

- 2 Sturdy PM, Victor CR, Anderson HR, Bland JM, Butland BK, Harrison BD, et al. Psychological, social and health behaviour risk factors for deaths certified as asthma: a national case-control study. *Thorax* 2002;57:1034-9.
- 3 Sears MR, Taylor DR, Print CG, Lake DC, Li QQ, Flannery EM, et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;336:1391-6.
- 4 Chung KF. The current debate concerning beta-agonists in asthma: a review. *J R Soc Med* 1993;86:96-100.
- 5 Beasley R, Pearce N, Crane J, Windom H, Burgess C. Asthma mortality and inhaled beta agonist therapy. *Aust N Z J Med* 1991;21:753-63.
- 6 Blais L, Ernst P, Suissa S. Confounding by indication and channeling over time: the risks of beta 2-agonists. *Am J Epidemiol* 1996;144:1161-9.
- 7 Meier CR, Jick H. Drug use and pulmonary death rates in increasingly symptomatic asthma patients in the UK. *Thorax* 1997;52:612-7.
- 8 Williams C, Crossland L, Finnerty J, Crane J, Holgate S, Pearce N, et al. Case-control study of salmeterol and near-fatal attacks of asthma. *Thorax* 1998;53:7-13.
- 9 Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501-6.
- 10 Lanes SF, Garcia Rodriguez LA, Huerta C. Respiratory medications and risk of asthma death. *Thorax* 2002;57:683-6.
- 11 Guite HF, Dundas R, Burney PG. Risk factors for death from asthma, chronic obstructive pulmonary disease, and cardiovascular disease after a hospital admission for asthma. *Thorax* 1999;54:301-7.
- 12 Suissa S, Hemmelgarn B, Blais L, Ernst P. Bronchodilators and acute cardiac death. *Am J Respir Crit Care Med* 1996;154:1598-602.
- 13 Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332-6.
- 14 Graham V, Lasserson T, Rowe BH. Antibiotics for acute asthma. *Cochrane Database Syst Rev* 2001;(2):CD 002741.
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Timing of birth and risk of multiple sclerosis: population based study

Cristen J Willer, David A Dymnt, A Dessa Sadovnick, Peter M Rothwell, T Jock Murray, George C Ebers for the Canadian Collaborative Study Group

Abstract

Objectives To determine if risk of multiple sclerosis (MS) is associated with month of birth in countries in the northern hemisphere and if factors related to month of birth interact with genetic risk.

Design Population based study with population and family based controls and a retrospective cohort identified from death certificates. A post hoc pooled analysis was carried out for large northern datasets including Sweden and Denmark.

Setting 19 MS clinics in major cities across Canada (Canadian collaborative project on the genetic susceptibility to multiple sclerosis); incident cases of MS from a population based study in the Lothian and Border regions of Scotland; and death records from the UK Registrar General.

Populations 17 874 Canadian patients and 11 502 British patients with multiple sclerosis.

Main outcome measure Diagnosis of multiple sclerosis.

Results In Canada (n = 17 874) significantly fewer patients with MS were born in November compared with controls from the population census and unaffected siblings. These observations were confirmed in a dataset of British patients (n = 11 502), in which there was also an increase in the number of births in May. A pooled analysis of datasets from Canada, Great Britain, Denmark, and Sweden (n = 42 045) showed that significantly fewer (80.5%) people with MS were born in November and significantly more (9.1%) were born in May. For recent incident data, the effect of month of birth was most evident in Scotland, where MS prevalence is the highest.

Conclusions Month of birth and risk of MS are associated, more so in familial cases, implying interactions between genes and environment that are related to climate. Such interactions may act during gestation or shortly after birth in individuals born in the northern countries studied.

Introduction

Studies of twins, adoptees, half siblings, and families¹⁻⁴ have led to a widely accepted notion that multiple sclerosis (MS) is a complex trait in which susceptibility is determined by the interplay of genes and environmental factors. Environment seems to influence risk at a population level, but specific details remain unclear. The most striking clue to the role of environment has always been the gradient with latitude (see bmj.com).

Studies of month of birth and risk of MS have been carried out in several cohorts of people with MS, but sample sizes, ethnic groups, and statistical methods differed for each study and findings have been inconsistent.⁵⁻⁹ Although significant differences in month of birth compared with population based controls have been reported, they have not been for the same months.

Methods

Data on month of birth, along with detailed information on demographics and clinical and family history, were collected as part of the population based longitudinal Canadian collaborative project on genetic susceptibility to multiple sclerosis¹⁰ in 17 874 patients with MS. The first control group comprised all the recorded births in Canada from 1926 to 1970 (Statistics Canada). A second control group comprised unaffected siblings of people with MS.

