and propensity. The analysis examining the relationship between stimulant medication and absolute height and weight at 14-year follow-up also controls for pre-medication height and weight (i.e. measured at 5 years). The analyses examining weight at 14-year follow-up also controls for pre-medication weight.

Given the impact of puberty upon both growth and cardiovascular function, puberty was also controlled for in each of the analyses.

Note: For the unadjusted means of each outcome measure by ADHD-diagnosis and medication-use, see Appendix B: Unadjusted means for outcomes measures.

## *8.1 Height*

The following section examines the association between stimulant medication-use and height. Two different outcome measures are employed. The first analysis examines the independent association between stimulant medication-use and the absolute height of the child at 14 years of age. The second analysis examines the 'growth' of the child's height relative to his or her peers. The 'growth' measure is the difference between height z-score at age 5 and height z-score at age 14. A negative score indicates less than expected growth and a positive score indicates greater than expected growth.

**Absolute height**

The outcome measure was the height of the child as measured by physical examination at the 14-year follow-up. The mean height for children with ADHD (n = 119) was 1.64m (SD = .091). The mean height for children without an ADHD diagnosis (n = 1424) was also 1.64 (SD = .079).

*Model Results*

After adjusting for all covariates, including child's height at 5 years, the results of Generalised Linear Model (n = 94) indicated no significant effect of Stimulant Exposure on height: $F(3, 78) = .1.42$, $p = 0.24$. Estimated marginal means are provided in table 5.

**Table 5. Estimated marginal means for child height (m) by stimulant medication exposure (adjusting for height at 5 years, gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 18 | 1.62 | .018 | 1.58 - 1.65 |
| 1 time point | 23 | 1.63 | .018 | 1.59 - 1.66 |
| 2 time points | 35 | 1.63 | .016 | 1.60 - 1.67 |
| 3 time points | 18 | 1.60 | .022 | 1.55 - 1.64 |

No significant association between height at 14 years and medication-use was noted.

**Change in height z-score**

The mean change in height z-score for children with ADHD (n = 109) was -.182 (SD = .091). This value was significantly different to the mean change in height z-score for children without

an ADHD diagnosis (n = 1281), which was -.024 (SD = .079); $t$ (1388) = 2.49, $p < .05$, indicating less than expected growth in children diagnosed with ADHD.

*Model Results*

After adjusting for all covariates, the results of Generalised Linear Model (n = 94) indicated no significant effect of Stimulant Exposure on change in height z-score: $F(3, 79) = 1.42$, $p = 0.24$. Estimated marginal means are provided in table 6.

**Table 6. Estimated marginal means for change in height z-score by stimulant medication exposure (adjusting for height at 5 years, gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 18 | -.390 | .245 | -.878 - .099 |
| 1 time point | 29 | -.051 | .241 | -.530 - .429 |
| 2 time points | 29 | -.135 | .227 | -.587 - .317 |
| 3 time points | 18 | -.479 | .301 | -1.08- .121 |

Whilst no significant result was noted, the trend was toward a lower than expected growth in height for children who had never received medication and those who had received medication at all three time points. There was little deviation from expected growth in height for children who had received medication at one or two time points.

## *8.2 Weight*

The following section examines the association between stimulant medication-use and weight. As with height two different outcome measures are employed. The first analysis examines the independent association between stimulant medication-use and the absolute weight of the child at 14 years of age. The second analysis examines the 'growth' of the child's weight relative to his or her peers. The 'growth' measure is the difference between weight z-score at age 5 and weight z-score at age 13. A negative score indicates less than expected growth and a positive score indicates greater than expected growth.

**Absolute weight**

The outcome measure was the weight of the child as measured by physical examination at the 14-year follow-up. The mean weight for children with ADHD (n = 119) was 58.90kg (SD = 13.98). The mean weight for children without an ADHD diagnosis (n = 1426) was 57.51kg (SD = 13.00)

Two analyses were carried out examining the relationship between stimulant medication and weight. The first used the 'Stimulant Exposure' measure to provide a rudimentary indication of a "dose-response" relationship. The second used the 'Current Medication' measure to provide

an indication of whether any effects of medication on weight are present in both the short- and long-term.

Stimulant Exposure

After adjusting for all covariates, the results of Generalised Linear Model (n = 94) indicated no significant effect of Stimulant Exposure on weight: $F(3, 78) = .287$, $p = 0.84$. Estimated marginal means are provided in table 7.

**Table 7. Estimated marginal means for child weight (kg) by stimulant medication exposure (adjusting for weight at 5 years, gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 18 | 55.91 | 3.54 | 48.87 - 62.96 |
| 1 time point | 23 | 57.86 | 3.57 | 50.75 - 64.97 |
| 2 time points | 35 | 58.97 | 3.18 | 52.64 - 65.30 |
| 3 time points | 18 | 56.44 | 4.31 | 47.85 - 65.02 |

Current use of stimulant medication

After adjusting for all covariates, the results of Generalised Linear Model (n = 94) indicated no statistically significant effect of Current Use of Stimulant Medication on weight: $F(3, 78) = 2.24$, $p = 0.09$. Estimated marginal means are provided in table 8.

It should be noted that there appeared to be a trend toward a higher weight in children who had had received medication in past but were not currently receiving it. This value was approximately 4.5 to 6.5kg higher than the other comparison groups. It should be reiterated, however, that this trend did not reach statistical significance.

**Table 8. Estimated marginal means for child weight by current stimulant medication use (adjusting for weight at 5 years, gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 18 | 55.54 | 3.41 | 47.75 - 61.64 |
| In the past | 29 | 62.68 | 3.32 | 56.08 - 69.29 |
| Currently, inconsistent in past | 29 | 55.41 | 3.13 | 49.17 - 61.64 |
| Consistently | 18 | 56.84 | 4.16 | 48.55 - 65.12 |

**Change in weight z-score**

The mean change in weight z-score for children with ADHD (n = 109) was .186 (SD = .835). The mean change in weight z-score for children without an ADHD diagnosis (n = 1285) was .289 (SD = .725). This difference was not statistically significant ($t(1392) = 1.41$, $p = .16$).

