Chapter 4

Distribution of Month of Birth of Individuals with Autism Spectrum Disorder Differs from the General Population in the Netherlands

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Abstract

The prevalence of autism spectrum disorders (ASDs) is causally dependent on genetic and environmental influences. We investigated whether autism spectrum disorders are associated with month of birth compared to the general population using a retrospective study, comparing ASD cases (n = 3478) with the general population (n = 2,716,876) born between 1995 and 2008. Associations were examined using χ^2 tests and Walter and Elwood's seasonality χ^2 tests for the total ASD group, and separately for autistic disorder and Asperger syndrome. For the total ASD group, the distribution of month of birth was different compared to the general population ($p < 0.0001$), with July as the highest contributor, and a season-of-birth effect was found for this group ($p = 0.02$). For the autistic disorder group, the months of birth distribution were different ($p = 0.01$), with July as the highest contributor. No season-of-birth effect over the year was found ($p = 0.09$). No association was found for the months of birth of individuals with Asperger syndrome ($p = 0.06$), with no seasonal trend over the year ($p = 0.60$). In conclusion, a drop in sun exposure during the first trimester of pregnancy might explain the peak in July births and the associated risk for ASD development.

Keywords: autism spectrum disorder, month of birth, seasonality, periodicity, sunlight exposure

1. Introduction

The study of associations between season of birth or conception and the occurrence of neurodevelopmental disorders such as autism can provide important clues about causes of such a disease with unknown etiology. Such associations would then suggest periodicity of an environmental etiologic agent acting during the prenatal, perinatal, or early postnatal phase of development. One such environmental factor with seasonal recurrence originally suspected to increase the risk for the development of autism was a viral infection, for example, rubella [1]. Other potentially relevant factors that frequently vary by season include variations in nutrient intake by (pregnant) mother and deficiencies in nutritional factors such as vitamin D [2], maternal allergies during pregnancies [3], and exposure to pesticides (organophosphates and organochlorines) [4]. Previous studies have shown variable conclusions as to a specific month of birth that contributed to an enhanced risk of development of symptoms of autism within the first few years of life [5–12]. However, not all studies have found an association between month or season of birth and autism [13–15]. These apparent discrepancies might be based on methodological differences among the studies reviewed, including the use of diverse diagnostic criteria, and the statistical analysis employed.

Although genetic factors are strongly suspected to be a cause of autism spectrum disorders (ASDs), concordance in monozygotic twins is 40–90% and the phenotypic expression of the disorder varies widely, even within monozygotic twins [16, 17]. Thus, environmental factors also seem to play an important causal role. The number of people with ASD in the Netherlands increased to 190,000 in 2009 from 90,000 in 2001 [18]. Although there are many possible explanations, including more frequent diagnosis and reporting [19], this increase strikingly coincided with the medical advice to avoid sun exposure [20, 21]. This advice has probably lowered vitamin D activation in the skin resulting in lower levels of activated vitamin D (calcitriol, a fat-soluble steroid hormone) in developing brain of the fetus. These findings are particularly relevant in view of emerging evidence suggestive of a role for vitamin D in neuropsychological functioning, including a range of diseases from autism to Alzheimer's [22]. A study in which the prevalence of ASD was correlated to the season birth showed a variation that was linked to latitude of the home region [19]. This would be consistent with maternal vitamin D deficiency being a risk factor for development of autism, possibly by affecting fetal brain development as well as possibly by affecting maternal immune system status during pregnancy [19]. A study from Lee et al. aimed to determine whether the birth date distribution for individuals with autism spectrum disorders (ASD), including singletons and multiple births, differed from the general population. The presence of seasonal trends in ASD singletons and concordant multiple births suggests a role for non-heritable factors operating during the pre- or perinatal period, even among cases with a genetic susceptibility [17]. Although several studies have been conducted on this topic [11, 12], it is potentially of great public health importance in view of the burden of ASD, which in European countries and the USA affects 60–100 per 10,000 children [18, 20, 23, 24].

The current study aimed to test our hypothesis that month of birth and ASD are associated. This hypothesis was investigated separately for people with autistic disorder and Asperger syndrome. We also explored the association between the sun exposure during pregnancy and ASD.

