Relative age and psychotropic drug use in preterm and term born children and young adults.

Christine S. Bachmann, MD,[a,b] Kari Risnes, MD, PhD,[b,c] Johan Håkon Bjørngaard, Professor,[a,d] Jorun Schei, MD, PhD,[e,f] Kristine Pape, MD PhD [a].

Affiliations: [a] Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway. [b] Children`s Clinic, St. Olav's University Hospital, Trondheim, Norway. [c] Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology, Norway. [d] Faculty of Nursing and Health Sciences, Nord University, Levanger, Norway. [e] Department of Mental Health, NTNU, Norwegian University of Science and Technology, Trondheim, Norway. [f] Department of Children and Youth, Division of Mental Healthcare, St. Olav's University Hospital, Trondheim, Norway.

Address correspondence to: Christine Strand Bachmann, NTNU, Faculty of Medicine and Health Sciences, Department of Public Health and Nursing, PB 8905, N-7491 Trondheim, Norway. [christine.s.bachmann@ntnu.no], 0047-97027625.

Short title: Relative age and psychotropic drug use in preterm youth

Funding Source: All phases of this study were supported by a grant from Central Norway Regional Health Authority (RHA).

Financial Disclosure: None of the authors have financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Clinical Trial Registration (if any): none.

Abbrevations:
MBRN = Medical Birth Registry of Norway
NorPD = the Norwegian Prescription Database
SD = Standard Deviation
GA = Gestational Age
OR = Odds Ratio
aOR = adjusted Odds Ratio
CI = Confidence Interval

Article Summary
Compared to peers born early in the school year, preterm and term individuals born late in the school year have increased use of psychostimulants.

What's Known on This Subject

Children born late in the school year, have increased risk of educational, social and mental health disadvantages, including ADHD and prescription of psychostimulants. Whether preterm born are particularly vulnerable to relative age effects on mental health is not known.

What This Study Adds

Preterm children born late in the school year have increased risk of psychostimulant prescription compared to preterm peers, not previously studied. This relative age effect seems to persist into young adulthood, in contrast to findings for term born.

Contributors' Statement Page

Christine Bachmann conceptualized and designed the study, carried out the initial analyses and interpretation of data for the work, drafted the initial manuscript, and revised the manuscript.

Kari Risnes and Johan Håkon Bjørngaard conceptualized and designed the study, contributed to interpretation of data for the work, and revised and reviewed the manuscript for important intellectual content.

Jorun Schei contributed to interpretation of data for the work and revised and reviewed the manuscript for important intellectual content.

Kristine Pape conceptualized and designed the study, coordinated data collection, supervised the initial analyses, contributed to interpretation of data for the work, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Background and Objectives

Being among the youngest within a school class is linked to disadvantages in various educational and mental health domains. This study aimed to investigate whether preterm born are particularly vulnerable to relative age effects on mental health, not previously studied.

Methods

We used registry data on all Norwegians born between 1989 and 1998 to compare prescription status for psychostimulants, antidepressants, hypnotics, anxiolytics and antipsychotics per year from age 10 to 23 (2004-2016) between exposure groups with different time of birth in the year (relative age) and different gestational age (preterm vs term).

Results

Of 488470 individuals, 29657 (6,1%) were born preterm. For term born in November/December, the adjusted Odds Ratio (aORs) for psychostimulant prescription compared to peers born in January/February was 1.80 (95% CI, 1.69-1.91) at ages 10 to 14 years, and 1.17 (95% CI, 1.08-1.27) at ages 20 to 23 years. Within preterm born, the corresponding results were 1.39 (95% CI, 1.13-1.69) and 1.34 (95% CI, 1,00-1.78) at ages 10-14 and 20-23 years, respectively.

Conclusions

Being relatively young within the school group was associated with increased psychostimulant prescription in the preterm as well as the term population. In contrast to term peers, the relative age effect for psychostimulant prescription seemed to persist to young adulthood for the preterm population. The results suggest that preterm individuals are vulnerable to long-term effects of relative immaturity and that they require careful consideration from both health care professionals and the school system.

Introduction

Children born preterm carry vulnerability from birth and into adulthood [1, 2], including increased risk of ADHD[3, 4] and psychiatric problems[5, 6], and there is evidence that they suffer more from social and cognitive disadvantages[7, 8] than term born peers.

In Norway all children born in the same calendar year start school together. Within a school class, the youngest children are almost 12 months younger than their oldest peers. Consequently, they are more immature regarding social, cognitive and motor development. Being compared with older and more mature peers may lead to problematization of relative immaturity and to overdiagnosis and medicalization, and negatively impact mental health and self-esteem[9-11]. Such influences on children of their chronological age *relative* to their classmates' age is often referred to as "relative age effect". Studies show that younger age in a school class increases the risk of being diagnosed with ADHD and prescribed psychostimulant medication[12-17], and that this effect is most pronounced in girls[13]. Relative age effects may be understood as a consequence of organization of the educational system, school entry and class environments, supported by research from e.g. Denmark, where delayed school start is practiced liberally and studies do not show these adverse effects of relative age.[18]

Children born preterm are relatively more immature compared to their term born peers with the same chronological age.[19] When starting school, this difference comes in addition to the age difference between the youngest and oldest children in the same class. Whether this "double burden" of immaturity may put children born preterm at particular risk, is of public health interest, since it may be imposed by societal structures, and may be reduced by modifying these.