Two analyses were carried out examining the relationship between stimulant medication and change in weight z-score for children diagnosed with ADHD. The first used the 'Stimulant Exposure' measure to provide a rudimentary indication of a "dose-response" relationship. The second used the 'Current Medication' measure to provide an indication of whether any effects of medication on weight are present in both the short- and long-term.

Stimulant Exposure

After adjusting for all covariates, the results of Generalised Linear Model (n = 94) indicated no significant effect of Stimulant Exposure on change in weight z-score: $F(3, 78) = .28$, $p = 0.84$. Estimated marginal means are provided in table 9.

**Table 9. Estimated marginal means for change in weight z-score by stimulant medication exposure (adjusting for weight at 5 years, gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 18 | -.019 | .279 | -.575 - .538 |
| 1 time point | 23 | .286 | .284 | -.279 - .852 |
| 2 time points | 35 | .255 | .255 | -.327 - .688 |
| 3 time points | 18 | -.049 | .345 | -.736 - .637 |

Current use of stimulant medication

After adjusting for all covariates, the results of Generalised Linear Model (n = 94) indicated no statistically significant effect of Current Use of Stimulant Medication on change in weight z-score: $F(3, 78) = .28$, $p = 0..84$. Estimated marginal means are provided in table 10.

Once again, no significant result was noted, however the trend was toward children who had received medication only in the past having higher than expected growth in comparison to children who had received no medication, consistent medication or were currently medicated.

**Table 10. Estimated marginal means for change in weight z-score by current stimulant medication use (adjusting for weight at 5 years, gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 18 | -.107 | .271 | .-647 - .271 |
| In the past | 29 | .550 | .267 | .020 - 1.081 |
| Currently, inconsistent in past | 29 | -.029 | .251 | -.529 - .470 |
| Consistently | 18 | -.018 | .333 | -.682 - .645 |

## *8.3 Limitations with weight and height analyses*

In all multivariable analyses in the current report there were a number of cases excluded due to missing values on the covariates in the models. Whilst these missing cases had minimal effect on most outcome measures, there appeared to be non-random 'missingness' associated with the analyses examining absolute weight and absolute height. This effect was seen chiefly in the group of *ADHD-diagnosed children* who had *not received medication*.

The raw mean of the absolute weight of the 26 participants falling within the 'never-medicated' group was 64.8kg (SD = 15.2). After adjusting for all covariates in the model, 8 participants were lost due to missing values. These excluded participants had a significantly greater raw mean in term of weight (M = 74.5kg, SD = 15.1) than the sample of children remaining in the analysis (M = 60.5, SD = 13.5) ($t(24) = 2.34$, $p < .05$)

A similar effect was observed with regard to absolute height. The raw mean of the absolute height for the entire 26 cases was 1.66 (SD = .08). The raw mean for the 8 missing cases (M = 1.71, SD = .08) was significantly higher than the mean for the 16 remaining cases (M = 1.64, SD = .07) ($t(24) = 2.16$, $p < .05$).

The significant difference between the excluded and included participants indicates that, in the case of the absolute weight and height analysis, the non-random 'missingness' may affect the validity of the model.

It should be emphasised that the analyses examining the 'change in z-score' for height and weight did *not* suffer the same limitations and that the results from these models may be more valid in determining the association between the use of stimulant medication and growth.

## *8.4 Heart Function*

### 8.4.1 Blood Pressure - Systolic

Systolic blood pressure was measured by physical examination at the 14-year follow-up. The mean systolic blood pressure for children with ADHD (n = 119) was 112.92mmHg (SD = 10.77). The mean for non-ADHD-diagnosed children (n = 1424) was 113.08mmHg (SD = 10.92). The difference of .161 was not statistically significant ($t(1541) = .15$, $p = .88$).

After adjusting for all covariates, the results of Generalised Linear Model (n = 101) indicated no significant effect of Current Use of Stimulant Medication on systolic blood pressure: $F(3, 93) = .590$, $p = .62$. Estimated marginal means are provided in table 11.

**Table 11. Estimated marginal means for systolic blood pressure by current stimulant medication use (adjusting for gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 20 | 109.4 | 3.18 | 103.1 - 115.7 |
| In the past | 29 | 113.8 | 3.33 | 107.2 - 120.4 |
| Currently, inconsistent in past | 34 | 111.8 | 2.93 | 106.0 - 117.6 |

| | | | | |
|---|---|---|---|---|
| Consistently | 18 | 115.4 | 4.08 | 107.3 - 123.5 |

## 8.4.2 Blood Pressure - Diastolic

Diastolic blood pressure was measured by physical examination at the 14-year follow-up. The mean diastolic blood pressure for children with ADHD (n = 119) was 57.87mmHg (SD = 6.83). The mean for children without a diagnosis of ADHD (n = 1424) was 59.52mmHg (SD = 7.34). This difference was statistically significant ($t(1541) = 2.33$, $p < .05$).

After adjusting for all covariates, the results of Generalised Linear Model (n = 101) indicated a statistically significant effect of Current Use of Stimulant Medication on diastolic blood pressure: $F(3, 93) = 4.768$, $p = .004$. Estimated marginal means are provided in table 12.

