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ADHD and subthreshold symptoms in childhood and life outcomes at 40 years in a prospective birth-risk cohort

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ABSTRACT

We investigated ADHD symptoms and life outcomes in adulthood and their association with childhood ADHD and subthreshold symptoms in a prospectively followed cohort with perinatal risks. We identified participants with childhood ADHD (cADHD, $n = 37$), subthreshold symptoms defined as attention problems (cAP, $n = 64$), and no ADHD or cAP (Non-cAP, $n = 217$). We compared the groups and a control group with no perinatal risks ($n = 64$) on self-reported ADHD symptoms, executive dysfunction, and life outcomes in adulthood. At age 40, 21.6% of the cADHD, 6.3% of the cAP, 6.0% of the Non-cAP group, and 1.6% of the controls reached a screener cutoff for possible ADHD. The cADHD group had lower educational level, more ADHD symptoms and executive dysfunction, and higher rates of drug use than the other groups. Childhood ADHD associated with perinatal risks persists into midlife whereas childhood subthreshold ADHD symptoms in this cohort were not associated with negative outcomes in adulthood.

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) has an estimated prevalence of 2–5% in adulthood (Kooij et al., 2010; Matte et al., 2015). The reports of persistence of ADHD from childhood to adulthood vary extensively with estimates ranging between 4% and 77% depending on the length of the follow-up and the definition of both childhood and adulthood ADHD (Faraone et al., 2006a; Sibley et al., 2016). Most longitudinal studies on ADHD only extend into adolescence or early adulthood, and prospective longitudinal studies continuing to the third and fourth decade are rare. The few studies extending beyond young adulthood have mostly consisted of clinic-referred boys (Klein et al., 2012; Satterfield et al., 2007). The persistence estimates for studies with a follow-up period of minimum 20 years range between 6% and 32% (Sibley et al., 2016). A recent cohort study over four decades found childhood-onset ADHD to continue into midlife in only 5% of cases (Moffitt et al., 2015).

Symptoms of ADHD form a continuum (Marcus and Barry, 2011). Focusing on subjects with an established diagnose thus excludes those with symptoms below a diagnostic threshold from research and clinical scope (Faraone and Biederman, 2016). Although ADHD symptoms usually decline with age (Biederman et al., 2000; Faraone et al., 2006a), the individual course of symptoms varies throughout childhood and adulthood (Karam et al., 2017; Larsson et al., 2011). An individual might thus fulfill the diagnostic criteria at one point during their life and remain at a subthreshold level at another. Importantly, comorbid psychiatric disorders, such as substance use disorder and conduct disorder (Shankman et al., 2009), and adverse psychosocial outcomes (Norén Selinus et al., 2016) frequently associated with ADHD (Kooij et al., 2010), have also been found in adolescents and adults with previous subthreshold ADHD symptoms.

Adverse life outcomes and functional impairment associated with ADHD in adulthood are well established (Barkley et al., 2008; Biederman et al., 2006; Shaw et al., 2012). ADHD is linked to lower educational and occupational level (Biederman et al., 2012; Shaw et al., 2012), and higher rates of unemployment (Biederman et al., 2006). Moreover, the risk for comorbid psychiatric disorders is elevated (Kooij et al., 2010), including a high probability for substance use

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disorder (Klein et al., 2012) and mood disorders (Biederman et al., 2012). Importantly, adults with a history of childhood ADHD exhibit adverse life outcomes and high levels of impairment even if ADHD symptoms are no longer severe (Caye et al., 2016; Moffitt et al., 2015). Dysfunction in executive functions has been proposed to be central in adult ADHD and partly explain these adverse outcomes (Adler et al., 2017; Barkley et al., 2008; Barkley and Fischer, 2011).

The long-term effects of early adverse events at birth on ADHD symptoms have been scarcely studied. In a recent review, low birth weight and preterm birth posed the greatest risk among perinatal complications for developing ADHD by age twelve (Serati et al., 2017). A longitudinal study to adolescence found complications in pregnancy and labor to be associated with ADHD symptoms throughout the follow-up period, with the association decreasing by age (Brinksma et al., 2017). Also, adults with ADHD symptoms have been reported to have a history of low birth weight or preterm birth more often than people with no ADHD symptoms (Halmøy et al., 2012; Strang-Karlsson et al., 2008).

This study examines ADHD symptom development and life outcomes in a cohort with perinatal risks followed prospectively from birth. Our primary aim was to investigate whether ADHD symptoms and executive dysfunction were elevated at age 40 in subjects with childhood ADHD or subthreshold symptoms. Our secondary aim was to examine life outcomes including education, occupation, psychiatric symptoms, and drug and alcohol use in relation to childhood ADHD and subthreshold symptoms. We also evaluated medical factors that may contribute to ADHD symptoms at age 40 in subjects who did not have ADHD in childhood.