We aimed to assess separately for preterm and term born, the importance of relative age in school on mental health, indicated by psychotropic drug use in adolescence and young adulthood. We hypothesized that the effect of relatively young age would be greater for preterm than term born individuals, and greater for girls than boys. Additionally, we aimed to study whether relative age effects persist beyond childhood.

Patients and methods

Study design

The study was based on a linkage between the Medical Birth Registry of Norway (NMBR)[20], the Norwegian Prescription Database (NorPD)[21] and Statistics Norway[22], using the unique Norwegian personal identification number. The NMBR includes all Norwegian citizens and provides maternal and perinatal variables. The NorPD provides information about all prescribed drugs dispensed by pharmacies. Information on education was collected from Statistics Norway. We followed individuals born from 1989 through 1998, with registered gestational age (GA) between 23+0 and 42+6 weeks, who had no registered congenital birth defects, were alive at 10 years and had registered maternal variables. Only individuals with birth weights more than 400 g and birth weights considered likely for GA were included.

The study was assessed and approved by the Regional Committees for Medical and Health Research Ethics (REC).

Follow-up

Individuals were followed between 2004 and 2016 with annual registrations, from the year they turned 10 until the year of their 24th birthday, emigration, or death – whichever occurred first.

Exposures

Gestational age (GA in week + days) was categorized in two groups according to the mother's last menstrual period; preterm (GA 23+0 to 36+6) and full term (GA 37+0 to 42+6). For sensitivity analyses, gestational age was further sub-categorized in four groups (GA 23+0 to 33+6, GA 34+0 to 36+6, GA 37+0 to 38+6 and GA 39+0 to 42+6).

Relative age was measured by month of birth in the year and categorized in two-months intervals. Individuals born in January/February were defined as relatively older, having a high relative age, while those born in November/December were defined as relatively younger, having a low relative age.

Outcomes

Outcomes were defined according to the ATC system: N06B psychostimulants for ADHD. Secondary outcomes were prescription status of four other categories of psychotropic drugs: N06A antidepressants, N05CD/N05CF/N05CH hypnotics and sedatives, N05B anxiolytics and N05A antipsychotics (Table S1). We registered prescription status (one (or more) prescription(s) vs no prescription) for each outcome every year from age 10 to 23 years.

Covariates

We included covariates considered as potential confounders in the relationship between relative age and gestational age and mental health. Child variables collected from the NMBR included birthyear, birthweight, multiple birth and sex. We created a z-score for birthweight according to Marsal et al's foetal growth standards[23], and identified individuals with birthweights more than 6 standard deviations (SD) below or more than 3 SD above the z-score (mean value), according to gestational age. Maternal variables, including parity and relationship status, were also collected from NMBR. Details of covariates are presented in Table S2.

Statistical analyses

We used generalized estimating equations (GEE) logistic regression models to compare the use of psychostimulants (primary outcome) per year from age 10 to 23 between exposure groups with different time of birth in the year (relative age) and different gestational age (preterm vs term). All analyses were repeated for each of the four secondary drug outcomes.

The primary analysis included the full study sample and assessed time of birth in the year in six two-month intervals, with an interaction term between time of birth category and gestational age group to explore differences in the impact of relative age between term and preterm born individuals. Analyses were performed for males and females separately and adjusted for participants' age (during follow-up), year of birth and multiple birth status and mothers' parity, relationship status, age in years and age in years squared, educational level, and county of birth. Estimates from the regression analyses were used to calculate and graphically present the percentage with the outcome in each exposure group, using average marginal effects (with covariates as observed).

In a subsample, we compared the group with the lowest relative age (born November/December) with the group with the highest relative age (born January/February) and assessed outcomes in three periods according to age in follow-up (10-14 years, 15-19 years and 20-23 years) by adding an interaction term between period and relative age groups in the analyses. Analyses were performed for term and preterm separately and adjusted for participants year of birth and multiple birth status and mothers' parity, relationship status, age in years and age in years squared, educational level, and country of birth.

We performed sensitivity analyses where preterm individuals were stratified into subgroups to explore differences in associations among very preterm and later preterm individuals.

All analyses were done using STATA statistical software version 15.1 (StataCorp).

Results

488 470 individuals were included in the primary analyses (251 525 [51,5%] male participants and 6,1 % were born preterm). Participants' birth month was evenly distributed over the year. Figure and table 1 show the study population and population characteristics, respectively.

