Early predictors of de novo and subthreshold late-onset ADHD in a child and adolescent cohort

Key words: ADHD, risk factors, outcome, adolescence

Declaration of Interest: All authors declare no conflict of interest.
Abstract

Objective
The study aimed to identify early childhood risk factors for de novo and subthreshold late-onset ADHD.

Method
ADHD symptoms were assessed in 9,875 participants from the Twins Early Development Study (TEDS) using the Conners’ Parent Rating Scale at ages 8, 12, 14 and 16 years, along with other childhood characteristics and adolescent outcomes. Multinomial logistic regressions were implemented to identify early childhood predictors of late-onset ADHD and childhood-onset persistent ADHD, with non-ADHD controls as the reference category.

Results
Male sex, increased childhood conduct problems and low socioeconomic status predicted de novo late-onset ADHD. Additional risk factors predicted subthreshold late-onset ADHD and childhood-onset persistent ADHD. Late-onset ADHD symptoms were also accompanied by increased co-occurring behavioural and emotional problems.

Conclusion
Findings of different childhood predictors between subthreshold and de novo late-onset ADHD suggest further investigation into time-varying environmental and biological factors driving psychopathological changes is warranted to fully characterise late-onset ADHD.
Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) has long been conceptualised as a childhood-onset disorder. According to the DSM-5, a diagnosis of ADHD requires the presence of several inattentive and/or hyperactive/impulsive symptoms by age 12 years (American Psychiatric Association & American Psychiatric Association. DSM-5 Task Force, 2013). However, recent evidence from population-based longitudinal studies suggests that a subgroup of individuals exhibit increasing ADHD symptoms later in their development, meeting criteria for ADHD for the first time during adolescence and young adulthood (Agnew-Blais et al., 2016; Caye et al., 2016; Cooper et al., 2018; Liu, Li, Viding, Asherson, & Pingault, 2018; Murray, Eisner, Obsuth, & Ribeaud, 2017; Pingault et al., 2011; Pingault et al., 2015). Compared with non-ADHD controls, late-onset ADHD shows poorer cognitive performance, elevated family adversity and increased behavioural and emotional problems in early childhood. Individuals with late-onset ADHD also exhibit more mental health problems and higher rates of substance misuse in early adulthood than those who have never met ADHD diagnosis (Agnew-Blais et al., 2016; Caye et al., 2016; Manfro et al., 2018). When compared with individuals with childhood onset of ADHD and persistence into young adulthood (childhood-onset persistent ADHD), late-onset ADHD shows fewer behavioural and emotional problems and better cognitive performance in childhood, however, the two groups have similar patterns of psychosocial impairment during the young adult years (Agnew-Blais et al., 2016, 2018).

Although late-onset ADHD has been studied extensively in the past few years, the late-onset ADHD diagnosis continues to be debated. A comprehensive review concluded that although current evidence supports the existence of late-onset ADHD, the definition and exclusion criteria of late-onset ADHD remain unresolved (Asherson & Agnew-Blais, 2019). For
example, an argument refuting the existence of late-onset ADHD asserts that late-onset ADHD may only reflect an undiagnosed childhood condition due to measurement limitations or protective environment, in particular for individuals with elevated childhood ADHD symptoms (Kosaka, Fujioka, & Jung, 2018; Sibley et al., 2018). Prior studies have divided late-onset ADHD into two groups according to their childhood ADHD symptoms: (i) individuals with 0-2 inattentive or hyperactive/impulsive symptoms before age 12 years (who have been called 'genuine' and that we call 'de novo' late-onset ADHD) (Cooper et al., 2018), and (ii) individuals with 3-5 inattentive or hyperactive/impulsive symptoms before age 12 ('subthreshold' late-onset ADHD). Some studies excluded subthreshold late-onset ADHD from the late-onset ADHD to avoid possible misclassification or due to the idea that only those with low childhood ADHD symptoms ('de novo' late-onset ADHD in the current study) reflect 'genuine' late-onset psychopathology (Cooper et al., 2018; Manfro et al., 2018; Sibley et al., 2018). Consequently, similarities and differences between de novo late-onset ADHD and subthreshold late-onset ADHD remain unclear.