As Scandinavian studies have shown an increase of MS in people born in spring, we hypothesised a similar increase, but we analysed each month separately. We compared the births in a single month with the 11 other months for cases and controls (population or siblings). For months for which we found no previous evidence of association, we corrected the P value for the 12 comparisons using Bonferroni correction.



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Department of Biostatistics, University of Michigan, Ann Arbor, MI 48109, USA

Cristen J Willer
postdoctoral fellow

Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN

David A Dymnt
doctoral student

Department of Medical Genetics and Faculty of Medicine (Division of Neurology), University of British Columbia, Vancouver, BC, Canada V6T 2B5
A Dessa Sadovnick
professor

Department of Clinical Neurology, Radcliffe Infirmary, University of Oxford OX2 6HE
Peter M Rothwell
professor

George C Ebers
action research
professor

Dalhousie University, Halifax, NS, Canada B3H 4R2
T Jock Murray
professor of medicine

Correspondence to: G C Ebers
george.ebers@cneuro.ox.ac.uk

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We obtained datasets of patients from England, Wales (n = 8702), and Scotland (n = 2356) from death certificates that mentioned "multiple sclerosis" and were registered in 1979-91. The controls for this sample were obtained from randomly selected death certificates of individuals born in the same year and country, with no mention of "multiple sclerosis." We also studied newly diagnosed cases from a population based study of the incidence of MS in the Lothian and Border regions of Scotland performed in 1992-5 inclusive (n = 444)¹¹ and used Scottish population birth records from 1940 to 1980 as controls (General Register Office Scotland).

Results

In the Canadian dataset (n = 17 874), 8.5% fewer people with MS were born in November; this was significant even after we corrected for the 12 monthly comparisons (1257 observed *v* 1373 expected, P = 0.013) (table 1). The peak birth month for people with MS was offset six months, in May, though this was not significant (P = 0.15). We found no difference within Canadian patients by sex, site of ascertainment, or decade of birth. Population control results, weighted to match patients with MS for year of birth, were similar to non-weighted controls (not shown). Among 67 Canadian patients born in the southern hemisphere, eight were born in November and two in May, suggesting a reversal of the pattern in northern countries.

When we compared the dataset of British patients with MS, ascertained through death certificates and from incident cases (n = 11 502), with controls obtained via similar methods we found significantly fewer people with MS had been born in November (10.0%, P < 0.0001) and significantly more had been born in May (16.3%, P = 0.0003) (see *bmj.com*). The number born in December was also significantly lower (P = 0.028), but this was not significant when we corrected for multiple comparisons. We combined the data and the confidence intervals of the odds ratios for May and November in each group substantially overlapped (odds ratio 1.30, 95% confidence interval 1.17 to 1.44, for cases from England and Wales; 1.17, 0.94 to 1.47, for Scottish death certificate cases; and 1.89, 1.09 to 3.28, for Scottish incident cases).

In a post hoc analysis we added Danish⁵ (n = 6276) and Swedish⁶ (n = 6393) samples to our Canadian

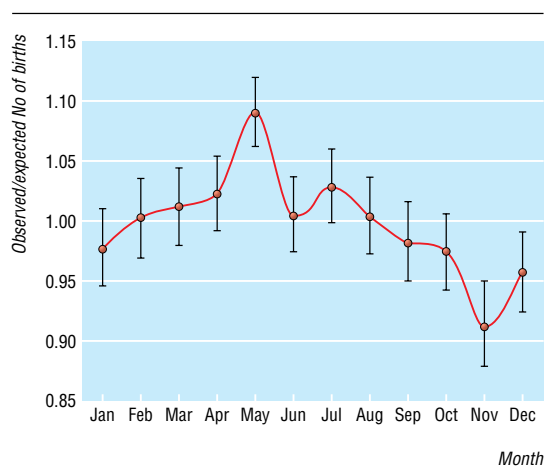


Fig 1 Pooled analysis of observed/expected births in people with multiple sclerosis in Canadian, British, Danish, and Swedish studies (n = 42 045) with 95% confidence intervals

(n = 17 874) and British samples (n = 11 502; total n = 42 045). In this combined sample significantly more people with MS were born in May (9.1%) and significantly fewer were born in November (8.5%) (P values for May and November were all < 0.0001) (fig 1). This represents a 19% (odds ratio 1.19, 95% confidence interval 1.14 to 1.25) decreased risk of MS for those born in November compared with those born in May.

