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Halldner, Linda; Tillander, Annika; Lundholm, Cecilia; Boman, Marcus; Långström, Niklas; Larsson, Henrik; Lichtenstein, Paul

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Relative immaturity and ADHD:

Findings from nationwide registers, parent- and self-reports

Linda Halldner *PhD*[1,2], Annika Tillander *MSc*[1], Cecilia Lundholm *MSc*[1], Marcus Boman *BS*[1], Niklas Långström *professor*[1], Henrik Larsson *associate professor*[1], Paul Lichtenstein *professor*[1]

[1]Department of Medical Epidemiology and Biostatistics, Box 281, Karolinska Institutet, SE-171 77 Stockholm, Sweden

[2]Karolinska Institutet Center of Neurodevelopmental Disorders (KIND), Gävlegatan 22B, 8th **floor, SE-113 30 Stockholm, Sweden**

Corresponding author: Dr Linda Halldner at Barn & ungdomspsykiatriskt forskningscentrum, CAP, Karolinska Institutet, Gävlegatan 22B, plan 8, SE-113 30 Stockholm, Sweden. Phone: +46-8-52482338. Email: linda.halldner@ki.se.

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Abstract

Background: We addressed if immaturity relative to peers reflected in birth month increases the likelihood of ADHD diagnosis and treatment.

Methods: We linked nationwide Patient and Prescribed Drug Registers and used prospective cohort and nested case-control designs to study 6-69 year-old individuals in Sweden from July 2005 to December 2009 (Cohort 1). Cohort 1 included 56,263 individuals diagnosed with ADHD or ever used prescribed ADHD-specific medication. Complementary population-representative cohorts provided DSM-IV ADHD symptom ratings; parent-reported for 10,760 9-year-old twins born 1995-2000 from the CATSS study (Cohort 2) and self-reported for 6,970 adult twins age 20-47 years born 1959-1970 from the STAGE study (Cohort 3). We calculated odds ratios (OR:s) for ADHD across age for individuals born in November/December compared to January/February (Cohort 1). ADHD symptoms in Cohorts 2 and 3 were studied as a function of calendar birth month.

Results: ADHD diagnoses and medication treatment were both significantly more common in individuals born in November/December vs. January/February; peaking at ages 6 (OR: 1.8; 95%CI: 1.5-2.2) and 7 years (OR: 1.6; 95%CI: 1.3-1.8) in the Patient and Prescribed Drug Registers, respectively. We found no corresponding differences in parent- or self-reported ADHD symptoms by calendar birth month.

Conclusion: Relative immaturity compared to class mates might contribute to ADHD diagnosis and pharmacotherapy despite absence of parallel findings in reported ADHD symptom loads by relative immaturity. Increased clinical awareness of this phenomenon may be warranted to decrease risk for imprecise diagnostics and treatment. We speculate that flexibility regarding age at school start according to individual maturity could reduce developmentally inappropriate demands on children and improve the precision of ADHD diagnostic practice and pharmacological treatment.

Keywords: ADHD, child development, pharmacotherapy, epidemiologic studies

Introduction

Research has suggested delayed brain maturity as an explanation to childhood ADHD symptoms (McAlonan et al., 2009; Shaw et al., 2007; Shaw et al., 2011). In recent studies from the USA and Canada, children born the month before the school eligibility cut-off were diagnosed with ADHD 30-70% more often than children born immediately after the cut-off. These children, the youngest in their class, were also up to twice as likely to be treated with ADHD medication (Elder, 2010; Evans, Morrill, & Parente, 2010; Morrow et al., 2012). Thus, although ADHD is a neurodevelopmental disorder with a strong genetic component that persists over time (Chang, Lichtenstein, Asherson, & Larsson, 2013; Larsson, Lichtenstein, & Larsson, 2006; Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010), a proportion of these genetic effects may be due to immaturity-related ADHD symptoms (Steffensson et al., 1999). Although initially considered a child disorder, ADHD in adults has recently attracted substantial attention (Adler & Chua, 2002; Matte, Rohde, & Grevet, 2012). Although some ADHD symptoms decline with age (Faraone, Biederman, & Mick, 2006; Larsson et al., 2006), adults diagnosed with ADHD do suffer from functional impairment (Biederman et al., 2006; Friedrichs, Igl, Larsson, & Larsson, 2012). If relative immaturity contributed to ADHD being diagnosed in childhood, the likelihood of a diagnosis would increase for the youngest children within a school class. In contrast, any such effect should no longer influence ADHD in adults due to the evening out of relative immaturity.