Figure 2 displays annual psychostimulant use by categories of birth month throughout the year, showing gradually higher proportions with psychostimulant prescription with increasing birth month from January/February to November/December for both preterm and term born males and females. Annual prescription for boys born in November/December was 1.0 %-point (95% CI 0.4-1.7) higher for preterm born and 1.3 %-point (95% CI 1.1-1.4) higher for term born,

compared to boys born in January/February (corresponding oddsratios (OR) 1.37 (95% CI 1.12-1.68) and 1.74 (95% CI 1.63-1.86), p for interaction between birth month category and preterm status 0.36). Corresponding figures for girls were 0.5%-point (95% CI -0.0-1.0) higher for preterm and 0.4%-point (95% CI 0.3-0.6) higher for

term born (ORs 1.39 (95% CI 0.98-1.96) and 1.43 (95% CI 1.30-1.57), p for interaction between birth month category and preterm status 0.93) – details provided in table S3.

The subsample used for further comparisons consisted of 152 725 individuals,79 022 born in January/February (4741 (6,0 %) were born preterm) and 73 703 individuals born in November/December (5076 (6,9 %) were born preterm) **(**table S4).

Figure 3 shows odds ratios of psychostimulant prescription at ages 10-14, 15-19 and 20-23 years for the relatively younger (born in November/December) group compared with their relatively older peers (born in January/February) in term and preterm born (p for interaction between relative age, age group and preterm status <0.001). While odds ratios of prescription for the relatively younger group compared with the relatively older group decreased with increasing age in the term population (from 1.80 (95% CI, 1.69-1.91) at ages 10 to 14 years to 1.17 (95% CI, 1.08-1.27) at ages 20 to 23 years), we observed a stable association over age in the preterm population (ORs 1.39 (95% CI, 1.13-1.69) at ages 10 to14 years and 1.34 (95% CI, 1.00-1.78) at ages 20 to 23 years). The relative age effect over age/time differed between males and females among term born (p for interaction between relative age, age group and sex <0.001), but less so

212 in the preterm population (p for interaction between relative age, age group and sex 0.10) (figure
213 S1).

214

215 The results indicated that relatively younger born late preterm (GA 34-36) have about 50%
216 increased risk of psychostimulant use from ages 10 through 23 when compared to their relatively
217 older peers (figure 4). However, the corresponding comparison for preterm born before week 34
218 did not indicate strong relative age effects, but estimates were imprecise due to relatively low
219 number in this group.

220

221 There were small changes in prescription of the four other psychotropic drug groups with
222 increasing birth month from January/February to November/December when studying the entire
223 period from 10 to 23 years (figure 5), neither for preterm nor term males or females. However, at
224 ages 10 to 14 years, ORs were increased for prescription of several drugs for the relatively
225 younger individuals, compared to relatively older peers, both in the term and to some extent in
226 the preterm born groups (figure 6) (e.g. ORs for antipsychotics at ages 10 to 14 years 1.39 (95%
227 CI 1.18 to 1.64) in term born and 2.43 (95% CI 1.39 to 4.27) in preterm born). Such relative age
228 effects were not present among the older age groups. Figure S2 shows the corresponding results
229 stratified by sex.

230

Discussion

Our findings showed that young relative age was associated with higher psychostimulant prescription across ages 10 to 23 years. Overall, psychostimulant use was higher in preterm than in term born, and the relative age effect for psychostimulants was seen within the preterm and the term born group. However, while the relative age effect for psychostimulant prescription decreased over age for the term population, we saw a stable trend over ages 10 to 23 years for the preterm population. Relatively younger term and preterm groups were more often prescribed antidepressants and antipsychotic drugs at 10-14 years compared to peers born early in the year, but this did not persist at later ages.

Our findings show an explicit relative age effect for psychostimulant prescription in both preterm and term boys and girls. Earlier literature supports the same tendency, without taking gestation into account, finding that children born late in the academic year are more often diagnosed with, and more often prescribed medication for, ADHD.[12-15, 24]

Earlier research on term born individuals suggests that relatively younger age is also related to other adverse mental health effects.[25] A recent study including ten million people found that low relative age was associated with diagnoses of anxiety, depressive disorders, ADHD, and with prescription of ADHD medication and antidepressants.[26] Other studies have found increased risk of depression[14], lower life satisfaction, more psychosomatic complaints, and increased risk of being overweight among relatively younger children.[10]

Our findings show relative age effects related to antidepressants and antipsychotics in ages 10 to 14 years for both preterm and term peers.