Here, we aimed to investigate the distinction between late-onset ADHD with low and subthreshold childhood ADHD symptoms and to examine what factors drive an increase in ADHD symptom development beyond childhood. To this end, we contrasted the early childhood characteristics and adolescent outcomes of the following three developmental categories with non-ADHD controls: de novo late-onset ADHD, subthreshold late-onset ADHD and childhood-onset persistent ADHD.

**Method**

**Study sample**

This study used data collected from birth to age 16 years from the Twins Early Development Study (TEDS), a UK population-based sample of twins recruited in England and Wales.
between 1994 and 1996 (Haworth, Davis, & Plomin, 2013). ADHD symptoms were assessed when participants were 8, 12, 14 and 16 years old. The TEDS sample consists of a total of 12,593 pairs of twins after excluding participants with extreme pre- and perinatal complications. For this study investigating late-onset ADHD, participants who had ratings of ADHD symptoms in childhood (age 8 or age 12) and adolescence (age 14 or age 16) were included, yielding a final study sample of 9,875 individuals. A comparison of the study sample with the initial sample is provided in Supplementary Table 1. ADHD symptoms were significantly higher in the initial sample compared to the present sample, but effect sizes of the difference were close to zero (Cohen’s d 0.02-0.07).

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects were approved by the Institute of Psychiatry, Psychology and Neurosciences Ethics Committee at King’s College London Psychology and Neuroscience Department. Written informed consent was acquired from parents prior to data collection.

**Measures**

**ADHD symptoms**

ADHD symptoms were assessed using the ADHD subscale of the Revised Edition of Conners’ Parent Rating Scale (CPRS-R) (C. K. Conners, Sitarenios, Parker, & Epstein, 1998). The 18 items of the CPRS-R are rated on a 4-point Likert scale reflecting the frequency of each item: with 0 as ‘not at all’ to 3 as ‘very much true’ (total score 0-54). Diagnostic effectiveness and reliability of the CPRS-R have been demonstrated across clinical and community settings (Gau, Soong, Chiu, & Tsai, 2006) and confirmed in one meta-analytic review (Chang, Wang, & Tsai, 2016). The CPRS-R was also shown to have
Low to moderate concordance with youth-reported ADHD symptoms (Kaner, 2011). Internal consistency of the CPRS-R was assessed separately in this study at each age (ages 8, 12, 14 and 16 years) and for each symptom domain using standardised Cronbach alphas, which ranged between 0.88 and 0.91 for inattention and 0.81 and 0.84 for hyperactivity/impulsivity.

**ADHD categories**

We categorised participants according to their ADHD ratings on the CPRS-R scale in childhood and adolescence. CPRS-R ratings were recoded to relate to symptom counting in clinical practice: endorsement of 0 or 1 was recoded as 0 (not indicative of symptom presence), while endorsement of 2 or 3 was recoded as 1 (indicative of symptom presence) (C Keith Conners, 1997). If more than four out of nine items in either domain (inattention or hyperactivity/impulsivity) were unanswered, the sum score of that domain was recoded as missing. Sum scores of the recoded CPRS-R, ranging from 0 to 9 separately for the two symptom domains indicated number of endorsed ADHD symptoms per individual. Sum scores were further divided into three levels according to the suggested threshold in the Diagnostic and statistical manual of mental disorders (DSM) and in previous studies (American Psychiatric Association & American Psychiatric Association. DSM-5 Task Force, 2013; C Keith Conners, 1997; Faraone et al., 2006; Takeda, Tsuji, Uwatoko, & Kurita, 2015): 6 and more as clinically significant, 3 to 5 as subthreshold and 0 to 2 as low.

Supplementary Table 2 details all possible combinations of these recoded scores across childhood and adolescence. We selected the following four categories to address our objectives (7084 out of 9875 eligible participants).