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2. Subjects and methods

2.1. Design and data acquisition

We compared cases with autism spectrum disorders with controls without such disorders regarding their date of birth. In this retrospective study, ASD cases were extracted from a registry held by Netherlands Society for Autism Spectrum Disorders (Dutch acronym: NVA), an interest group of people with autism and their relatives [25]. Approval to use from their database anonymous data on month of birth and type of autism according to DSM IV criteria was obtained from the chairman, F. Stekelenburg. As one of its activities, it distributes since 2007 a personalized pass that Dutch citizens with an ASD can use to avoid difficult situations, such as police arrest, queues at public facilities, or events. Such passes are issued only when the application form is accompanied by an affidavit, signed by a psychiatrist, psychologist, educationist, or a representative of an institution for ASD diagnosis to certify that the holder has an autistic disorder, Asperger syndrome, pervasive developmental disorder-not otherwise specified (PDD-NOS) as categorized by the DSM IV criteria that were valid at the time of diagnosis. Other diagnoses, including multiple complex developmental disorder (McDD)/Rett syndrome, were not considered because the number of cases was too low for meaningful analysis. Based on the permission we obtained, we extracted information on date of birth, gender, autism diagnosis but no other personal information from persons in this registry who were born in the period 1995–2008. This period contained the largest number of patient entries with at least 150 per year, and for whom full information on all items was available. As controls, we used the general population of people born in the Netherlands in the same period, for whom the distribution of date of birth is publicly available in aggregated form from the Dutch Central Bureau of Statistics (Statistics Netherlands, http://www.cbs.nl/en-GB/) [26].

Data on the cumulative number of sun hours per month, averaged over the Netherlands for the period 1998 until 2008, were obtained from the Royal Netherlands Meteorological Institute [27]. These data were used to approximate the number of hours of sun during pregnancy for each trimester.

2.2. Statistical analysis

Data were analyzed using MS Excel and STATA version 10.1 (StataCorp, College Station, Texas, USA). Group differences were assessed by Pearson's χ^2 test, which evaluates a null hypothesis that the frequency distribution of the binary variable indicating cases and controls is equally distributed over the months of the year. This test treats all response variables as nominal, that is, it does not take the ordering of the months into account and makes no assumptions about seasonal variation. An alternative method of data analysis is to test birth data against a sinusoidal function. Thus, in addition, we used Walter and Elwood's seasonality test [28, 29], which evaluates the adequacy of a sinusoidal curve over time, with one maximum and one minimum for the frequency of births per year, using a goodness-of-fit χ^2 statistic. Compared to the Pearson's χ^2 test, the Walter and Elwood's seasonality test has greater power for detecting seasonal trends that follow a sinusoidal pattern, but it has the limitation that it may have limited power for seasonal trends that follow a non-sinusoidal pattern [30].

We then explored what time period during pregnancy is critical for being associated with ASD. For each person, we calculated maternal sun exposure, expressed as the cumulative number of sun hours per month, during the first plus second pregnancy trimester, the second plus third trimester, and the total duration of pregnancy, under the presumption that all pregnancies were carried to term and lasted 9 months. Thus, it became possible to assess the association between ASD and maternal sun exposure during pregnancy. As an example of such a calculation of the average sun exposure in hours per month: when born in January, sun hours in the last 3 months were calculated as ((0.5*sun hours in January) + sun hours in December + sun hours in November + (0.5* sun hours in October)). This value divided by 3 is the mean sun exposure in hours per month for the last 3 months of pregnancy.

Goodness-of-fit χ^2 tests can be difficult to interpret because of the arbitrary designation of months to season and their lack of power relative to other statistical tests. Bolton et al. discuss these limitations and point out that any one method of data analysis will likely be insufficient if used alone [15].

3. Results

In this retrospective study, we compared month of birth between a convenience sample of individuals with ASD registered with the Netherlands Society for Autism Spectrum Disorders and born between and including 1995 and 2008 (n = 3478) and persons born in the Netherlands in the same period (n = 2,716,876). **Table 1** shows the total number of cases and controls, and the number of individuals for each ASD disorder, broken down by sex.