**Table 12. Estimated marginal means for diastolic blood pressure by current stimulant medication use (adjusting for gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 20 | 55.79 | 2.00 | 51.81 - 59.76 |
| In the past | 29 | 60.46 | 2.10 | 56.29 - 64.62 |
| Currently, inconsistent in past | 34 | 59.53 | 1.84 | 55.87 - 63.19 |
| Consistently | 18 | 66.58 | 2.57 | 61.48 - 71.68 |

Between group comparisons indicated a significant difference ($p = .001$) between children who had never been on medication (mmHg = 55.79) and those who consistently received medication (mmHg = 66.58). In comparison to never receiving medication, consistently receiving medication was associated with an increase in diastolic blood pressure of 10.79mmHg (SE = 2.19).

A significant difference ($p = .006$) of 6.12mmHg (SE = 2.18) was also noted between children who had received medication in the past (but had not received it at the 14-year follow up) (mmHg = 59.53) and those who consistently received medication (mmHg = 66.58).

A significant difference was also noted between children who were currently receiving medication (mmHg = 59.53) and those who consistently received medication (mmHg = 66.58). In comparison with currently receiving medication (but not consistently receiving in the past), consistently receiving medication was associated with an increase in diastolic blood pressure of 7.05mmHg (SE = 2.19) which was statistically significant ($p = .002$).

Whilst the group of children who had received medication in the past had a mean diastolic blood pressure higher than those children who had never received medication, this difference was not statistically significant ($p = .118$).

Similarly whilst the group who were currently receiving medication (but had not consistently received medication in the past) had a marginal mean diastolic blood pressure higher than children who had never received medication, this difference was not statistically significant ($p$ = .171).

To place these differences in context, there needs to be some comparison between the populations included in the analysis and the average blood pressure of the overall population of children without ADHD. Without this, we cannot be sure whether stimulant medication elevates blood pressure to values higher than those in the general population or whether children with ADHD have lower than average blood pressure and the use of stimulant medication elevates it to levels similar to those of the population.

The nature of the generalised linear model (i.e. adjusted for multiple covariates) prevents the above values from being compared directly with unadjusted means. Thus, to place the above results in context the diastolic blood pressure of the group of children with ADHD who weren't on medication was compared to that of the group of children in the Raine sample who had no diagnosis of ADHD.

It was found that the average blood pressure of children without ADHD was 59.52 (SD = 7.43) and the average blood pressure for children with ADHD that had never received medication was 55.73 (SD = 5.80). The difference of 3.79 was statistically significant; $t(1448) = 2.58$, $p$ = .01.

The finding that the consistent use of stimulant medication was associated with an increase of 10.79 mmHg (compared to non-medicated children with ADHD) should be interpreted with the knowledge that, on average, children with ADHD who have never received medication have an average diastolic blood pressure approximately 3.8 mmHg lower than the general population.

### 8.4.3 Resting Heart Rate

Resting heart rate was measured by physical examination at the 14-year follow-up. The mean resting heart rate for children with ADHD (n = 119) was 81.74bpm (SD =13.85). The mean resting heart rate for non-ADHD-diagnosed children (n = 1423) was 77.82 (SD = 10.69). This difference of 3.92 was significantly different ($t(1540) = 3.75$, $p$ <.001).

After adjusting for all covariates, the results of Generalised Linear Model (n = 101) indicated no significant effect of Current Use of Stimulant Medication on resting heart rate: $F(3, 93)$ = .590, $p$ = .62. Estimated marginal means are provided in table 13.

**Table 13. Estimated marginal means for resting heart rate pressure by current stimulant medication use (adjusting for gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 20 | 79.16 | 3.87 | 71.48 - 86.85 |
| In the past | 29 | 80.69 | 4.06 | 72.73 - 88.76 |
| Currently, inconsistent in past | 34 | 82.30 | 3.56 | 75.22 - 89.39 |
| Consistently | 18 | 89.85 | 4.97 | 79.98 - 99.72 |

Whilst the results were not statistically significant, it is worth noting that there is a non-significant trend toward a higher resting heart rate in children who had consistently received medication (as compared to all other stimulant medication-use categories).

## *8.5 Summary*

Contrary to some existing literature, after adjusting for covariates the current analyses did not detect a significant effect of medication usage on weight or height. This was true for both absolute measures of weight and height and for change in z-score.

The lack of a significant effect of stimulant medication on growth measures in the current study may reflect inadequate power to detect a significant difference (additionally, it should be reiterated that the validity of the analyses examining *absolute* height and weight may be threatened due to non-random missing values). However, it should be noted that with regard to change in z-scores, the change in growth for those having never received medication was very similar to that observed for those having been consistently on medication. Given previous research indicating a significant effect of stimulant medication on growth measures, it was expected that the largest difference would be observed when comparing these two groups.

In terms of cardiovascular function, consistent use of stimulant medication was found to be associated with a statistically significant increase in blood pressure of approximately 10.8 mmHg when compared to not ever having received medication.

Additionally, consistent use of medication was associated with a 7.05mmHg increase as compared to just current use of medication (i.e. without consistent use in the past).

These findings suggest that there may be an elevation in diastolic blood pressure associated with the use of stimulant medication that can not be fully attributable to the immediate short-term effects on cardiovascular function.

However, it should be noted that the 'current' use of stimulant medication was identified by a parent indicating their child had received medication within the six months prior to filling out the questionnaire. Thus, it is not able to be ascertained which children were actually experiencing the short-term effects of stimulant medication during the physical exam.

Additionally, the dosage of medication (and adherence to) was not measured as part of the Raine study. It may be the case that there are differences in dosage/adherence to medication regime between currently medicated and consistently medicated groups that could account for differences in diastolic blood pressure.

It should also be noted that the average diastolic blood pressure for non-medicated ADHD-diagnosed children was significantly lower than that of the general population of non-diagnosed 14-year olds (3.79mmHg). This should be taken into account when interpreting the effect associated with consistent stimulant medication use. The 10.79mmHg elevation brings the mean diastolic blood pressure to 7mmHg above the average for 14-year old children.