In the Canadian dataset, we used a second control group of matched unaffected siblings. We had complete data on 9248 unaffected siblings from 7450 patients with MS. Index cases were matched with one non-twin sibling, which resulted in a dataset of 4232 affected-unaffected sibling pairs. We compared affected siblings with their matched unaffected siblings furthest in age for November birth and observed 273 pairs in which the affected member of the pair was born in November and 343 where the unaffected sibling was born in November (P = 0.0048).

We tested whether the environmental component related to month of birth might contribute to familial risk, perhaps by interacting with susceptibility genes predictably enriched in families with multiple cases of MS.¹⁰ Among affected people with a family history of MS we found 16.2% fewer were born in November relative to population controls compared with 3.0%

Observed number of people in Canada with multiple sclerosis (MS) compared with expected number, according to month of birth

Month	All births (1926-70) (n = 13 675 451)	People with MS (n = 17 874)		Observed/expected births (95% CI)	Month specific χ^2 test of association	P value
		Observed No of births	Expected No of births			
Jan	1 096 651	1425	1433	0.99 (0.94 to 1.05)	0.05	0.82
Feb	1 032 882	1369	1350	1.02 (0.96 to 1.07)	0.29	0.59
Mar	1 187 630	1533	1552	0.99 (0.93 to 1.04)	0.26	0.61
Apr	1 168 350	1532	1527	1.00 (0.95 to 1.06)	0.02	0.89
May	1 238 935	1675	1619	1.04 (0.99 to 1.09)	2.10	0.15
Jun	1 202 046	1512	1571	0.96 (0.91 to 1.01)	2.43	0.12
Jul	1 193 942	1608	1561	1.03 (0.98 to 1.08)	1.58	0.21
Aug	1 156 480	1553	1512	1.03 (0.98 to 1.08)	1.24	0.27
Sept	1 157 627	1525	1513	1.01 (0.96 to 1.06)	0.10	0.75
Oct	1 114 282	1455	1456	1.00 (0.95 to 1.05)	0.00	0.97
Nov	1 050 758	1257	1373	0.91 (0.85 to 0.97)	10.67	0.0011
Dec	1 075 868	1430	1406	1.02 (0.96 to 1.07)	0.44	0.51

*P = 0.013 after Bonferroni correction for multiple comparisons.

fewer among those with no family history of MS ($\chi^2 = 3.92$, $P = 0.050$).

We also compared the odds ratio for increased risk of MS for people born in May compared with November. The highest odds ratio for May/November risk was in Scotland, followed by Denmark, Sweden, and Canada (fig 2).

Discussion

We have conclusively shown the association between month of birth and risk of MS in northern countries. The sample size, internal replications, and selection of appropriate controls indicate that this is unlikely to be an artefact. Our pooled data show that being born in May is associated with increased risk, and the Canadian and British datasets clearly show that people born in November have the lowest risk. Correlation of specific years of increased risk related to season with features such as ultraviolet radiation, temperature, or weather patterns may help to elucidate this effect further.

Although the birth month results in MS now seem clear, the interpretation is not. May and November show significance in the pooled analysis and the peaks of altered risk are exactly six months apart. Although the reduced risk for November seems to also exist for December births in some datasets, the changes in risk are remarkably discrete. The abrupt change in risk by month suggests a threshold effect for both increased and decreased risk, something that is not easily explained.

Possible explanations of association

The risk factor(s) responsible for the effect of timing of birth must vary seasonally and probably interact with development of the central nervous system or immune systems, or both. Among candidate factors are maternal folate,¹² correlates of infant birth weight and virus infection, and factors also implicated in the effect of season of birth on schizophrenia.¹³ Undoubtedly other cyclic interactions remain to be identified.

Previous findings of associations between higher latitudes and risk of MS (Sardinians and Sami being notable exceptions) have suggested that exposure to the

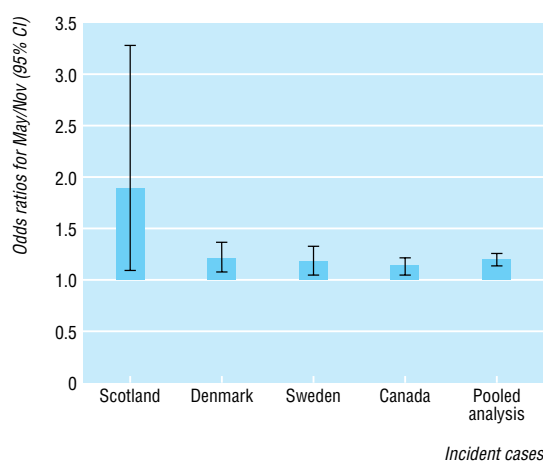


Fig 2 Odds ratios for people with multiple sclerosis being born in May/November among incident cases in northern hemisphere countries