	Cases				**Controls**	
	Total	**Male**	**Female**	**Unknown**	**Male**	**Female**
ASD	3478	2895	554	29	1,392,415	1,324,461
Autistic disorder	911	775	131	5	NI	
Asperger syndrome	627	547	75	5	NI	
PDD-NOS	1718	1407	293	18	NI	
Other*	297	227	67	3	NI	

Total numbers of autism cases (3478) and control population (2,716,876) births in the period 1995–2008 in the Netherlands. Unknown: The gender of these individuals was not included in the forms, but these individuals are included in the analysis. ASD: Autism spectrum disorders; NI: Not indicated; PDD-NOS: Pervasive developmental disorder not otherwise specified.

*Not analyzed further.

Table 1. Number of ASD cases and controls from the general population, by disorder and sex.

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3.1. ASD versus general population

The distribution of month of birth for individuals with ASD was different from that of the general population ($p < 0.0001$; χ^2-test), with the strongest divergence occurring in the period July–September (**Figure 1**). The month of birth distribution for the total group of individuals with ASD was associated with a sinusoidal curve, indicating the presence of a season-of-birth effect ($p = 0.02$; Walter and Elwood's χ^2-test).

3.2. Autism disorder versus general population

The distribution of month of birth for individuals with autistic disorder differed from that of the general Dutch population ($p = 0.01$; χ^2 test), with a peak in July (**Figure 2**). There seemed to be an excess of births in individuals with autistic disorder in the period from May to October, and a decline during November–April, with a nadir in February. However, there was no strong statistical support for sinusoidal trends over the year ($p = 0.09$; Walter and Elwood's χ^2).

3.3. Asperger syndrome versus general population

There was evidence, albeit limited, that the distribution of month of birth of individuals with Asperger was differently distributed than the distribution of the general population (**Figure 3**; $p = 0.06$; Pearson's χ^2 test). Births among individuals with Asperger syndrome seemed to peak in September and were relatively infrequent in June, while being approximately equally distributed over the remaining months of the year. In agreement with a visual inspection of the

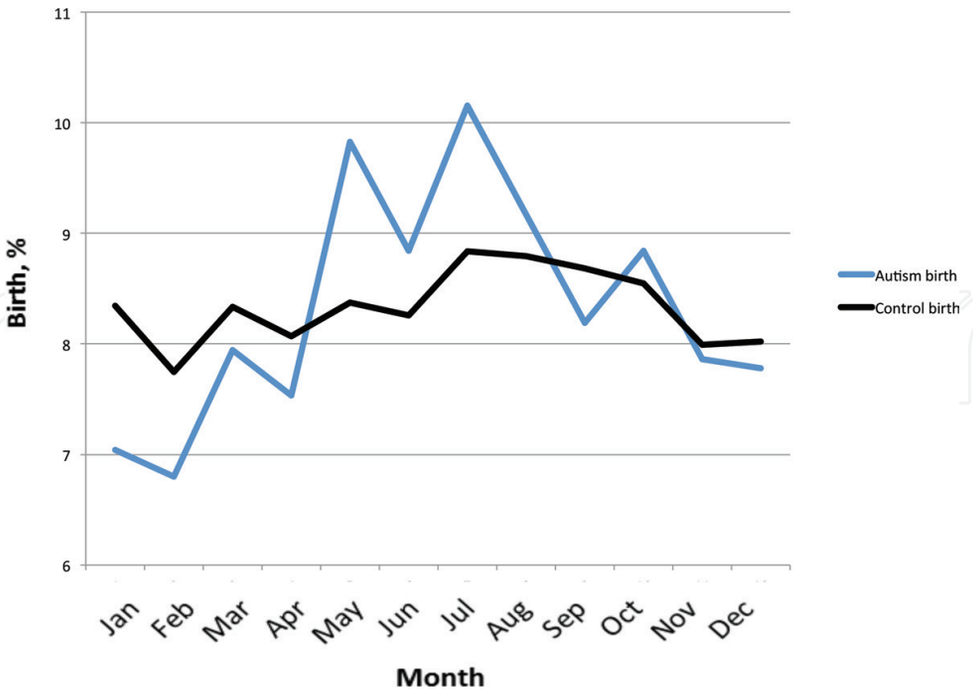

Figure 1. Relative distribution of births per month in ASD and the general population births born between 1995 and 2008. ASD birth reflect autism (blue line) and control birth reflect general population (black line).