- Non-ADHD control (n=6509, 65.9%): participants with low ADHD symptom level (sum score 0-2) across childhood and adolescence.
• De novo late-onset ADHD (n=123, 1.2%): individuals with a low level of ADHD symptoms (sum scores 0-2) across childhood (age 8 and age 12) who developed significant ADHD symptoms (6 and more) in adolescence (by age 14 or age 16).

• Subthreshold late-onset ADHD (n=164, 1.7%): individuals with a subthreshold level (sum score 3-5) of ADHD symptoms in childhood (by age 8 or age 12) who developed significant ADHD symptoms (sum score 6 and more) in adolescence (by age 14 or age 16).

• Childhood-onset persistent ADHD (n=288, 2.9%): individuals with a significant level of ADHD symptoms (sum score 6 and more) in both childhood (age 8 or age 12) and adolescence (age 14 or age 16).

*Early childhood characteristics*

Early childhood characteristics found to distinguish late-onset ADHD from non-ADHD controls in prior research were selected for current analyses (Agnew-Blais et al., 2016; Moffitt et al., 2015). Childhood characteristics in the current study were categorised into 1) prenatal and perinatal factors, 2) family environment factors, and 3) clinical characteristics. Prenatal and perinatal factors included birth weight and a composite score reflecting maternal medical problems during pregnancy and childbirth. The maternal medical risk score comprised several measures: alcohol and tobacco use during pregnancy, pregnancy-related medical complications, psychological distress during pregnancy, whether there was a fertility treatment before pregnancy and slow growth of the baby.

Family environment factors included family socioeconomic status, maternal depression and harsh parenting. Family socioeconomic status (SES) was the standardised composite score of highest parental educational level and occupational rankings at initial contact. Maternal depression was evaluated using the 10-item Edinburgh Postnatal Depression Scale (Cox, Holden, & Sagovsky, 1987). The current analysis used the average of the scores at 3 and 4
Late-onset ADHD

years of age. Harsh parenting was assessed via parents’ responses on an adapted questionnaire tapping the frequency (1: rarely or never; 5: usually) of parental disciplinary strategies (‘smacking and slapping’ and ‘telling off and shouting’) (Deater-Deckard, Dodge, Bates, & Pettit, 1998). We used the average of the ratings at 3, 4, and 7 years old to index harsh parenting.

Clinical characteristics included general cognitive performance, and behavioural and emotional problems. Early childhood general cognitive performance was computed as the average of the standardised parent-based MacArthur Communicative Development Inventory (MCDI: UK short form) for verbal performance (L. Fenson et al., 1994; Larry Fenson et al., 2000) and the standardised Parent Report of Children’s Abilities (PARCA) (Saudino et al., 1998) for non-verbal performance at age 2, 3 and 4.

Behavioural and emotional problems were assessed with the parent-reported Strengths and Difficulties Questionnaires (SDQ) (Goodman, 2001). The SDQ comprises five subscales tapping conduct problems, emotional problems, hyperactivity/inattention, peer relational problems and prosocial behaviours experienced by the child. We used the average parent-reported SDQ scores collected at ages 4 and 7 as early childhood SDQ. We did not include ratings of the SDQ hyperactivity/inattention subscale because of its overlap with the CPRS-R.

Adolescent outcomes

Adolescent outcomes at age 16 years included cognitive performance and co-occurring behavioural and emotional problems. General cognitive performance was the average standardised scores of Raven’s test (Raven, 1938; Van der Elst et al., 2013) for non-verbal IQ and the WISC-III-PI vocabulary test (Kaplan, 1999). Academic performance was assessed as the scores of the General Certificate of Secondary Education (GCSE), a standardised examination in the UK taken by students at the end of compulsory education. GCSE scores
were obtained by questionnaires sent via mail and by telephone interviews of parents and youth participants.