There are indications of immaturity contributing to ADHD and ADHD medication (Elder, 2010; Evans et al., 2010; Morrow et al., 2012; Zoega, Valdimarsdottir, & Hernandez-Diaz, 2012), including two large North American studies based on insurance and health databases, respectively (Evans et al., 2010; Morrow et al., 2012). However, although large cohorts were studied, the age distribution was limited and no information available on ADHD in adulthood (22,371 7-17 year-olds and 937,943 6-12 year-olds, respectively). The study by Elder (Elder,

2010) was a longitudinal, multi-site Kindergarten cohort study from the US (initially including 18,644 children) with follow-ups until eighth grade including symptom ratings from both parents and teachers. The only European study of ADHD and relative immaturity in the school setting so far, was a population-based cohort study including all 9-12 year old children on Iceland (n=11,785)(Zoega et al., 2012). Among these, poorer school results and a 50% increased risk for ADHD medications was found among the youngest pupils in a class. However, compared to Sweden and other Nordic countries, Iceland has traditionally had higher prescription rates of ADHD medication (Zoega et al., 2011) and may not be representative for prescription patterns in the Nordic countries.

We used a Swedish total population sample with linked diagnostic register data including both children and adults to study relative immaturity; that is early vs. late birth months by calendar year as a risk factor for ADHD across age. To further delineate at what level possible effects may occur, we also studied the impact of birth month on parent- and self-reported ADHD symptoms in children and adults, respectively. Our specific questions were: Does relative immaturity alter 1) the rate of ADHD diagnoses; and 2) the rate of ADHD medication? We also investigated 3) if the effect of relative immaturity changes with age; if relative immaturity alter 4) parents' perception of ADHD symptoms in their children; and 5) self-rating of ADHD symptoms amongst adults?

Methods

Cohort 1: Total population cohort with register-based ADHD

Subjects. Using the Swedish Total Population, Migration and Cause of Death Registers, we identified all individuals born 1940 or later, living and residing in Sweden during July 2005-

December 2009. To identify individuals diagnosed with ADHD, the National Patient Register (NPR) and Prescribed Drug Register (PDR) were used. The NPR started in 1964 and contains best-estimate diagnoses assigned by attending clinicians to patients assessed or treated at different levels of healthcare. The NPR was recently been validated (Ludvigsson et al., 2011) and has almost full coverage of all psychiatric inpatient care in Sweden since 1973. Non-GP specialist outpatient care is included since 2001 (Forsberg, Rydh, Jacobsson, Nyqvist, & Heurgren, 2009). The PDR contains individualized information on all prescribed and dispensed prescription drugs from all Swedish pharmacies since July 2005 (Wettermark et al., 2007).

The base rate of ADHD diagnoses in the NPR among was low in those below 6 years of age and ADHD medication is not recommended in Sweden for children below age 6 years. Hence, we only included subjects age 6 or older. Individuals 70 years and older were excluded as the use of stimulants on other indications than ADHD increase with age (Zetterqvist, Asherson, Halldner, Langstrom, & Larsson, 2012).

Measures. ADHD caseness was defined either as a diagnosis (ICD-10 hyperkinetic disorders: F90) in the NPR, or as one or more dispensed prescriptions of ADHD medications amphetamine, dexamphetamine, methylphenidate or atomoxetine (Anatomical Therapeutic Chemical [ATC] codes NO6BA01, N06BA02, NO6BA04 and NO6BA09, respectively) in the Prescribed Drug Register from July 2005 through December 2009. With these definitions, we identified 41,452 individuals in the NPR, and 45,762 individuals in the PDR (of which 30,951 individuals were found in both registers), resulting in 56,263 unique individuals with ADHD (cases).

Analyses. First, we used a nested case-control design to study if birth month was related to ADHD caseness. We randomly selected ten controls for each ADHD case individual. The controls were defined as not being cases in either of the two registers, and were matched for birth year, sex and municipality of residence (at time of first appearance in either register). We analysed data with conditional logistic regression modelling and stratified by age bands 6-11 years, 12-17, 18-24, 25-34, and 35-69 years (Figure 1).

Second, the birth month-effect was further studied in the total cohort by comparing all individuals from each birth cohort born in November or December with all those born in January or February the following year. Importantly, although these individuals are very close in age they will be placed in different school grades, since the cut-off date for school eligibility in Sweden is December 31. However, while children born in November/December will be the youngest in their respective class, those born in January/February will be the oldest in theirs. We analyzed prevalent ADHD as outcome using conditional logistic regression, where strata were formed by individuals with the same age but born in two consecutive years (e.g., in November/December 1992 vs. January/February 1993), to avoid confounding by calendar effects due to increased rates of ADHD diagnosis and medication. Analyses were repeated for different ages starting from age 6 years; a year was defined as starting the month of the birthday and ending the month before the following birthday.