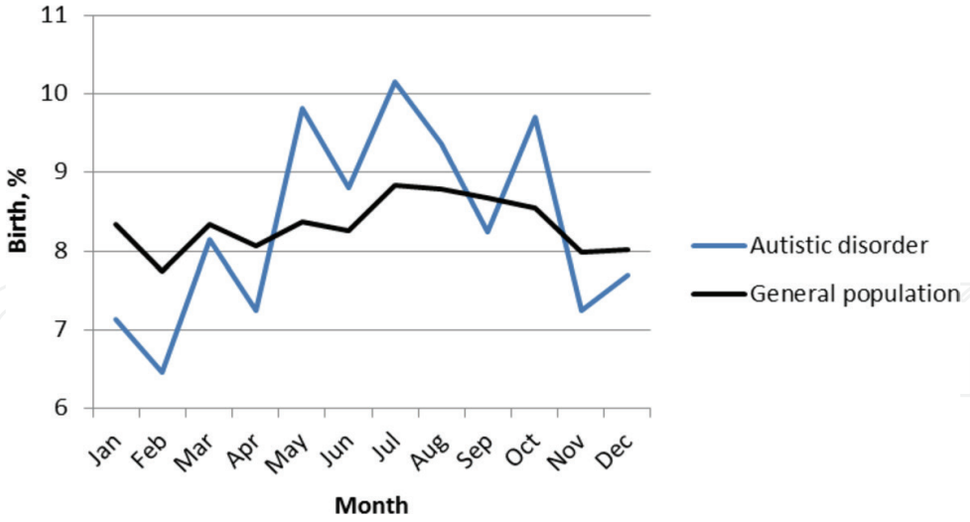

Figure 2. Relative distribution of births per month in autistic disorder and the general population births born between 1995 and 2008. Autistic disorder birth with blue line and general population with black line.

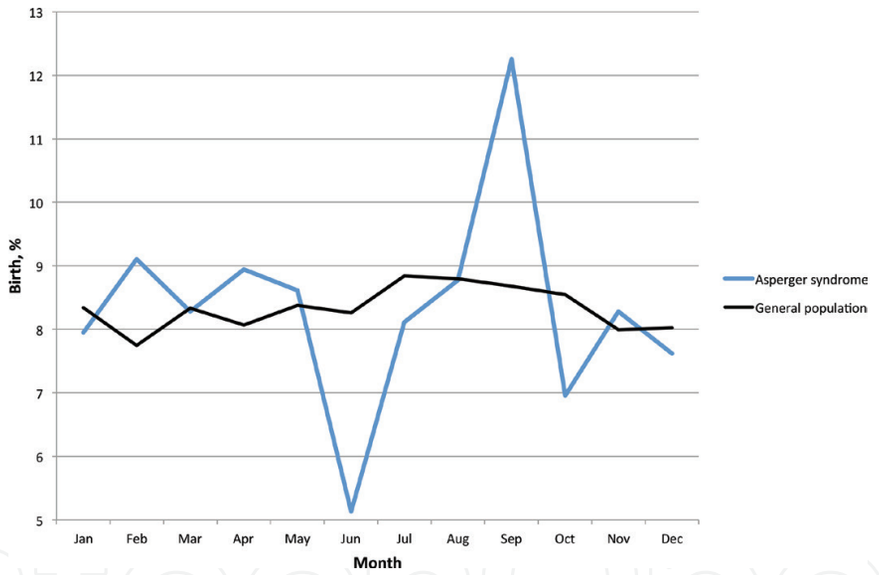

Figure 3. Relative distribution of births per month in Asperger and the general population births born between 1995 and 2008. Asperger syndrome birth with blue line and general population birth with black line.

data (**Figure 3**), there was no evidence that the birth distribution of the Asperger cases over the year was distributed as a sinusoid curve ($p = 0.60$; Walter and Elwood's χ^2).

3.4. Cumulative hours of sun in the Netherlands

Figure 4 shows the raw meteorological data of the mean number of hours of sun per month, averaged over the period 1998–2008 and averaged over the Netherlands. This number peaked in May and June and was lowest in November–January. From these data we calculated sun exposure, that is, the mean hours of sun during a period (trimester) in pregnancy (**Figure 5**).