The short-version Mood and Feeling Questionnaire (MFQ) was collected from the children and their parents. The MFQ consists of 13 questions tapping core depressive symptoms of the child in the past two weeks (Angold, Erkanli, Costello, & Rutter, 1996). The parent-reported Anxiety-Related Behaviours Questionnaire (ARBQ) was used to index anxiety level of the child (Eley et al., 2003). The parent-reported SDQ at age 16 was used to assess co-occurring conduct problems, peer relational problems and emotional/anxiety problems.

The timeline of the measures used longitudinally in the current study can be found in Supplementary Table 3.

Data Analyses

Analyses were performed with R Software Version 3.4.0 (Team, 2017). We fitted multinomial regression models with ADHD categories as the outcome, using the package ‘multgee’ (Generalised estimating equations (GEE) solver for correlated nominal or ordinal multinomial responses, version 1.5.0). GEE was used to account for the non-independence within twin pairs in the sample: we set the covariance structure to ‘exchangeable’ (i.e. no specific order within the pair) and we computed robust standard errors.

De novo late-onset ADHD, subthreshold late-onset ADHD and persistent ADHD were compared with non-ADHD controls in terms of childhood characteristics and adolescent outcomes. Pairwise comparisons between late-onset ADHD and persistent ADHD were also performed. Finally, we used the multinomial logistic regression to examine early childhood characteristics predictive of de novo late-onset ADHD and subthreshold late-onset ADHD (with non-ADHD controls as the reference group). A model comparing late-onset ADHD to childhood-onset persistent ADHD can be found in Supplementary Table 4.
Results

Descriptive statistics and pairwise comparisons for childhood characteristics and adolescent outcomes are displayed separately for the non-ADHD controls, de novo late-onset ADHD, subthreshold late-onset ADHD, and persistent ADHD in Table 1.

Childhood characteristics

Compared with non-ADHD controls, the proportion of males was higher in the three ADHD groups. De novo late-onset ADHD and persistent ADHD had elevated maternal health risk during pregnancy (Table 1). Elevated single parenthood, lower SES, increased harsh parenting, and higher maternal depression were found in the three ADHD groups compared to non-ADHD controls with varying effect sizes (Cohen’s d=0.03-0.77). Comparison between different ADHD categories showed differences in the level of harsh parenting and maternal depression, but not in single parenthood and SES.

Clinical characteristics including general cognitive performance and the parent-rated SDQ were also significantly different between the three ADHD groups and non-ADHD controls, particularly for SDQ conduct problems (Cohen’s d=0.64-1.45). Pairwise comparison further showed childhood-onset persistent ADHD had the highest ratings in conduct problems and peer problems among the three ADHD groups, while subthreshold late-onset ADHD exhibited more conduct problems (Cohen’s d=0.33, p=0.02) than de novo late-onset ADHD.

Adolescent outcomes
Adolescent cognitive performance, ratings of parent-reported SDQ and co-occurring depression and anxiety were all significantly worse in the three ADHD groups compared with non-ADHD controls (Table 2). The largest effect size when compared to non-ADHD controls was found in adolescent conduct problems (Cohen’s d=1.65-1.78) followed by parent-reported MFQ (Cohen’s d=1.13-1.38). In contrast to the observations in childhood, the three ADHD groups presented a similar level of impairment at age 16 years. Pairwise comparisons showed that ratings of general cognitive performance and co-occurring behavioural and emotional problems were comparable among the three ADHD groups, except for GCSE performance, which was worse in childhood-onset persistent ADHD.