We also computed incidence rate ratios (IRR) for the same cohort from 6-69 years of age with Cox proportional hazards regression and age as the analysis time scale. Follow-up started July 1, 2005 for children who were ≤ 6 years at that time. For subjects older than 6 years on July 1, 2005 the follow-up started on July 1, 2006. Subjects with diagnosis or medication prior to start of follow-up were excluded, to avoid including prevalent cases. A potential explanation to an increased ADHD risk for children born in November/December could be that ADHD is discovered earlier in children born late in the year than children born early and that there subsequently would be a catch up among those born in January/February. Therefore the time scale was split in age intervals (yearly from 6 to 17 years, 18-24, 25-34 and 35-69 years) and interaction terms between age interval and birth month were included in the model, to allow for different IRR estimates for each age interval. If there was a catch up effect we would find IRR>1 at lower ages and IRR<1 at higher ages.

Cohort 2: Parent-reported ADHD symptoms

Subjects. Considering the observed increased rate of ADHD diagnosis and treatment in children born late during the year, we wanted to study if there were a birth month effect also on parental perception of child ADHD symptoms. For this purpose, we used data from the Child and Adolescent Twin Study in Sweden (CATSS). CATSS is an ongoing prospective twin study that started in 2004 and targets all twins in Sweden born July 1995 or later (Anckarsater et al., 2011). In connection to the twins' 9th birthday, parents are contacted for a telephone interview regarding their children's social environment, somatic and mental health. We selected all 9-year-olds in the CATSS born 1995-2000 (n=10,760).

Measures. Neurodevelopmental problems were screened for with the *Autism – Tics, ADHD and other Comorbidities* (A-TAC) inventory (Hansson et al., 2005; Larson et al., 2010). Parents reported twins' ADHD-related inattention and hyperactivity/impulsivity symptoms according to 19 items based closely on the 18 DSM-IV ADHD criteria and one supplementary symptom. Items were scored 0 (=no), 0.5 (=yes, to some extent) or 1 (=yes) and summed to a total score ranging from 0-19 points. Different cut-offs for identifying ADHD symptoms in this sample have been suggested for identifying cases with high sensitivity and specificity, respectively. We used scores 4 or higher as our definition of ADHD symptomatology, the lowest cut-off for identifying cases with high sensitivity.

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Analyses. The effect of birth month on ADHD total symptom scores were analyzed dichotomously, using multiple cut-offs ranging from ≥5 s to ≥17 symptoms, all of which were compared to the <4 symptoms reference group. Data were analyzed using generalized estimating equations (logit link) and an unstructured correlation matrix to account for relatedness within twin pairs.

Cohort 3: Adult twins with self-reported ADHD symptoms

Subjects. To address the birth month-effect on self-perceived ADHD symptoms in adulthood, we used data from the Study of Twin Adults: Genes and Environment (STAGE). In 2005-2006, STAGE research staff approached twins in Sweden born in 1959-1985. Hence, 20-47 year-old twins where both survived their first year of life were invited via regular mail to participate in research regarding common complex diseases. Participants could choose to respond to a web questionnaire or a telephone interview complemented with a mailed paper questionnaire for sensitive topics (Larsson et al., 2013; Lichtenstein et al., 2006). We selected STAGE participants born 1959-1970 (n=6970).

Measures. Adult ADHD symptoms were assessed by self-report of 18 items closely corresponding to DSM-IV diagnostic criteria, with some small adaptions to fit adult respondents better. Items were published in Larsson et al (Larsson et al., 2013) and scored "no" (=0), "yes, to some extent" (=0.5) or "yes" (=1) and summed to a total score ranging from 0 to 18.

Analyses. We used a logistic model with sliding cut-offs since data were not normally distributed. Again, to account for twin relatedness in our data, we used a GEE model with twins clustered and a logit link function.

Logistic regressions and generalized estimating equations were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and Cox regressions were conducted with Stata version 12 (StataCorp, College Station, TX, USA). The Regional ethics review board in Stockholm approved the project (D nr 2009/939-31/5).

Figure 1 about here

Results

Cohort 1: Total population cohort with register-based diagnoses

First, we compared rates of ADHD diagnoses in the Swedish total population by calendar birth month. Overall, absolute rates of ADHD were higher in children compared to adults, with the highest odds for children born at the end of the year (Figure 1). This trend seemed to decline from age 18 years and was no longer discernible among those 35 years and older.