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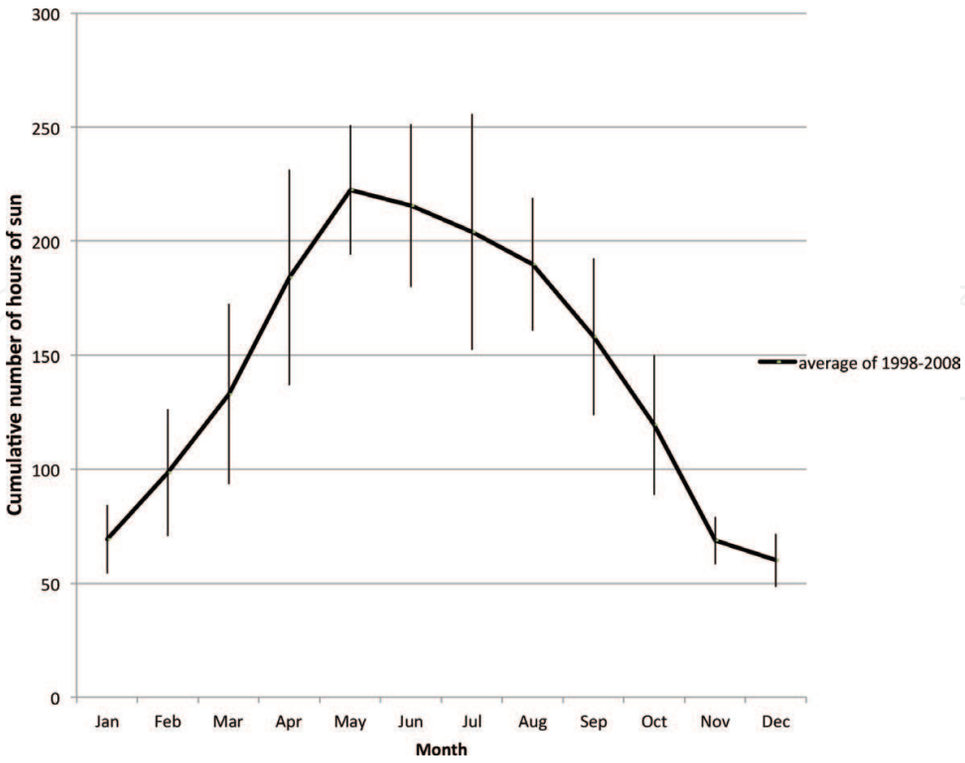

Figure 4. Mean monthly number of hours of sun (average ± 1SD) over the years 1998–2008, averaged over the Netherlands.