For the preterm born, we are not aware of earlier studies assessing the impact of relative age effects on mental health , but findings from studies on academic performance are relevant to consider since academic performance is linked to mental health and mental health disorders.[27] A British cohort study from 2013 conducted by Odd et al [28] looked at academic outcomes, and showed a gradual reduction in scores on reading, writing and mathematics from oldest to youngest students in class in ages 5 to 7 years, including for preterm individuals. The same authors found that special educational needs were maintained until the age of 16 among preterm pupils enrolled in school based on date of birth, compared to those enrolled based on expected date of delivery.[29] Individuals born preterm experienced some catch-up on test results to their term peers during ages 5 to 16 years but did not totally close the gap.[30]

Whether relative age effects persist into adolescence and young adulthood, indicating difficulties of a more chronic nature, is of essential concern. As children grow older and the developmental differences between those born late and early in the year become smaller, one also would expect diminishing relative age effects. Most of the earlier research in this field concludes that relative age effects for ADHD diagnosis and prescription are largest during early years of school[15, 31-33]. Also, relative age effects related to internalizing symptoms, poorer peer relationships and mental health impairment decreased over time from ages 11-12 years[9] in one study. However, other studies suggest sustained effects of relative age on mental health, e.g. a Japanese study showing increased mortality due to suicide at ages 19 to 21 years.[34] For the term population in our study, we observed decreasing relative age effects regarding psychostimulant prescription from ages 10-14 to ages 20-23 years, in concordance with most earlier studies. However, for the preterm population, we found a more stable relative age effect for psychostimulants across ages 10 to 23

years, supporting findings of the relatively long-term educational outcomes Odd et al found for preterm individuals.[28-30]

It is well known that adolescents born preterm are more prone to having an ADHD diagnosis.[3, 4] Also, there is increasing evidence of a "preterm behavioral phenotype", associated with symptoms of anxiety, inattention and social difficulties.[35, 36] These vulnerabilities could possibly explain less resilience to suboptimal or inappropriate social and educational environments, and to the experience of coming up short compared to peers in terms of social skills and athletic and academic performance in preterm born. This could further contribute to lasting effects with reduced level of functioning.

For antidepressants, hypnotics, anxiolytics and antipsychotics, our findings did not affirm sustained relative age effects through adolescence and into young adulthood. While this could indicate that there is no lasting connection between relative age and mental health disorders other than ADHD, it is also possible that medication use is a less robust indicator of these disorders, especially in older adolescents and young adults.

In line with findings from numerous countries and earlier studies[12, 13, 33, 37, 38], the total proportion of boys getting a psychostimulant prescription was higher than for girls in early ages (10-14 and 15-19 years), but the association between younger relative age and psychostimulant prescription was more pronounced among female than male participants. Surprisingly, this trend was not seen among the youngest preterm girls (10-14 years). A possible explanation for a small relative age effect regarding psychostimulant prescription among the youngest preterm girls could be that relative immaturity in this group for some reason to a lesser extent is interpreted as ADHD, or

298 rather interpreted as other types of psychopathology. However, relatively broad confidence
299 intervals in the preterm group does not support any firm conclusion from this observation.

300

301 A minority of studies, including from Denmark[18], show no relative age effects concerning
302 ADHD diagnosis/ medication. A suggested explanation for this is that a considerable proportion
303 of children born late in the year delay school start in Denmark, thus being more mature at the
304 time. Also, enrolling preterm pupils in school based on expected date of delivery instead of
305 actual delivery date has shown to reduce the need of special education.[29] Findings suggest that
306 children with initial learning difficulties predominantly linked to slow maturation and lack of
307 self-regulation could benefit from delayed school enrollment.[39] On the other hand, there are
308 studies suggesting that delayed school entry could deprive children with developmental
309 difficulties from one important year of educational support.[40]

310

311 Strengths of this study is the study design, with a large naturally selected population across all
312 gestational ages, with complete follow-up using high quality registry data over several years
313 across youth.

314

315 Although we have adjusted for several perinatal and maternal covariates considered possible
316 confounders in this context, gestational age is a complex phenomenon and residual confounding
317 is still likely to be present. Although we cannot rule out that some people plan birth to a specific
318 month of the year, we assume that birth month is more or less randomly distributed. We

therefore consider confounding by gestational age as less important for the comparison between relatively younger and older groups.

Prescription of medication must be considered as one of several possible ways of measuring mental health in young people, reflecting a certain functional impairment (lack of sleep, anxiety, mood, hyperactivity/concentration), although it is not necessarily correlated with the prevalence of psychiatric disorders. However, psychostimulants in Norway must meet diagnostic criteria and be *initiated* by a specialist in child and adolescent psychiatry, pediatrics or neurology, and an earlier Norwegian study has shown a high correlation between ADHD diagnoses and dispensed ADHD medication. [12]

Finally, for subgroup analyses some ORs in the study are narrow, and although relevant at the population level, individual risk must be interpreted with caution.

Conclusion/final remarks

Our findings suggest that the preterm population has sustained relative age effects, compared to term peers. Currently, the cause of this remains uncertain, but may be linked to the higher prevalence of developmental and cognitive difficulties in preterm children. More research into mechanisms for, and interventions to reduce relative age effects in the preterm population is necessary. Nevertheless, our findings suggest need for approaches at various levels. Universal and system level approaches are needed to reduce relative age effects among school children in countries where such effects exist. Examples could be delayed/ flexible school entry or more inclusive school practices. In addition, both healthcare and educational professionals should give particular attention to preterm children born late in the school year in the transition to school.