An elevation in diastolic blood pressure of 7 to 10mmHg does not necessarily represent a movement outside of the 'normal' range. This was mirrored by the fact that none of the children in the ADHD-diagnosed sample recorded a diastolic blood pressure that fell above the cut-off for the 95$^{th}$ percentile (i.e. 79mmHg). However it should be noted that a meta-analysis examining cardiovascular function in adults found that elevated diastolic blood pressure, even falling within the 'normal range', significantly increases the risk of stroke and coronary heart disease. Prolonged elevation in diastolic blood pressure of 7.5 to 10mmHg was associated with 46% to 56% more stroke and 29% to 37% more coronary heart disease (MacMahon et al., 1990). However, whether similar long-term effects are associated with elevated blood pressure during **childhood** has not yet been studied.

The current findings suggest that further research into the long-term effects of stimulant medication on diastolic blood pressure and the implications for long-term cardiovascular health is warranted.

In terms of other measures of cardiovascular function, stimulant medication was found to have no statistically significant relationship with systolic blood pressure or resting heart rate. However, a non-significant trend toward higher resting heart rate in consistently medicated children was noted.

# 9. Changes in key ADHD symptoms in comparison to peers

Two of the key defining symptoms of ADHD are externalising behaviour and attention problems. The following section examines the change in these symptoms from age 5 to age 14 and whether the use of stimulant medication was related to any improvement/decline in ADHD symptoms.

This section may be confounded due to the possibility of the short-term effects of medication impacting upon the measures of attention and behaviour at the 14-year follow-up. This effect is likely to be minimal, however, as the ratings were provided by the parent of the child; and as the majority of children were on short-acting medication, the parents were unlikely to observe the short-term 'on-board' effects of medication. Thus, whilst the measure is somewhat flawed, it is likely to give an indication of the long-term effects of medication.

General linear models were conducted examining the impact of stimulant use on symptom change scores after adjusting for propensity score and sociodemographic measures. Given that stimulant medication may have both short-term and long-term impacts upon symptom change scores, analyses were conducted using both 'Stimulant Exposure' and the 'Current Stimulant Use' predictor measures.

Note: For the unadjusted means of each outcome measure by ADHD-diagnosis and medication-use, see Appendix B: Unadjusted means for outcomes measures.

## *9.1 Externalising Behaviour*

The Externalising Behaviour Change Score was calculated by subtracting the CBCL-Externalising score at the 14-year follow-up from the CBCL-Externalising score at the 5-year follow-up. Thus, negative scores indicate an improvement in externalising behaviour and positive score indicate an elevation in externalising behaviour. The mean externalising behaviour change score for children with a diagnosis of ADHD (n = 122) was -2.25 (SD = 11.96). The mean change score for children without a diagnosis of ADHD (n = 1511) was -3.76 (SD = 9.54). This difference was not statistically significant ($t(1631) = 1.64$, $p = .10$).

These scores indicated little change in parent-rated externalising behaviour between ages five and fourteen. However, the trend was toward a slight improvement in symptoms for both ADHD-diagnosed and non-ADHD-diagnosed children.

*Model Results*

After adjusting for all covariates, the results of Generalised Linear Model (n = 103) indicated no significant effect of Stimulant Exposure on Externalising Behaviour Change Score: $F(3, 100) = .621$, $p = .603$. Estimated marginal means are provided in table 14.

There was a trend toward higher exposure to medication (at 2 and 3 time points) being associated with an improvement in parent-rated externalising behaviour compared to lower exposure to medication (at 1 and 2 time points). However this trend was not statistically significant.

**Table 14. Estimated Marginal Mean Externalising Behaviour Change Score by stimulant medication exposure (adjusting for gender, propensity, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 22 | .34 | 3.16 | -6.62 - 5.93 |
| 1 time point | 31 | .28 | 3.27 | -6.76 - 6.20 |
| 2 time points | 40 | -2.73 | 3.00 | -3.23 - 8.70 |
| 3 time points | 19 | -4.00 | 4.20 | -4.35 -12.33 |

The model examining the relationship between Externalising Behaviour Change Score and Current Stimulant Medication-Use also found no significant effect $F(3, 100) = .667$, $p = .574$ (see table 15 for estimated marginal means).

Whilst no statistically significant effect was observed, it should be noted that there appeared to be a slight trend toward the improvement of ADHD symptoms in children who had received medication in the past or who had consistently received medication (compared to those who had never received medication or had only received it at the latest follow-up). This difference was slight, however.

**Table 15. Estimated Marginal Mean Externalising Behaviour Change Score by current stimulant medication use (adjusting for gender, propensity, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 22 | .52 | 3.15 | -6.77 - 5.74 |
| In the past | 35 | -3.30 | 3.23 | -3.10 - 9.08 |
| Currently, inconsistent in past | 36 | -.16 | 3.00 | -5.80 - 6.12 |
| Consistently | 19 | -4.57 | 4.22 | -3.81 - 12.94 |

## *9.2 Attention Problems*

The Attention Problem Change Score was calculated by subtracting the CBCL-Attention Problem score at the 14-year follow-up from the CBCL-Attention Problem score at the 5-year follow-up. Thus, negative scores indicate an improvement in attention and positive score indicate an elevation in attention problems. The mean attention problem change score for

children with ADHD (n = 122) was .836 (SD = 10.88) and the mean change score for non-ADHD-diagnosed children (n = 1511) was -1.28 (SD = 5.53). This difference was statistically significant ($t(1631) = 3.70$, $p < .001$), and indicated a slight improvement in attention for children without a diagnosis of ADHD but not in children with a diagnosis.

*Model Results*

After adjusting for all covariates, the results of Generalised Linear Model (n = 103) indicated no significant effect of Stimulant Exposure on Attention Problem Change Score score: $F(3, 100) = 1.49$, $p = .222$. Estimated marginal means are provided in table 16.