2. Methods

2.1. Participants

The participants are from a longitudinal research project (Perinatal Adverse Events and Special Trends in Cognitive Trajectory, PLASTICITY) (Hokkanen et al., 2013). The prospective birth cohort (1196 infants) consists of individuals born in one maternity hospital in Helsinki in 1971–1974 (Michelsson et al., 1978). The participants had one or several pre-defined perinatal risks, such as low birth weight (see Table S1). Subjects who had severe disabilities (cerebral palsy, severe sensory deficits, intellectual disability), or died before the age of 5 were excluded (see Fig. 1) (Launes et al., 2014). A control group of 164 singletons with no perinatal risks born in the same hospital was also followed from childhood. For the latest follow-up at 40 years, risk cohort members and controls whose addresses were found in the Population Registry Center of Finland (n = 1061) were invited via mail, of whom 607 responded. We included subjects who had participated in both childhood follow-ups at ages 5 and 9 (risk cohort n = 318, control group n = 64). Brain MRI scans (see Table S2) were used to exclude participants due to traumatic brain injuries or strokes. Visual assessment of the images was performed by a specialist in neuroradiology (RV), who was blinded to all clinical parameters. Participation is illustrated in Fig. 1. The project was approved by Ethical Review Board of the Helsinki and Uusimaa hospital district (number 147/13/3/00/2013). Written informed consent was gathered from all participants.

2.2. Defining childhood symptom groups

The risk cohort participants were grouped into three different categories: childhood ADHD (cADHD n = 37), attention problems (cAP; n = 64) and no ADHD or attention problems (Non-cAP, n = 217). The cADHD group had a disorder identified earlier (Tervo et al., 2017), whereas in the cAP group symptoms were not severe enough to warrant an ADHD diagnosis. The cAP group had symptoms of either inattention or hyperactivity/ impulsivity or both. The control group (n = 64) had no perinatal risks, cADHD, or cAP. The childhood symptom grouping was based on multiple study observations, informant reports, and assessments at 5 and 9 years of age (see Tables S3-S6). ADHD was not a diagnosis in use at the time of the childhood follow-up and was diagnosed retrospectively by the first principal investigator of the project (KM) using all the information described above (Hokkanen et al., 2013). Subthreshold symptoms were identified with a norm-based approach (Barkley et al., 2008; Sibley et al., 2016), in which scores of the controls were used to create threshold percentiles. The complete protocol for childhood symptom assessments is described in the supplementary materials.

2.3. Measures

Childhood socioeconomic status (SES) was defined as the highest median status of mother and father recorded in childhood assessments (0, 5, and 9 years). Four classes, based on occupational level, were originally used, but the two lowest categories were merged due to small numbers. Level 1 represents the highest SES class. Information on mother's education was collected in the latest follow-up and divided into three levels: basic, secondary and tertiary. Current information on ADHD symptoms and life outcomes was gathered through a questionnaire filled online or on paper, and during on-site neurological and neuropsychological evaluations in 2014–2016.

Current subjective ADHD symptoms were estimated with the World Health Organization Adult ADHD Self-Report Screening Scale, ASRS-v1.1 (Kessler et al., 2005). The ASRS screener measures inattention and hyperactivity according to DSM-IV criteria (American Psychiatric Association, 2000) with six questions. The wording of the questions was modified to fit the broader questionnaire. The general score of the ASRS (range 0–24) was analyzed and participants were grouped according to a cutoff point (scores at or above 14) (Kessler et al., 2007). In our sample, a cutoff point of two standard deviations above the control group mean, a cutoff point suggested in the literature (Barkley et al., 2008; Sibley et al., 2016), coincided with the recommended cutoff score of 14. Scores for hyperactivity and inattention were summed to assess ADHD symptom domains. There were 20 missing values in the screener, which were imputed with the average of the corresponding childhood group.

Executive dysfunction was assessed with the Behavior Rating Inventory - Adult version (BRIEF-A) (Roth et al., 2005). BRIEF-A self-report results in a General Executive Composite (GEC) and two indexes, Behavioral Regulation Index (BRI), and Metacognition Index (MI). The MI consists of scales Initiate, Working Memory, Plan/ Organize, Task Monitor, and Organization of Materials. The BRI is consists of scales Inhibit, Shift, Emotional Control, and Self-Monitor. The BRI assesses regulation of behavior and emotions, and the MI ability to plan and monitor activities. The raw score was compared to normative data in the manual and transformed into T-scores, with a threshold of $T \geq 65$ for elevated score (Roth et al., 2005).

Data on the participants' education, occupation, mental health, smoking, as well as alcohol and drug use were gathered with the questionnaire. Highest educational degree was classified into three levels: Basic (9 years), secondary (10–12 years) and tertiary education (13+ years). Grade average from comprehensive school (around age 16) was collected. The lowest possible grade is 4 and highest 10. Occupational status was recorded as currently employed or unemployed. Future work ability was assessed by asking the participants to estimate the number of years they would be able to continue working. Psychiatric symptoms were assessed using the short version of the Depression Anxiety Stress Scales (DASS-21) (Lovibond and Lovibond, 1995), which was translated and modified by transformation into a 5 item Likert scale. Alcohol use was assessed with the Finnish version of the Alcohol Use Disorders Test (AUDIT) (World Health Organization, 2001). Life-time drug use was asked separately for cannabis and other illicit drugs but combined for the analysis.

All subjects underwent a semi-structured medical and