Early childhood characteristics predicting late-onset ADHD

Table 3 presents early childhood characteristics predicting de novo late-onset ADHD, subthreshold late-onset ADHD, and childhood-onset persistent ADHD. Male sex and increased conduct problems differentiated all ADHD categories from non-ADHD controls. In addition to male sex and conduct problems, only lower SES predicted de novo late-onset ADHD (OR 0.70, 95%CI 0.54-0.90, p=0.006). However, SES was not a significant predictor of subthreshold late-onset ADHD or childhood-onset persistent ADHD. Besides male sex and conduct problems, two additional risk factors predicted subthreshold late-onset ADHD: harsh parenting (OR 1.81, 95%CI 1.37-2.39, p<0.001) and higher maternal depression (OR 1.07, 95%CI 1.03-1.11, p=0.001); whereas five additional risk factors predicted childhood-onset persistent ADHD: lower birth weight (OR 0.74, 95%CI 0.55-0.99, p=0.043), single parenthood (OR 1.93, 95%CI 1.10-3.36, p=0.021), harsh parenting (OR 1.51, 95%CI 1.23-1.85, p<0.001), higher maternal depression (OR 1.06, 95%CI 1.02-1.10, p=0.002) and peer problems (OR 1.31, 95%CI 1.19-1.46, p<0.001).
Complementary analyses identifying early-childhood characteristics differentiating late-onset ADHD from childhood-onset persistent ADHD are presented in Supplementary Table 4.

**Discussion**

De novo late-onset ADHD and subthreshold late-onset ADHD were more common in males, in those with increased childhood conduct problems and those with adverse family environment. When compared with childhood-onset persistent ADHD, both de novo late-onset ADHD and subthreshold late-onset ADHD showed fewer conduct problems and fewer peer problems in early childhood. However, the three ADHD groups developed similar levels of behavioural and emotional problems in adolescence. Among early childhood predictors, low SES was specific to de novo late-onset ADHD and harsh parenting and maternal depression were specific to subthreshold late-onset ADHD. Additional childhood predictors were identified for childhood-onset persistent ADHD.

**Late-onset ADHD, childhood ADHD and comorbid symptoms**

Consistent with previous findings, we found that individuals with late-onset ADHD already exhibited increased behavioural and emotional problems compared to non-ADHD controls before meeting the symptom threshold for ADHD diagnosis (Agnew-Blais et al., 2016; Cooper et al., 2018; Manfro et al., 2018; Sibley et al., 2018). Interestingly, the level of co-occurring behavioural problems was related to the level of childhood ADHD symptoms: childhood-onset persistent ADHD had the highest ratings of conduct and peer problems, followed by subthreshold late-onset ADHD, and then de novo late-onset ADHD. These findings are consistent with previous research showing that childhood ADHD symptoms and related impairment are dimensionally distributed in the population (Noren Selinus et al.,
Late-onset ADHD (2016). Our study further shows that the increase in ADHD symptoms across childhood and adolescence, which underlies the emergence of late-onset ADHD, is accompanied by an increase in comorbid behavioural and emotional problems. In adolescence, the three ADHD groups all exhibited similar levels of ADHD symptoms and co-occurring behavioural and emotional problems. This warrants further investigation into risk factors underlying a shared psychopathological liability or possible feedback networks between dimensions of psychopathology to explain symptom co-development over time (Borsboom, 2017; Caspi et al., 2014).

Childhood characteristics predicting late-onset ADHD

We found that low SES specifically predicted de novo late-onset ADHD. This result corresponds to prior studies showing that the negative impact of low family income and low parental education on neurodevelopment persists across childhood and adolescence (Noble et al., 2015; Noble, Houston, Kan, & Sowell, 2012). Our findings suggest that the negative contribution of low SES may accumulate throughout development, leading to a deterioration of attention and impulse control later in life. However, there are other potential explanations. It is possible that the negative influences of low SES on neurodevelopment are small in early childhood, and thereby went unidentified in our study until effects accumulated to detectable levels during adolescence. Alternatively, children with low SES and high ADHD symptoms early in life may be inadequately represented in the current study and SES effects may not be specific to late-onset ADHD but due to differential selection. Further research is warranted to arbitrate between alternative explanations. It is noteworthy that our findings are at odds with the argument that late-onset ADHD simply uncovers 'masked' childhood-onset ADHD. Such argument stipulates that a protective family environment can help affected individuals to
compensate better in childhood and make early detection of ADHD more difficult (Kosaka et al., 2018). On the contrary, we found de novo late-onset ADHD experienced lower SES than non-ADHD controls. The role of SES in creating a challenging early environment is well documented and SES has been linked to more health-related adversity and a range of mental health problems including ADHD (Hagan, Roubinov, Adler, Boyce, & Bush, 2016; Luby, Barch, Whalen, Tillman, & Belden, 2017; Russell, Ford, & Russell, 2015). In addition, our finding that harsh parenting and maternal depression specifically linked to subthreshold late-onset ADHD further supports the role of parenting behaviour and parental mental health problems in the development of ADHD symptoms in offspring (Tung, Brammer, Li, & Lee, 2015; Wolford et al., 2017). Altogether, these findings add to the accumulating evidence showing the detrimental impact of adverse family environment on psychological development throughout childhood and adolescence (Sharp, Mangalmurti, Hall, Choudhury, & Shaw, 2019). The specific association of low SES with de novo late-onset ADHD also suggests that interventions targeting early risk factors such as low socioeconomic status may have an impact on curbing the development of ADHD symptoms beyond childhood.