A slightly higher improvement in attentional problems was associated with receiving medication at two time points (and, to a lesser extent, three time points). However the difference between these values and those of the groups who had received medication at one time point, or had received no medication or did not reach statistical significance.

**Table 16. Estimated Marginal Mean Attention Problems Change Score by stimulant medication exposure (adjusting for gender, propensity, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 22 | .07 | 2.74 | -5.50 - 5.36 |
| 1 time point | 31 | 1.70 | 2.83 | -7.32 - 3.91 |
| 2 time points | 40 | -3.76 | 2.60 | -1.43 - 8.89 |
| 3 time points | 19 | -1.55 | 3.64 | -5.68 - 877 |

The model examining the relationship between Attention Problem Change Score and Current Stimulant Medication-Use also found no significant effect $F(3, 100) = .396$, $p = .756$ (see table 17 for estimated marginal means).

Compared to not having received medication, or receiving medication at age fourteen (but not consistently in the past), there seemed to be a slight improvement in attentional problems in children who had received medication in the past (but not at age 14) or consistently. However, all differences were small and between-group comparisons indicated no statistically significant differences.

**Table 17. Estimated Marginal Mean Attention Problems Change Score from age 5 to 14 by current stimulant medication use (adjusting for gender, propensity, mother's age, family structure, family income)**

| Stimulant Exposure | n | Estimated marginal mean | Std. Error | 95% CI |
|---|---|---|---|---|
| None | 22 | .38 | 2.78 | -5.89 - 5.13 |
| In the past | 35 | -2.93 | 2.84 | -2.70 - 8.57 |
| Currently, inconsistent in past | 36 | -.42 | 2.65 | -4.82 - 5.67 |
| Consistently | 19 | -2.14 | 3.71 | -5.23 - 9.51 |

## *9.3 Summary*

The results from this section suggest that the use of stimulant medication may not be associated with a significant long-term improvement in either of the key symptoms of ADHD: externalising behaviour or attention problems. On average, there was very little change in externalising behaviour or attention problems from the ages of five to 14 years in children with ADHD, regardless of medication use.

Where non-significant trends were noted, these were in the direction of consistent and current stimulant medication being associated with a slight improvement in symptoms and a study with higher power may have detected a significant effect. It should be reiterated however, that these effects were small and were not statistically significant.

The lack of an association between stimulant medication-use and long-term change in core ADHD symptoms is not unexpected, as medication is used for temporary management for these symptoms, and is not seen as ‘cure’.

Some concern may be raised over the apparent lack of a strong effect with regard to children ‘currently’ on medication, as it would be expected that some short-term reduction in symptoms would be observed. However, the lack of a short-term effect can be explained by the fact that *parents* completed the assessments of core symptoms. Given that medication is taken mostly during school hours, the ‘onboard’ effects of medication may not be apparent to parents.

With regard to interpreting the lack of improvement in attention, it is also worth noting that the Attention Problems subscale on the version of the CBCL that was available when the Raine study follow-ups were conducted has been found to have poor psychometric properties (Heubeck, 2000). This may affect the validity of the findings with regard to changes in attention problem in the current study.

# 10. Key Findings/Overview

The Raine Study provides a unique opportunity to identify events/experiences a child undergoes from pregnancy through to adolescence and how these events impact upon later life. The current study utilised Raine data to examine the long-term outcomes (at 14 years) associated with the use of stimulant medication across childhood in children diagnosed with ADHD.

Whilst the Raine Study allowed for the long-term outcomes associated with stimulant medication to be explored in a way that is lacking in the extant literature, it should be noted at the outset that a number of limitations must be considered when interpreting the results of the analyses (outlined in more detail in section 11. Limitations). These limitations prevent any strong causal inferences from being made with regard to the relationship between stimulant medication and long-term outcomes. Despite these limitations, however, there were a number of results observed in the current study that provide a strong impetus for further research into the long-term benefits and side-effects arising from the use of stimulant medication in the treatment of ADHD.

*Diagnosis of ADHD and poorer long-term outcomes*

Children with a diagnosis of ADHD as reported by parents (regardless of medication use), perform significantly worse at age 14 years on measures of depression, self perception, social functioning, academic performance, school enjoyment and attention than those without a diagnosis.

This finding is consistent with previous research and suggests that children diagnosed with ADHD have an underlying condition that impacts negatively on a range of long-term life skills.

*Social, Emotional and Academic Outcomes; Improvement in key symptoms*

One key finding of the current study was the lack of a significant association between medication-use and social and emotional outcomes at the age of 14 years. As the key underlying symptoms of ADHD are suspected in the development of poor long-term social and emotional well-being it would be hypothesised that treatment ameliorating these symptoms would result in improved long-term outcomes. However, it was found that even children who had consistently received medication from the age of eight years up until 14 years did not differ significantly from children who had never received stimulant medication. Equally, there was no evidence for deterioration in emotional outcomes for children on medication.

With regard to academic functioning, the use of stimulant medication was associated with a *greater* likelihood of performing below expected for age (as rated by teacher) for children

diagnosed with ADHD. This is contrary to what would be expected based on the theoretical benefits of stimulant medication (Carlson & Bunner, 1993). Whilst it is possible that this result reflected that children with a functional impact of symptoms on academic performance may be more likely to be medicated, this finding indicates a need for a better understanding into the relationship between stimulant medication and long-term academic outcomes.

Additionally, it was noted that the use of stimulant medication was not found to be associated with a long-term improvement in attention or externalising behaviour. This result is perhaps unsurprising, as stimulant medication is not seen as a 'cure' for the core symptoms of ADHD. Rather, medication temporarily assists in the management of symptoms. However it should be noted that the direction of non-statistically-significant trend leant toward a slight improvement in symptoms associated with the use of stimulant medication and a study with higher power may have detected a significant effect.