References

1. Van Lieshout RJ, Ferro MA, Schmidt LA, et al. Trajectories of psychopathology in extremely low birth weight survivors from early adolescence to adulthood: a 20-year longitudinal study. *J Child Psychol Psychiatry*. Nov 2018;59(11):1192-1200. doi:10.1111/jcpp.12909

2. Kajantie E, Strang-Karlsson S, Evensen KAI, Haaramo P. Adult outcomes of being born late preterm or early term - What do we know? *Semin Fetal Neonatal Med*. Feb 2019;24(1):66-83. doi:10.1016/j.siny.2018.11.001

3. Ask H, Gustavson K, Ystrom E, et al. Association of Gestational Age at Birth With Symptoms of Attention-Deficit/Hyperactivity Disorder in ChildrenAssociation of Gestational Age at Birth With Symptoms of ADHD in ChildrenAssociation of Gestational Age at Birth With Symptoms of ADHD in Children. *JAMA Pediatrics*. 2018;172(8):749-756. doi:10.1001/jamapediatrics.2018.1315 %J JAMA Pediatrics

4. Lindström K, Lindblad F, Hjern A. Preterm Birth and Attention-Deficit/Hyperactivity Disorder in Schoolchildren. *Pediatrics*. 2011;127(5):858-865. doi:10.1542/peds.2010-1279

5. Nosarti C, Reichenberg A, Murray RM, et al. Preterm birth and psychiatric disorders in young adult life. *Arch Gen Psychiatry*. Jun 2012;69(6):E1-8. doi:10.1001/archgenpsychiatry.2011.1374

6. Pyhala R, Wolford E, Kautiainen H, et al. Self-Reported Mental Health Problems Among Adults Born Preterm: A Meta-analysis. *Pediatrics*. Apr 2017;139(4)doi:10.1542/peds.2016-2690

7. Fevang SKE, Hysing M, Markestad T, Sommerfelt K. Mental Health in Children Born Extremely Preterm Without Severe Neurodevelopmental Disabilities. *Pediatrics*. 2016;137(4)doi:10.1542/peds.2015-3002

8. D'Onofrio BM, Class QA, Rickert ME, Larsson H, Långström N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. *JAMA Psychiatry*. Nov 2013;70(11):1231-40. doi:10.1001/jamapsychiatry.2013.2107

9. Patalay P, Belsky J, Fonagy P, et al. The Extent and Specificity of Relative Age Effects on Mental Health and Functioning in Early Adolescence. *J Adolesc Health*. Nov 2015;57(5):475-81. doi:10.1016/j.jadohealth.2015.07.012

10. Fumarco L, Baert S, Sarracino F. Younger, dissatisfied, and unhealthy - Relative age in adolescence. *Econ Hum Biol*. May 2020;37:100858. doi:10.1016/j.ehb.2020.100858

11. Thompson AH, Barnsley RH, Battle J. The relative age effect and the development of self-esteem. *Educational Research*. 2004/09/01 2004;46(3):313-320. doi:10.1080/0013188042000277368

12. Karlstad Ø, Furu K, Stoltenberg C, Håberg SE, Bakken IJ. ADHD treatment and diagnosis in relation to children's birth month: Nationwide cohort study from Norway. *Scand J Public Health*. Jun 2017;45(4):343-349. doi:10.1177/1403494817708080

13. Vuori M, Martikainen JE, Koski-Pirila A, et al. Children's Relative Age and ADHD Medication Use: A Finnish Population-Based Study. *Pediatrics*. Oct 2020;146(4)doi:10.1542/peds.2019-4046

14. Root A, Brown JP, Forbes HJ, et al. Association of Relative Age in the School Year With Diagnosis of Intellectual Disability, Attention-Deficit/Hyperactivity Disorder, and Depression. *JAMA Pediatr*. Nov 1 2019;173(11):1068-1075. doi:10.1001/jamapediatrics.2019.3194

15. Sayal K, Chudal R, Hinkka-Yli-Salomaki S, Joelsson P, Sourander A. Relative age within the school year and diagnosis of attention-deficit hyperactivity disorder: a nationwide population-based study. *Lancet Psychiatry*. Nov 2017;4(11):868-875. doi:10.1016/S2215-0366(17)30394-2

16. Zoëga H, Valdimarsdóttir UA, Hernández-Díaz S. Age, academic performance, and stimulant prescribing for ADHD: a nationwide cohort study. *Pediatrics*. Dec 2012;130(6):1012-8. doi:10.1542/peds.2012-0689

17. Holland J, Sayal K. Relative age and ADHD symptoms, diagnosis and medication: a systematic review. *Eur Child Adolesc Psychiatry*. Nov 2019;28(11):1417-1429. doi:10.1007/s00787-018-1229-6