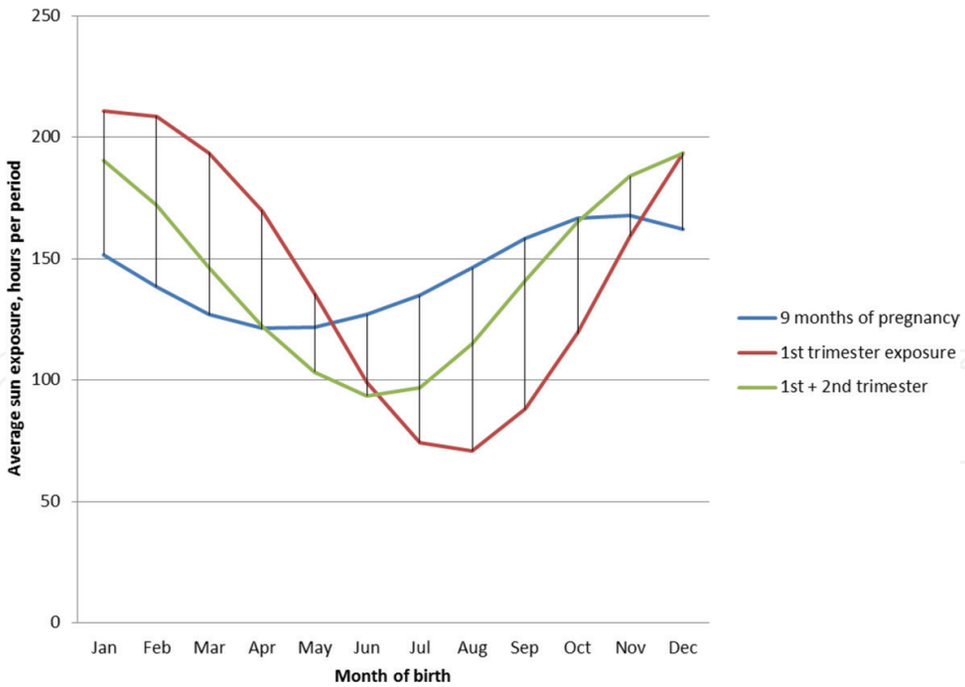

Figure 5. Trends of distribution of sun exposure during a given period in pregnancy, by month of birth. Data from the complete 9 months of pregnancy reflected in blue line, data from only the first trimester of pregnancy in red line, and data from first plus second trimester of pregnancy reflected with green line. For example, the mother of a person born in August had increasing exposure to sunlight in the first, second and third trimesters of the pregnancy that led to the birth of that person. Data from aggregated trimesters are effectively averaged estimates of individual trimesters.

Comparing these data to the complete 9 months pregnancy period, it became clear that the drop in sun exposure during the first trimester, more than the combination of first and second trimester, might explain the peak in July births of ASD. Such a relation was not observed when analyzing the second and third trimester or when combining the sun exposure of other combinations of trimesters (data not shown). These data support that sun exposure might be a risk factor for ASD.

4. Discussion

This retrospective study showed a difference in the distribution of months of birth for individuals with ASD compared to the general Dutch population, using a dataset several times larger than the largest autism study to date. For autistic disorder, an increased ASD births in July contributes to this difference. The birth data of ASD are distributed as a sinusoidal curve, implying seasonality over the year. This distribution of births per month for individuals with autistic disorder did differ from the distribution in the general Dutch population. In contrast, the distribution of births per month of individuals with Asperger was different from the general population and did not show a seasonal birth effect.

As the children included in this analysis were all diagnosed at the time when the DSM IV criteria were still valid and widely used we adopted this original classification [31]. The characteristic heterogeneity in disease expression was captured through the different categorical diagnoses, including autism, Asperger's syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS), as well as other regressive neurodevelopmental disorders of early childhood frequently associated with autistic symptoms (Rett's syndrome and childhood disintegrative disorder). With successive research the PDD-NOS group appeared increasingly doubtful, and all categories were eventually dropped in the current DSM V criteria [32]. Because of the large degree of heterogeneity also observed in our PDD-NOS group, we did not further analyze this group in the current study.

The ratio male versus female cases in this study was approximately 4:1, similar as that known in the general ASD population [17]. The χ^2 test with 11 df data for male and female ASD was not shown, but this test was significant for male ASD births, while not for female ASD births. This implies a difference in distribution of month of birth of male individuals with ASD compared to the general population. A study on singleton and multiple ASD births described birth peaks in April, July, and October for singleton ASD births [8]. Our study confirmed the birth peak in July for the ASD births, but not for October, while April showed the lowest number of ASD births in this study. Hebert et al. studied the association of ASD with season of birth in the UK and described an association between ASD and spring births, but the analysis was weak due to the small sample size (86 children with ASD) [9]. This study differs with our findings, as April had the smallest number of ASD births. The study of Hebert used a cohort that recruited pregnant women resident in Avon, UK, while we studied the total Dutch population of ASD. A Dutch study in 2000 compared mentally retarded autistic disorder patients and mentally retarded individuals with PDD-NOS, with each other and with birth data of the

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general Dutch national population [18]. No difference was observed in birth distribution of the patients with autistic disorder compared to the general Dutch population, contrary to our findings. This difference might be explained by the difference in case numbers, (540 vs. 911) and the variation in years of birth of the case between 1932 and 1992, while in our study the year of birth span was 14 years only.

An association was suggested based on the According to the Centers for Diseases Control and Prevention, February is the month with the highest percentage of influenza cases (nearly 50% of all cases). This research identifies environmental factors that are possibly relating to autistic disorder. Early life history reveals increased prevalence of viral insult and manifestation of neurological signs in the early development of the ASD children that also reach statistical significance. Several of these, stiffness upon delivery, generalized seizures and infantile spasms, and sleep disturbance might be further investigated as early risk signs.