Overall, the results suggest that whilst stimulant medication may be effective in managing the immediate symptoms of ADHD, these short-term effects may not translate into long-term benefits to the child's social and emotional outcomes, school-based performance, or symptom improvement. Furthermore, the results indicated that the use of stimulant medication was associated with *poorer* teacher-rated general academic performance.

It is reiterated that these findings should be interpreted with the limitations of the current study in mind: particularly the difficulty in controlling for symptom severity (see section 11: Limitations). This makes it difficult to make any strong claims regarding the *role* of medication in the long-term social, emotional, academic, and symptom improvement. However, the findings of this research indicate that more rigorously designed longitudinal studies determining whether the use of stimulant medication has any measurable long-term benefits should be a priority for future research.

*Cardiovascular function*

The most noteworthy finding in the study was the association between stimulant medication and diastolic blood pressure. Compared to not receiving medication the consistent use of stimulant medication was associated with a significantly higher diastolic blood pressure (of over 10mmHg)

This effect did not appear to be solely attributable to any short-term effects of stimulant medication, as when comparing groups who were currently receiving medication, it was found that those who had consistently received medication at all time points had a significantly higher mean diastolic blood pressure than those who had not consistently received medication in the past (difference of 7mmHg).

These findings indicate there may be a lasting longer-term effect of stimulant medication on diastolic blood pressure above and beyond the immediate short-term side-effects.

This finding indicates that further research into the long-term effects on cardiovascular health is required to understand the potential cardiovascular side-effects of stimulant medication.

# 11. Limitations

There are a number of limitations associated with the current study that must be carefully considered when interpreting its results.

Small Sample Size

The limited number of children in each of the categories of stimulant use impacted upon a number of aspects of the study.

The first, and most obvious, is the lack of power to detect a statistically significant effect. This means that we cannot accurately determine whether a lack of a statistically significant effect in this study indicates a lack of power or the fact that stimulant medication has little bearing on the outcome.

The second limitation associated with the small number of children in each of the categories was that a number of categorical/dichotomous measures commonly associated with ADHD (e.g. risk-taking behaviour, level of puberty) could not be analysed due to a lack of cases present in the cells.

Controlling for Systematic Differences between Comparison Groups

The naturalistic nature of the current study means that there may be a number of systematic differences between comparison groups. These differences may mask significant effects, or create misleading results.

These were to be controlled for by using the ‘propensity for medication’ score, the symptom severity before commencement of medication treatment, and a number of sociodemographic measures.

However, this adjustment was limited by the inclusion of measures that were available. Additionally, propensity scores have their limitations and it can not be told how well the propensity scores in the current study controlled for systematic differences between the test groups.

Controlling for Symptom Severity

Symptom severity is likely to be a confounding factor, with children who are more severe being more likely to go on medication and more likely to experience negative outcomes (independent of medication use). Without adequately controlling for this, results may spuriously indicate that ADHD medication causes negative long-term outcomes (J. Swanson et al., 2008).

The measures of symptom severity in the current study suffered from a number of limitations (outlined in section 4.1 Controlling for potential systematic differences between medication groups) which may reduce the validity of the multivariable models. It is likely that the CBCL was an inadequate measure of pre-treatment severity. Lack of teacher rated measures of symptoms pre and post medication also made analysis difficult.

No separate effects for medication type

Due to sample size issues, dextroamphetamine and methylphenidate use were combined into one composite group: 'stimulant use'. This prevented the effects of the different medications on the various outcomes to be identified.

Dosage and adherence

Dosage and adherence to medication was not measured as part of the study. Medication usage at each of the time points was determined by the mother reporting that the medication had been used in the 6 months prior to completing the questionnaire.

This may result in the measures of 'exposure to stimulant medication' and 'current use of stimulant medication' lacking a refined indication of stimulant use.

No validation of ADHD diagnosis

The current study was not able to validate the diagnosis of ADHD; rather the diagnosis of the disorder by a qualified professional was used to classify the children. This could result in a number of children who had been misdiagnosed being included within the study.

ADHD subtypes

Additionally, the two different subtypes of ADHD were not able to be analysed separately, once again due to sample size issues. This may result in effects of stimulant specific to ADHD subtypes being masked in the current analyses.

Non-random missing values for absolute weight and height measures

The significant difference between the participants that were excluded due to missing values and those that were included in the analyses indicates that, in the case of the absolute weight and height analysis, the non-random 'missingness' may affect the validity of the model.

# 12. Conclusions/Recommendations

The current study provides a unique longitudinal view of the social, emotional, academic, physical, and cardiovascular outcomes associated with the use of stimulant medication in the treatment of ADHD.

Whilst limitations to the current study prevent causal relationships from being identified, the associations that were noted strongly suggest that more methodologically rigorous into the long-term outcomes associated with ADHD should be conducted.

Future research into the long-term effects of stimulant medication in ADHD treatment should take the form of a matched-control prospective study that collects information at multiple time-points on: ADHD subtype diagnosis (with validation), symptom severity, type of medication used, medication dosage, and medication adherence. With a large enough sample size, this form of study would allow the long-term effects of medication (especially suspected social, emotional and academic benefits, and long-term cardiovascular side-effects) to be thoroughly examined.

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# Appendix A. Creation of propensity score

To reduce the bias due to systematic differences between test groups 'propensity scores' were created. This method uses a number of sociodemographic and symptom severity measures to classify a child as having a 'high' or 'low' likelihood of being given stimulant medication.

The measures used to create the propensity scores were: child's gender, sociodemographic measures at child's birth (family income, mother's education, mother's work status, family structure), Externalising Behaviour Problems at 5 years of age, and Attention Problems at 5 years of age.

These predictors were entered into a binary logistic regression model predicting the use of stimulant medication for children with a diagnosis of ADHD. A comprehensive model, including all interactions between independent variables in predicting stimulant use was designed and conducted. The probability of a case going on to receive stimulant medication based on the model was produced.