18. Pottegard A, Hallas J, Hernandez D, Zoega H. Children's relative age in class and use of medication for ADHD: a Danish Nationwide Study. *J Child Psychol Psychiatry*. Nov 2014;55(11):1244-50. doi:10.1111/jcpp.12243

19. Gould JF, Fuss BG, Roberts RM, Collins CT, Makrides M. Consequences of using chronological age versus corrected age when testing cognitive and motor development in infancy and intelligence quotient at school age for children born preterm. *PLoS One*. 2021;16(9):e0256824. doi:10.1371/journal.pone.0256824

20. Medical Birth Registry of Norway. Norwegian Institute of Public Health. Updated 2019. Accessed 22.06, 2020. https://www.fhi.no/en/hn/health-registries/medical-birth-registry-of-norway/medical-birth-registry-of-norway/

21. Norwegian Prescription Database. Norwegian Institute of Public Health. Updated 2016. Accessed 22.06, 2020. https://www.fhi.no/en/hn/health-registries/norpd/norwegian-prescription-database/

22. Statistics Norway. Accessed 22.06, 2020. https://www.ssb.no/en

23. Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. Jul 1996;85(7):843-8. doi:10.1111/j.1651-2227.1996.tb14164.x

24. Whitely M, Phillimore J, Lester L, Robinson S. Influence of birth month on the probability of Western Australian children being treated for ADHD. *Med J Aust*. Sep 18 2017;207(6):268-269. doi:10.5694/mja17.00165

25. Goodman R, Gledhill J, Ford T. Child psychiatric disorder and relative age within school year: cross sectional survey of large population sample. *BMJ*. Aug 30 2003;327(7413):472. doi:10.1136/bmj.327.7413.472

26. Chen MH, Huang KL, Hsu JW, et al. Effect of relative age on childhood mental health: A cohort of 9,548,393 children and adolescents. *Acta Psychiatr Scand*. Aug 2021;144(2):168-177. doi:10.1111/acps.13327

27. Agnafors S, Barmark M, Sydsjö G. Mental health and academic performance: a study on selection and causation effects from childhood to early adulthood. *Soc Psychiatry Psychiatr Epidemiol*. May 2021;56(5):857-866. doi:10.1007/s00127-020-01934-5

28. Odd D, Evans D, Emond A. Preterm birth, age at school entry and educational performance. *PLoS One*. 2013;8(10):e76615. doi:10.1371/journal.pone.0076615

29. Odd D, Evans D, Emond A. Preterm Birth, Age at School Entry and Long Term Educational Achievement. *PLoS One*. 2016;11(5):e0155157. doi:10.1371/journal.pone.0155157

30. Odd D, Evans D, Emond AM. Prediction of school outcome after preterm birth: a cohort study. *Arch Dis Child*. Apr 2019;104(4):348-353. doi:10.1136/archdischild-2018-315441

31. Halldner L, Tillander A, Lundholm C, et al. Relative immaturity and ADHD: findings from nationwide registers, parent- and self-reports. *J Child Psychol Psychiatry*. Aug 2014;55(8):897-904. doi:10.1111/jcpp.12229

32. Hoshen MB, Benis A, Keyes KM, Zoega H. Stimulant use for ADHD and relative age in class among children in Israel. *Pharmacoepidemiol Drug Saf*. Jun 2016;25(6):652-60. doi:10.1002/pds.3962

33. Morrow RL, Garland EJ, Wright JM, Maclure M, Taylor S, Dormuth CR. Influence of relative age on diagnosis and treatment of attention-deficit/hyperactivity disorder in children. *Cmaj*. Apr 17 2012;184(7):755-62. doi:10.1503/cmaj.111619

34. Matsubayashi T, Ueda M. Relative Age in School and Suicide among Young Individuals in Japan: A Regression Discontinuity Approach. *PLoS One*. 2015;10(8):e0135349. doi:10.1371/journal.pone.0135349

35. Johnson S, Marlow N. Preterm birth and childhood psychiatric disorders. *Pediatr Res*. May 2011;69(5 Pt 2):11r-8r. doi:10.1203/PDR.0b013e318212faa0

36. Fitzallen GC, Taylor HG, Bora S. What Do We Know About the Preterm Behavioral Phenotype? A Narrative Review. *Front Psychiatry*. 2020;11:154. doi:10.3389/fpsyt.2020.00154

37. Whitely M, Raven M, Timimi S, et al. Attention deficit hyperactivity disorder late birthdate effect common in both high and low prescribing international jurisdictions: a systematic review. *J Child Psychol Psychiatry*. Apr 2019;60(4):380-391. doi:10.1111/jcpp.12991

38. Raman SR, Man KKC, Bahmanyar S, et al. Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases. *Lancet Psychiatry*. Oct 2018;5(10):824-835. doi:10.1016/s2215-0366(18)30293-1

39. Dee TS, Sievertsen HH. The gift of time? School starting age and mental health. *Health Econ*. May 2018;27(5):781-802. doi:10.1002/hec.3638

40. Jaekel J, Strauss VY, Johnson S, Gilmore C, Wolke D. Delayed school entry and academic performance: a natural experiment. *Dev Med Child Neurol*. Jul 2015;57(7):652-659. doi:10.1111/dmcn.12713

Tables and figures

Figure 1: Study population.