Next, we analyzed the likelihood of ADHD caseness for individuals born in November/December compared to those born in January/February the following year (Table 1). The odds for ADHD were significantly higher for individuals born at the end of the preceding year (ORs 1.1 to 1.6). Further, having had any dispensed prescription of ADHD medication was significantly more common (ORs 1.2 to 1.8) for individuals born in November/December compared to those born in January/February the following year. The effect was attenuated with increasing age and no longer seen in adult age (35+ years for an ADHD diagnosis and 18+ for ADHD medication; Table 1). Further, the pattern with increased likelihood for ADHD was similar across sex (Supplemental Tables 1 and 2) and when data from the NPR and PDR registers were studied separately (Table 1).

Table 1 about here

In the Cox proportional hazards regression analysis, we found no catch-up in incidence rate ratios (Table 2). Thus, increased rates of ADHD in individuals born in November/December were unlikely to be explained by diagnosis and treatment occurring later in life for individuals born in January/February compared to individuals born in November/December.

Table 2 about here

Cohorts 2 and 3: Parent- and self-reported ADHD symptoms

Parent reports of child symptoms or self-reports are alternative methods to capture ADHD symptomatology compared to register-based, best-estimate clinical diagnoses and medication. In a representative, nationwide cohort of 9-year-old twins (born 1995-2000, Cohort 2) with parent-reported ADHD symptoms there was no indication of a clear birth month-effect (Table 3). Mean ADHD values for the children by month are presented in Supplemental Figure 1.

Table 3 about here

In the nationwide, representative cohort of 35-47-year old adult twins (born 1959-1970; Cohort 3), self-reported ADHD symptoms did not differ significantly between subjects born in November/December compared to January/February during the same calendar year (data not shown); mean values by birth month are presented in Supplemental Figure 1.

Discussion

We addressed if ADHD is related to an individual's relative immaturity measured as early or late birth months within the calendar year. We used data from longitudinal, nationwide registers of ADHD diagnoses and medication. Both ADHD diagnosis and its pharmacological treatment was more common in children born late during the year (hence being the youngest in their classes at school) compared with those born early (the oldest in their classes at school). Since the birth month-effect also seemed to decline with age and was no longer significant from young adulthood, this supports the immaturity hypothesis of ADHD (McAlonan et al., 2009; Shaw et al., 2007; Shaw et al., 2011). To further elucidate the cause of the observed effect, we also analysed representative population cohorts of 9-year-old children with parent-reported ADHD symptoms and 35 to 47-year-old adults who self-reported ADHD symptoms. However, we found no corresponding association between parent-reported ADHD symptoms and birth month in children. Neither did we find a birth

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month-effect on self-perceived ADHD symptoms among adults in the general population. In line with Shaw et al. (Shaw et al., 2011), this finding may suggest a complex picture with overlap between true ADHD symptoms of neuropsychological immaturity aetiology and misdiagnosed ADHD due to relative immaturity.

Although the National Patient Registry is not complete for outpatient physician specialist care (where most ADHD is diagnosed and treated), we find it unlikely that this would cause substantial bias from differential health care-seeking and reporting for patients with certain birth months. The Prescribed Drug Register contains all dispensed prescriptions given out at Swedish pharmacies. However, this register was not initiated until July 2005, and the resulting relatively short time window may have affected the results. Firstly, due to changing practice of diagnosis and treatment over time, some of the observed age-related differences in the birth month-effect could be due to birth cohort effects. However, our analyses were adjusted for birth cohort and such effects could not explain reported effects. Secondly, the short time span studied may also have affected results from the Cox proportional hazards regression if the birth month-effect is in fact changing over time. Our data were not in accord with the possibility that individuals born in the beginning of the calendar year are diagnosed and treated *later in life* (as opposed to a lesser extent) than individuals born at the end of the year. However, our data could not rule out that ADHD might be *underdiagnosed* and *undertreated* in those born early in a year. Their higher degree average of maturation, proportionally quite high during the early school years, may compensate for or conceal clinically relevant ADHD-related symptoms.

Although we did not know each individual's exact age at school start, the results suggest that a child's age relative to his or her classmates while entering first class contributes to a higher likelihood of an ADHD diagnosis and treatment, at least in childhood and adolescence. We identified a tendency towards similar birth month-effects for ADHD also in some adult age groups when analysing register data from the National Patient and Prescribed Drug Registers (Table 1, Figure 1) that was not observed with self-reported ADHD symptoms among adults in Cohort 3 (Appendix Figure 1). Although we cannot exclude chance findings due to multiple testing (i.e., 30 tests in Table 1), being born late in the year, and probably being relatively more immature than compulsory school classmates, could impact adult age ADHD diagnosis and medication.