Quintiles of the probability score were calculated. Cases that fell in the bottom quintile were defined as having a 'low' propensity for medication. Cases that fell into the top 4 quintiles were defined as having a 'high' propensity for medication.

See Table A.1 for the relationship between the propensity score and the use of stimulant medication

Table A.1. Propensity for Medication and Use of Medication

| | | Never used Medication | Used Medication | Total |
|---|---|---|---|---|
| Low Propensity | Count | 17 | 6 | 23 |
| | % within Propensity Category | 73.90% | 26.10% | 100.00% |
| High Propensity | Count | 5 | 84 | 89 |
| | % within Propensity Category | 5.60% | 94.40% | 100.00% |
| Total | Count | 22 | 90 | 112 |
| | % | 19.60% | 80.40% | 100.00% |

# Appendix B. Unadjusted means and proportions for outcome measures

Table B.1. Means of continuous social, emotional, and academic outcome measures by ADHD diagnosis and 'medication exposure'

| | | BDI t-score | ASPP | ASPP - S | School Enjoyment |
|---|---|---|---|---|---|
| Non ADHD | Mean | 42.02 | 128.98 | 32.42 | 33.84 |
| | N | 1420 | 1419 | 1426 | 1383 |
| | Std Dev | 8.21 | 15.36 | 5.45 | 6.75 |
| ADHD, No Medication | Mean | 42.28 | 128.27 | 32.19 | 33.19 |
| | N | 25 | 26 | 26 | 26 |
| | Std Dev | 6.75 | 13.13 | 4.30 | 5.59 |
| ADHD, Medication at 1 time point | Mean | 44.88 | 124.28 | 29.27 | 32.58 |
| | N | 33 | 32 | 33 | 31 |
| | Std Dev | 9.57 | 19.52 | 8.22 | 8.58 |
| ADHD, Medication at 2 time points | Mean | 43.33 | 124.00 | 28.65 | 31.35 |
| | N | 39 | 39 | 40 | 37 |
| | Std Dev | 8.44 | 16.18 | 7.10 | 7.99 |
| ADHD, Medication at 3 time points | Mean | 44.55 | 129.84 | 31.50 | 32.75 |
| | N | 20 | 19 | 20 | 20 |
| | Std Dev | 9.38 | 16.64 | 8.96 | 9.00 |
| Total | Mean | 42.15 | 128.75 | 32.24 | 33.73 |
| | N | 1537 | 1535 | 1545 | 1497 |
| | Std Dev | 8.25 | 15.47 | 5.65 | 6.84 |

Table B.2. Proportions of categorical educational measures by ADHD diagnosis and 'medication exposure'

| | | Teacher-rated academic performance | | | Proportion of days absent | | |
|---|---|---|---|---|---|---|---|
| | | Average or above | Below Average | Total | <10% | >10% | Total |
| Non ADHD | N | 805 | 159 | 964 | 688 | 236 | 924 |
| | % within group | 83.5% | 16.5% | 100.0% | 74.5% | 25.5% | 100.0% |
| ADHD, no medication | N | 14 | 6 | 20 | 14 | 6 | 20 |
| | % within group | 70.0% | 30.0% | 100.0% | 70.0% | 30.0% | 100.0% |
| ADHD, Some medication | N | 25 | 32 | 57 | 40 | 20 | 60 |
| | % within group | 43.9% | 56.1% | 100.0% | 66.7% | 33.3% | 100.0% |
| Total | N | 844 | 197 | 1041 | 742 | 262 | 1004 |
| | % within group | 81.1% | 18.9% | 100.0% | 73.9% | 26.1% | 100.0% |

Table B.3. Mean absolute height and weight by ADHD diagnosis and 'medication exposure'

| | | Mean Weight (kg) | Mean Height (m) |
|---|---|---|---|
| Non ADHD | Mean | 57.5 | 1.64 |
| | N | 1426 | 1424 |
| | Std Dev | 13.0 | 0.08 |
| ADHD, No Medication | Mean | 64.8 | 1.66 |
| | N | 26 | 26 |
| | Std Dev | 15.2 | 0.08 |
| ADHD, Medication at 1 time point | Mean | 56.6 | 1.65 |
| | N | 33 | 33 |
| | Std Dev | 11.4 | 0.09 |
| ADHD, Medication at 2 time points | Mean | 58.5 | 1.63 |
| | N | 40 | 40 |
| | Std Dev | 14.6 | 0.10 |
| ADHD, Medication at 3 time points | Mean | 55.9 | 1.62 |
| | N | 20 | 20 |
| | Std Dev | 13.5 | 0.08 |
| Total | Mean | 57.6 | 1.64 |
| | N | 1545 | 1543 |
| | Std Dev | 13.1 | 0.08 |

Table B.4 Mean absolute weight by ADHD diagnosis and 'current use of stimulant medication'

| | | Mean weight (kg) |
|---|---|---|
| Non ADHD | Mean | 57.5 |
| | N | 1426 |
| | Std Dev | 13.0 |
| ADHD, No Medication | Mean | 64.8 |
| | N | 26 |
| | Std Dev | 15.2 |
| ADHD, medicated in the past | Mean | 60.4 |
| | N | 35 |
| | Std Dev | 13.2 |
| ADHD, currently medicated, inconsistent in past | Mean | 55.1 |
| | N | 38 |
| | Std Dev | 12.9 |
| ADHD, consistently medicated | Mean | 55.9 |
| | N | 20 |
| | Std Dev | 13.5 |
| Total | Mean | 57.6 |
| | N | 1545 |
| | Std Dev | 13.1 |