Figure 2: Estimated proportion with psychostimulant prescription (per year) age 10-23 (in percent, with 95% CI) according to two-month intervals of birth month throughouth the year for preterm and term groups. Model adjusted for birth year, age, multiple birth status, mothers' age and mothers' age squared, parity, relationship status, country of birth and education.

Figure 3: Oddsratios (OR, with 95% CI) of annual psychostimulant prescription at ages 10-14, 15-19 and 20-23 years among the relatively younger preterm and term groups born in November/December, compared to the relatively older groups born in January/February.

- Figure footnote:
  P-values for interaction between relative age and age group
  [a]0.46 [b]<0.001

Figure 4: Oddsratios (OR, with 95% CI) of annual psychostimulant prescription at ages 10-14, 15-19 and 20-23 years among preterm groups with GA 23-33, 34-36, 37-38 and 39-42 born in November/December, compared to the same groups born in January/February.

Figure 5: Estimated proportion with prescription of psychotropic drugs (per year) age 10-23 (percent, 95% CI) according to two-month intervals of birth month throughouth the year for preterm and term groups. Model adjusted for birth year, age, multiple birth status, mothers' age and mothers' age squared, parity, relationship status, country of birth and education.

Figure 6: Oddsratios (OR, with 95% CI) of annual prescription of antidepressants, anxiolytics, hypnotics and antipsychotics at ages 10-14, 15-19 and 20-23 years among the relatively younger preterm and term groups born in November/December, compared to the relatively older groups born in January/February.

- Figure footnote:
  P-values for interaction between relative age and age group
  [a]0.15 [b]<0.001 [c]0.38 [d]<0.001 [e]0.03 [f]<0.001 [g]<0.001 [h]<0.001

	Jan/ Feb[a]	March/ Apr[b]	May/ Jun[c]	Jul/ Aug[d]	Sep/ Oct[e]	Nov/ Dec[f]	All
	n (%) / Mean (SD)	n (%) / Mean (SD)	n (%) / Mean (SD)	n (%) / Mean (SD)	n (%) / Mean (SD)	n (%) / Mean (SD)	n (%) / Mean (SD)
Total:	79 022 (16,2)	87 941 (18,0)	84 712 (17,3)	83 157 (17,0)	79 935 (16,4)	73 703 (15,1)	488 470 (100)
Gender:							
Boys	40 625 (51.4)	45 386 (51,6)	43 861 (51,8)	42 771 (51,4)	41 091 (51,4)	37 791 (51,3)	251 525 (51,5)
Girls	38 397 (48,6)	42 555 (48,4)	40 851 (48,2)	40 386 (48,6)	38 844 (48,6)	35 912 (48,7)	236 945 (48,5)
Mean birthweight, g (SD):	3 520 (582)	3 540 (572)	3 528 (579)	3 527 (577)	3 531 (581)	3 508 (597)	3526 (597)
GA:							
23-36 weeks[g]	4 741 (6,0)	5 031 (5,7)	5 185 (6,1)	4 953 (6,0)	4 671 (5,8)	5 076 (6,9)	29 657 (6,1)
- 23-33 weeks[h]	1 269 (26,8)	1 267 (25,2)	1 323 (25,5)	1 201 (24,3)	1 276 (27,3)	1 428 (28,1)	7 764 (26,2)
- 34-36 weeks[i]	3 472 (73,2)	3 764 (74,8)	3 862 (74,5)	3 752 (75,8)	3 395 (72,7)	3 648 (71,9)	21 893 (73,8)
37-42 weeks[j]	74 281 (94,0)	82 910 (94,3)	79 527 (93,9)	78 204 (94,0)	75 264 (94,2)	68 627 (93,1)	458 813 (93,9)
- 37-38 weeks[k]	11 666 (15,7)	12 688 (15,3)	12 215 (15,4)	11 873 (15,2)	11 137 (14,8)	11 048 (16,1)	70 627 (15,4)
- 39-42 weeks[l]	62 615 (84,3)	70 222 (84,7)	67 312 (84,6)	66 331 (84,8)	64 127 (85,2)	57 579 (83,9)	388 186 (84,6)
Small for gestational age[m]:	2 084 (2,6)	2 138 (2,4)	2 129 (2,5)	2 254 (2,7)	2 077 (2,6)	2 054 (2,8)	12 736 (2,6)
Large for gestational age[n]:	2 093 (2,7)	2 443 (2,8)	2 333 (2,8)	2 291 (2,8)	2 186 (2,7)	2 043 (2,8)	13 389 (2,7)
Mother's relationship status:							
Married/ cohabitant	72 400 (91,6)	81 077 (92,2)	78 020 (92,1)	76 332 (91,8)	73 222 (91,6)	67 158 (91,1)	448 209 (91,8)
Other	6 622 (8,4)	6 864 (7,8)	6 692 (7,9)	6 825 (8,2)	6 713 (8,4)	6 545 (8,9)	40 261 (8,2)
Multiple births:							
Singeltons	76 707 (97,1)	85 492 (97,2)	82 374 (97,2)	80 802 (97,2)	77 715 (97,2)	71 397 (96,9)	474 487 (97,1)
Twins	2 250 (2,9)	2 380 (2,7)	2 239 (2,6)	2 270 (2,7)	2 132 (2,7)	2 207 (3,0)	13 487 (2,8)