Our study contained a large sample size (3478 ASD children) with a large number of cases and controls per month, strengthening our analysis. However, our test would even be more valid when instead of births in the general Dutch population, the date of birth of relatives of the case group (for example, siblings of the individuals with ASD) would be used as controls. This study included only Dutch ASD so confounding from inter-country-specific factors was not applicable for this study. In this study, there was no recall bias, because the date of birth is fixed information that does not interfere with the detection of ASD. Sun exposure was also not a confounding factor, as it has no influence on the date of birth. Interfering genetic factors cannot count for a 100% risk while environmental factors also contribute to the risk of developing ASD. This study is an initial step to generating hypotheses and data of cumulative hours of sun per month can be used for an explorative analysis to find an association. The distribution of month of birth within the ASD group showed that the birth in July coincided with almost the lowest sun exposure in the first trimester and first plus second trimester of pregnancy. This also counted for the peak in July births for autistic disorder. Comparing the distribution of month of birth for autistic disorder with the sun exposure, we observed a decrease in September with an associated highest sun exposure in the first and second trimester for the trimesters separately.

A previous study [11] showed that the birth date distribution for individuals with autism spectrum disorders (ASD), including singletons and multiple births, differed from the general population. The presence of seasonal trends in ASD singletons and concordant multiple births suggested a role for non-heritable factors operating during the pre- or perinatal period, even among cases with a genetic susceptibility [8]. When analyzing the variation in season of birth and the ASD prevalence a correlation was found with the effective latitude and this is consistent with maternal vitamin D being a risk factor for development of autistic disorder. Maternal vitamin D affects fetal brain development and the maternal immune system status during pregnancy [11]. Support for the maternal vitamin D deficiency theory has been reported based on rat studies, but specifically for multiple sclerosis and schizophrenia [19, 20]. However, rat study by Féron et al. showed that vitamin D deficiency reduces the expression of a number of genes involved in neuronal structure [21]. The fetus is during development entirely dependent on the mother for its supply of 25-hydroxyvitamin D(25(OH)D [25],

which is a product of the vitamin D metabolism after the metabolizing step in the skin by exposure to ultraviolet light. From 4 weeks of gestation to birth, 25(OH)D diffuses across the placenta [26], of which 1,25(OH)2 vitamin D is produced by the fetal kidneys and the placenta [23, 27]. 1,25(OH)2D does not readily cross the placenta [27]. It is also known that cord blood 25(OH)D concentrations in infants, as in maternal blood, vary seasonally [28, 29]. The brain develops mostly in the later stages of pregnancy [22]. Maternal infectious diseases during pregnancy can be an indicator for a vitamin D deficiency, and thus maternal infectious diseases can adversely affect brain development [11]. Maternal serum level of 1,25-dihydroxyvitamin D more than doubles early in the first trimester in human pregnancy [23, 24], indicating a high need for vitamin D during pregnancy and supports that a low sun exposure is a risk factor for ASD.

In conclusion, a drop in sun exposure in the first trimester of pregnancy might explain the peak in July births with an associated risk for ASD development. As a result, a deficiency of vitamin D in the first trimester of pregnancy is a risk factor for ASD as vitamin D deficiency in the developing brain of a fetus may disturb the development of the brain and therefore causes functional defects [10, 19]. The action of UV rays in sunlight on the skin is the most powerful natural source of vitamin D generation, and factors that reduce the amount and intensity of sunlight significantly increase the risk of vitamin D deficiency [30]. These results support the need for future study of autistic birth dates with detailed pre- and perinatal information that may lead to discovering specific risk factors for autism in select groups.

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References

[1] Chess S. Autism in children with congenital rubella. J Autism Child Schizophr 1971;1:33–47.

[2] Cannell JJ. Autism and vitamin D. Med Hypotheses 2008;70:750–759.

[3] Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. Arch Pediatr Adolesc Med 2005;159:151–157.

[4] Roberts EM, English PB, Grether JK, Windham GC, Somberg L, Wolff C. Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. Environ Health Perspect 2007;115:1482–1489.