Table B.5. Mean change in height and weight z-scores by ADHD diagnosis and 'medication exposure'

| | | Change in height z-score | Change in weight z-score |
|---|---|---|---|
| Non ADHD | Mean | -0.02 | 0.29 |
| | N | 1281 | 1285 |
| | Std Dev | 0.63 | 0.73 |
| ADHD, No Medication | Mean | -0.19 | 0.17 |
| | N | 22 | 22 |
| | Std Dev | 0.59 | 0.69 |
| ADHD, Medication at 1 time point | Mean | 0.01 | 0.30 |
| | N | 29 | 29 |
| | Std Dev | 0.76 | 0.73 |
| ADHD, Medication at 2 time points | Mean | -0.26 | 0.13 |
| | N | 39 | 39 |
| | Std Dev | 0.83 | 0.95 |
| ADHD, Medication at 3 time points | Mean | -0.32 | 0.14 |
| | N | 19 | 19 |
| | Std Dev | 0.73 | 0.91 |
| Total | Mean | -0.04 | 0.28 |
| | N | 1390 | 1394 |
| | Std Dev | 0.64 | 0.73 |

Table B.6. Mean change in weight z-score by ADHD diagnosis and 'current use of stimulant medication'

| | | Change in weight z-score |
|---|---|---|
| Non ADHD | Mean | 0.29 |
| | N | 1285 |
| | Std Dev | 0.73 |
| ADHD, No Medication | Mean | 0.17 |
| | N | 22 |
| | Std Dev | 0.69 |
| ADHD, medicated in the past | Mean | 0.43 |
| | N | 34 |
| | Std Dev | 0.91 |
| ADHD, currently medicated, inconsistent in past | Mean | -0.03 |
| | N | 34 |
| | Std Dev | 0.76 |
| ADHD, consistently medicated | Mean | 0.14 |
| | N | 19 |
| | Std Dev | 0.91 |
| Total | Mean | 0.28 |
| | N | 1394 |
| | Std Dev | 0.73 |

Table B.7. Mean values of cardiovascular measures by ADHD diagnosis and 'current use of stimulant medication'

| | | Systolic Blood Pressure (mmHg) | Diastolic Blood Pressure (mmHg) | Resting Heart Rate (bpm) |
|---|---|---|---|---|
| Non ADHD | Mean | 113.08 | 59.52 | 77.82 |
| | N | 1424 | 1424 | 1423 |
| | Std Dev | 10.92 | 7.43 | 10.69 |
| ADHD, No Medication | Mean | 112.54 | 55.73 | 76.96 |
| | N | 26 | 26 | 26 |
| | Std Dev | 12.31 | 5.80 | 11.96 |
| ADHD, medicated in the past | Mean | 113.20 | 57.74 | 81.03 |
| | N | 35 | 35 | 35 |
| | Std Dev | 11.08 | 6.65 | 12.09 |
| ADHD, currently medicated, inconsistent in past | Mean | 112.89 | 57.53 | 82.92 |
| | N | 38 | 38 | 38 |
| | Std Dev | 9.54 | 6.97 | 15.27 |
| ADHD, consistently medicated | Mean | 112.95 | 61.55 | 86.95 |
| | N | 20 | 20 | 20 |
| | Std Dev | 11.11 | 7.16 | 14.94 |
| Total | Mean | 113.06 | 59.39 | 78.12 |
| | N | 1543 | 1543 | 1542 |
| | Std Dev | 10.90 | 7.40 | 11.01 |

Table B.8. Mean change in core symptom z-score by ADHD diagnosis and 'stimulant exposure'

| | | Change in CBCL Behaviour Problems t-score | Change in CBCL Attention Problems t-score |
|---|---|---|---|
| Non ADHD | Mean | -3.7631 | -1.2846 |
| | N | 1511 | 1511 |
| | Std Dev | 9.54332 | 5.53147 |
| ADHD, No Medication | Mean | -3.0400 | -2.2000 |
| | N | 25 | 25 |
| | Std Dev | 13.37124 | 10.70825 |
| ADHD, Medication at 1 time point | Mean | -3.4000 | 1.1500 |
| | N | 40 | 40 |
| | Std Dev | 11.34042 | 9.52069 |
| ADHD, Medication at 2 time points | Mean | .4737 | 2.8947 |
| | N | 38 | 38 |
| | Std Dev | 11.47203 | 9.49193 |
| ADHD, Medication at 3 time points | Mean | -4.2632 | .0526 |
| | N | 19 | 19 |
| | Std Dev | 12.27392 | 15.44335 |
| Total | Mean | -3.6503 | -1.1261 |
| | N | 1633 | 1633 |
| | Std Dev | 9.74853 | 6.11521 |

Table B.9. Mean change in core symptom z-score by ADHD diagnosis and 'current use of stimulant medication'

| | | Change in CBCL Behaviour Problems t-score | Change in CBCL Attention Problems t-score |
|---|---|---|---|
| Non ADHD | Mean | -3.7631 | -1.2846 |
| | N | 1511 | 1511 |
| | Std Dev | 9.54332 | 5.53147 |
| ADHD, No Medication | Mean | -3.0400 | -2.2000 |
| | N | 25 | 25 |
| | Std Dev | 13.37124 | 10.70825 |
| ADHD, medicated in the past | Mean | -.2500 | 4.3611 |
| | N | 36 | 36 |
| | Std Dev | 12.89380 | 10.52929 |
| ADHD, currently medicated, inconsistent in past | Mean | -2.5952 | -.0238 |
| | N | 42 | 42 |
| | Std Dev | 10.18382 | 8.07733 |
| ADHD, consistently medicated | Mean | -4.2632 | .0526 |
| | N | 19 | 19 |
| | Std Dev | 12.27392 | 15.44335 |
| Total | Mean | -3.6503 | -1.1261 |
| | N | 1633 | 1633 |
| | Std Dev | 9.74853 | 6.11521 |

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