Triplets/ quadruplets	65 (0,1)	69 (0,1)	99 (0,1)	85 (0,1)	88 (0,1)	99 (0,1)	505 (0,1)
Parity:							
Primiparae	32 927 (41,7)	34 595 (39,3)	34 305 (40,5)	34 752 (41,8)	33 753 (42,2)	31 635 (42,9)	201 967 (41,4)
Para 1	28 301 (35,8)	32 967 (37,5)	31 022 (36,6)	29 422 (35,4)	27 683 (34,6)	25 200 (34,2)	174 595 (35,7)
Para 2	13 146 (16,6)	15 176 (17,3)	14 493 (17,1)	14 143 (17,0)	13 647 (17,1)	12 265 (16,6)	82 870 (17,0)
Para 3	3 454 (4,4)	3 888 (4,4)	3 640 (4,3)	3 552 (4,3)	3 526 (4,4)	3 298 (4,5)	21 358 (4,4)
Para 4 or more	1 194 (1,5)	1 315 (1,5)	1 252 (1,5)	1 288 (1,6)	1 326 (1,7)	1 305 (1,8)	7 680 (1,6)
Maternal mean age, years (SD):	29,0 (5,0)	28,9 (4,9)	28,8 (4,9)	28,6 (5,0)	28,5 (5,0)	28,3 (5,1)	28,7 (5,0)
Maternal education:							
Lower secondary education	22 780 (28,8)	24 568 (27,9)	23 744 (28,0)	23 284 (28,0)	22 477 (28,1)	21 321 (28,9)	138 174 (28,3)
Upper secondary education	33 877 (42,9)	37 928 (43,1)	36 280 (42,8)	35 151 (42,3)	34 035 (42,6)	31 240 (42,4)	208 511 (42,6)
Higher education	22 365 (28,3)	25 445 (28,3)	24 688 (29,1)	24 722 (29,7)	23 423 (29,3)	21 142 (28,7)	141 785 (29,0)
Maternal country of birth:							
Norway	73 065 (92,5)	81 561 (92,8)	78 162 (92,3)	76 718 (92,3)	73 542 (92,0)	67 588 (91,7)	450 636 (92,3)
Other	5 957 (7,5)	6 380 (7,3)	6 550 (7,7)	6 439 (7,7)	6 393 (8,0)	6 115 (8,3)	37 834 (7,8)
Psychotropic drugs[o]:							
Psychostimulants	3 039 (3,9)	3 540 (4,0)	3 662 (4,3)	3 885 (4,7)	4 107 (5,1)	4 086 (5,5)	22 319 (4,6)
Antidepressants	7 000 (8,9)	7 705 (8,8)	7 405 (8,7)	7 272 (8,8)	6 957 (8,7)	6 508 (8,8)	42 847 (8,8)
Anxiolytics	4 540 (5,8)	4 900 (5,6)	4 656 (5,5)	4 593 (5,5)	4 453 (5,6)	4 177 (5,7)	27 319 (5,5)
Hypnotics/ sedatives	6 982 (8,8)	7 767 (8,8)	7 565 (8,9)	7 470 (9,0)	7 346 (9,2)	6 863 (9,3)	43 993 (9,0)
Antipsychotics	2 858 (3,6)	3 070 (3,5)	3 001 (3,5)	2 952 (3,6)	2 802 (3,5)	2 688 (3,7)	17 370 (3,6)

Table 1. Sociodemographic characteristics and perinatal variables of the total population.

[a] Born in January or February.
[b] Born in March or April.

[c] Born in May or June.
[d] Born in July or August.
[e] Born in September or October.
[f] Born in November or December.
[g] Gestational age, 23 wk and 0 d to 36 wk and 6 d.
[h] Gestational age, 23 wk and 0 d to 33 wk and 6 d.
[i] Gestational age, 34 wk and 0 d to 36 wk and 6 d.
[j] Gestational age, 37 wk and 0 d to 42 wk and 6 d.
[k] Gestational age, 37 wk and 0 d to 38 wk and 6 d.
[l] Gestational age, 39 wk and 0 d to 42 wk and 6 d.
[m] Birth weight <2,5th percentile for gestational age.
[n] Birth weight >97,5th percentile for gestational age.
[o] For the entire periode (ie, ages 10-23 years)