[5] Bartlik BD. Monthly variation in births of autistic children in North Carolina. J Am Med Womens Assoc 1981;36:363–368.

[6] Barak Y, Ring A, Sulkes J, Gabbay U, Elizur A. Season of birth and autistic disorder in Israel. Am J Psychiatry 1995;152:798–800.

[7] Gillberg C. Do children with autism have March birthdays? Acta Psychiatr Scand 1990;82:152–156.

[8] Mouridsen SE, Nielsen S, Rich B, Isager T. Season of birth in infantile autism and other types of childhood psychoses. Child Psychiatry Hum Dev 1994;25:31–43.

[9] Konstantareas MM, Hauser P, Lennox C, Homatidis S. Season of birth in infantile autism. Child Psychiatry Hum Dev 1986;17:53–65.

[10] Tanoue Y, Oda S, Asano F, Kawashima K. Epidemiology of infantile autism in southern Ibaraki, Japan: differences in prevalence in birth cohorts. J Autism Dev Disord 1988;18:155–166.

[11] Lee LC, Newschaffer CJ, Lessler JT, Lee BK, Shah R, Zimmerman AW. Variation in season of birth in singleton and multiple births concordant for autism spectrum disorders. Paediatr Perinat Epidemiol 2008;22:172–179.

[12] Hebert KJ, Miller LL, Joinson CJ. Association of autistic spectrum disorder with season of birth and conception in a UK cohort. Autism Res 2010;3:185–190.

[13] Kolevzon A, Weiser M, Gross R, et al. Effects of season of birth on autism spectrum disorders: fact or fiction? Am J Psychiatry 2006;163:1288–1290.

[14] Landau EC, Cicchetti DV, Klin A, Volkmar FR. Season of birth in autism: a fiction revisited. J Autism Dev Disord 1999;29:385–393.

[15] Bolton P, Pickles A, Harrington R, Macdonald H, Rutter M. Season of birth: issues, approaches and findings for autism. J Child Psychol Psychiatry 1992;33:509–530.

[16] Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, Charman T. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). Lancet 2006;368:210–215.

[17] Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics 2004;113:e472–e486.

[18] Autism Spectrum Disorders: a lifetime of difference. The Hague: Health Council of the Netherlands. Nr. 2009/09; ISBN: 978-90-5549-760-7.

[19] Grant WB, Soles CM. Epidemiologic evidence supporting the role of maternal vitamin D deficiency as a risk factor for the development of infantile autism. Dermato-Endocrinology 2009;1(4):223–228.

[20] Fombonne E. Epidemiology of autistic disorder and other pervasive developmental disorders. J Clin Psychiatry 2005;66(suppl 10):3–8.

[21] Cannell JJ. Autism and vitamin D. Med Hypotheses 2008;70(4):750–759.

[22] Ross AC, Taylor CL, Yaktine AL, Del Valle HB, Eds. Dietary Reference Intakes Calcium and Vitamin D. Institute of Medicine, The national Academies Press, Washington DC, US; 2011, pp. 75–124.

[23] Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res 2009; 65(6):591–598.

[24] https://www.cdc.gov/ncbddd/autism/documents/addm-fact-sheet---comp508.pdf

[25] http://www.autisme.nl/media/48545/engelse_vertaling.pdf

[26] van der Ven E, Termorshuizen F, Laan W, Breetvelt EJ, van Os J, Selten JP. An incidence study of diagnosed autism-spectrum disorders among immigrants to the Netherlands. Acta Psychiatr Scand. 2013;128(1):54–60.

[27] http://www.knmi.nl/nederland-nu/klimatologie/maand-en-seizoensoverzichten

[28] Walter SD, Eldwood JM. A test for seasonality of events with a variable population at risk. Br J Prev Soc Med 1975;29:18–21.

[29] Disanto G, Handel AE, Para AE, Ramagopalan SV, Handunnetthi L. Season of birth and anorexia nervosa. Br J Psychiatry 2011;198(5):404–405.

[30] Walter SD. Seasonality of mania: a reappraisal. Br J Psychiatry 1977;131(10):345–350.

[31] http://dsm.psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890420249.dsm-iv-tr

[32] http://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596