Previous studies have identified age-specific genetic and environmental contributions to ADHD symptom development at different stages of life (Pingault et al., 2015). Therefore it is likely that late-onset ADHD symptoms are also in part attributable to time-varying risk factors across development, whether environmental (e.g. school transitions) (Langberg et al., 2008) or biological (e.g. genetic) (Greven, Asherson, Rijsdijk, & Plomin, 2011; Pingault et al., 2015), as reflected in developmental changes at the neurobiological level (Shaw et al., 2013). Interestingly, we found that the number of independent early childhood predictors was related to the level of childhood ADHD symptoms: more predictors were found for individuals with full childhood ADHD symptoms, compared to those with subthreshold
Late-onset ADHD symptoms, and, finally, those with low childhood ADHD symptoms. The fact that we detected fewer predictors for the late-onset ADHD categories compared to persistent ADHD implies that measurement of early childhood risk factors might not be sufficient for predicting late-onset ADHD. As such, research using a developmentally sensitive design, which incorporates time-varying covariates (Brammer, Galan, Mesri, & Lee, 2016) across different developmental stages, is warranted to better understand the aetiology of late-onset ADHD. The fact that predictors of de novo late-onset ADHD versus subthreshold late-onset ADHD were not completely overlapping warrants future investigation to examine whether distinct aetiological pathways of the two conditions can be identified.

Limitations
Several limitations should be considered when interpreting our results. Participants were categorised into different diagnostic groups based on parent-rated CPRS-R in childhood and adolescence. The sole reliance on parent reports may affect the reliability of ADHD diagnosis, especially in retrospective studies and in adult samples (Angold et al., 1996). However, parental ratings on the CPRS-R have been demonstrated to differentiate ADHD cases and non-cases with moderate to high accuracy among children and adolescents (Chang et al., 2016; Gau et al., 2006) and were also significantly correlated with youth-reported symptom burden (Kaner, 2011). ADHD diagnosis was based on questionnaires that did not include other criteria such as functional impairment and situational pervasiveness, which may result in false positive or negative (Parker & Corkum, 2016). We categorised subthreshold ADHD based on symptom levels with cut-off thresholds of 3 to 5 symptoms in either inattention or hyperactivity/impulsivity domain. Although these cut-off values have been widely used in previous studies, they remain, to some extent, arbitrary. Therefore, replications using full diagnostic criteria in larger cohorts are needed. Analyses were conducted using a population-
based twin birth cohort of predominantly white Caucasian individuals in the UK. Therefore, results may not generalise to other populations.

**Conclusion**

We found that both de novo and subthreshold late-onset ADHD differ substantially from childhood-onset persistent ADHD on a range of co-occurring behavioural problems and cognitive characteristics in childhood, but that this difference had largely dissipated in adolescence. Our results suggest interventions targeting early risk factors including low socioeconomic status may have an impact on curbing the development of ADHD symptoms beyond childhood. Future research into the time-varying environmental and biological factors driving psychopathological changes after early childhood will be necessary to better understand the aetiology of late-onset ADHD.
References


Late-onset ADHD