Our findings agree with previously reported patterns of ADHD diagnosis and treatment in less comprehensive studies from the United States, Canada and Iceland (Elder, 2010; Evans et al., 2010; Morrow et al., 2012; Zoega et al., 2012). Zoega et al (Zoega et al., 2012) studied data from Icelandic national registers of prescribed drugs and standardized scholastic examinations. In contrast to our and the Icelandic study, Morrow et al (Morrow et al., 2012) reported stronger effects for girls compared to boys. It is likely that this finding is a chance effect or may be due to national differences. Similar to us, the Early Childhood Longitudinal Study – Kindergarten cohort (ECLS-K; Elder, 2010) found weak effects on parental ratings, whereas they found a stronger effect of teacher ratings, again suggesting a relative immaturity effect. Our results agree with theirs in that the increase in ADHD rates found by us was confined primarily to the school years and disappeared when parent-rated symptoms of ADHD was studied in Cohort 2. Altogether, these findings are consistent with the idea that delayed maturation accounts for part of the aetiology of childhood ADHD (Steffensson et al., 1999) and its medication.

The lack of association between birth month and self-reported ADHD symptoms in adults support the hypothesis of relative immaturity as a factor misinterpreted as, or aggravating ADHD symptoms. The lack of an effect of birth month on parent-reported ADHD symptoms is not as obvious, but may indicate that parents compare their children´s symptoms with same-aged peers (and not only to class mates) or expose them to more developmentally appropriate demands. This lack of effect is more in line with the results of Biederman et al (Biederman, Petty, Fried, Woodworth, & Faraone, 2012) who concluded that ADHD symptoms are not affected by age at school entry in a large clinical sample. Additionally, ADHD-related functional impairment was not considered in parent reports, in contrast to when a clinical ADHD diagnosis is considered in school settings and elsewhere.

Putative season of birth-effects have been studied for numerous psychiatric and other medical conditions, and a solid effect reported for schizophrenia (Torrey, Miller, Rawlings, & Yolken, 1997). Corresponding studies on ADHD and similar neuropsychiatric conditions have yielded less consistent findings (Brookes et al., 2007; Atladottir et al., 2007, Liederman, & Flannery, 1994; Mick, Biederman, & Faraone, 1996). Notably, however, the effect reported here is not a seasonal one; the risk of ADHD diagnosis and medication increased almost progressively with later birth month but abruptly returned to the lowest risk at the beginning of the following year. This latter effect, has been observed also for outcomes such as poorer sports achievement (Abel, & Kruger, 2005; Turnidge, Hancock, & Coté, 2012; Lemez, Baker, Horton, Watties, & Weir 2013), higher suicide risk in youth (Thompson, Barnsley, & Dyck, 1999), and for school performance (Zoega et al., 2012). Altogether, these findings support the contribution of a relative-to-peer interactional risk factor for adverse developmental outcomes.

Conclusion

Relatively more immature children (i.e., born late in the year) are more likely to be diagnosed with ADHD and receive pharmacological treatment for this condition. Importantly, this seemed to occur without parallel increases of parent- and self-reported ADHD symptoms in two complementary population-based cohorts of 9-year old and adult twins. Following previous work (Elder, 2010; Evans et al., 2010; Morrow et al., 2012; Zoega et al., 2012), a probable mechanism behind the birth month-effect is that children that are more immature than the class average face too high demands during the early school years. This could, in turn, contribute to ADHD-related functional impairment. The inverse interpretation is also possible; that children born earlier during the calendar year and, hence, on average more mature, may conceal or make up for clinically relevant ADHD-related symptoms. If this suggestion holds, child health care clinicians should consider not only the child's age in years but also his/her birth month in relation to classmates to provide more developmentally well-informed ADHD diagnoses and treatment. Legislators and school administrators might also consider discussing a more flexible timing of school start according to individual child maturity and birth month.

Supplemental tables 1 and 2 and Supplemental figure 1 suggested for online publishing

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Key points:

- Prior research from countries with high rates of ADHD diagnoses and medication suggests that children that are less mature relative to their class mates more often receive ADHD diagnoses and medication.
- We compared nationwide register information on diagnoses and ADHD medication with ADHD symptom counts in population-representative data in Sweden. We investigated also with adults if relative immaturity increases ADHD symptoms, medication, and diagnoses.

- Results suggested that relative immaturity compared to class mates contributed to ADHD diagnosis and pharmacotherapy, but not to ADHD symptoms. Effects were not significant for adults. The findings did not support that relatively more mature children are rather diagnosed and treated later in life.
- To increase the precision of ADHD diagnostics and treatment, the relative immaturity effect warrants increased awareness from child health clinicians.

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