What is already known on this topic

Susceptibility to multiple sclerosis (MS) is influenced by genetic and environmental factors

An association with latitude in early life has been shown in migrants from regions of differing risk

A maternal parent of origin effect shown in half siblings with MS from Canada suggested that environment acts in gestation or the neonatal period to determine risk for this adult onset disease

What this study adds

In northern countries the risk of MS is greater for people born in May and lower for those born in November

This effect is greater in Scotland, where the population prevalence of this disease is highest

These findings support suggestions from studies in twins and half siblings that the gestational or neonatal environment, or both, influence the risk of MS later in life

sun may account for the geographical variation of MS.¹⁴ Most biologically active vitamin D is generated in the skin with exposure to ultraviolet radiation¹⁵ and an increased risk of MS related to month of birth could reflect well documented seasonal deficiency in maternal concentrations of vitamin D.¹⁶ Vitamin D treatment reduces severity of symptoms and progression in experimental autoimmune encephalomyelitis (EAE), which is a mouse model of MS.¹⁷ Furthermore, exposure to sun during childhood is associated with a reduced risk of multiple sclerosis,¹⁸ and this may also extend to timing of birth. If the excess of MS in those born in May is related to maternal vitamin D deficiency, studies on blood concentrations suggest that the end of the second or the third trimester are the crucial time points.¹⁶ Vitamin D receptors are present in the brain, and gestational vitamin D deficiency has striking effects on brain development in experimental animals.¹⁹

The observed May/November birth ratio in living incident cases from Scotland (1.89), Denmark (1.22),⁵ Sweden (1.18),⁶ and Canada (1.13) decreases in order of population prevalence (fig 2). This suggests that the seasonal birth effect may be connected with environmental factors determining prevalence rates. These are powerful, seem to act at a broad population level,¹⁻³ and may hold the key to disease prevention. The “parent of origin” effect, recently reported in MS,²⁰ may suggest that, at least in part, environmental effects are maternally mediated and influence development in the nervous or immune system, or both.

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Group includes D W Paty, S A Hashimoto, V Devonshire, J Hooge, J Oger, L Kastrukoff, and T Traboulsee (Vancouver); L Metz (Calgary); S Warren (Edmonton); W Hader (Saskatoon); R Nelson and M Freedman (Ottawa); D Brunet (Kingston); J Paulseth (Hamilton); G Rice and M Kremenchutzky (London); P O'Connor, T Gray, and M Hohol (Toronto); P Duquette and Y Lapierre (Montreal); J-P Bouchard (Quebec City); V Bhan and C Maxner (Halifax); and W Pryse-Phillips and M Stefanelli (St Johns).

Contributors: See bmj.com

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Competing interests: None declared.

Ethical approval: The study was approved by the University of Western Ontario and the University of British Columbia, which were the two main sites of data collection. Each Canadian MS clinic obtained ethical approval from their local review board.

- 1 Willer CJ, Dymant DA, Risch NJ, Sadovnick AD, Ebers GC. Twin concordance and sibling recurrence rates in multiple sclerosis. *Proc Natl Acad Sci USA* 2003;100:12877-82.
- 2 Ebers GC, Sadovnick AD, Risch NJ. A genetic basis for familial aggregation in multiple sclerosis. Canadian Collaborative Study Group. *Nature* 1995;377:150-1.
- 3 Ebers G, Sadovnick A, Dymant D, Yee I, Willer C, Risch N, et al. A parent of origin effect in multiple sclerosis: observations in half siblings. *Lancet* 2004;363:847-50.
- 4 Ebers GC, Yee IM, Sadovnick AD, Duquette P. Conjugal multiple sclerosis: population-based prevalence and recurrence risks in offspring. Canadian Collaborative Study Group. *Ann Neurol* 2000;48:927-31.
- 5 Kurtzke JF, Beebe GW, Norman JE, Jr. Epidemiology of multiple sclerosis in US veterans: I. race, sex, and geographic distribution. *Neurology* 1979;29:1228-35.
- 6 Dean G. Annual incidence, prevalence, and mortality of multiple sclerosis in white South-African-born and in white immigrants to South Africa. *BMJ* 1967;ii:724-30.

- 7 Sadovnick AD, Yee IM. Season of birth in multiple sclerosis. *Acta Neurol Scand* 1994;89:190-1.
- 8 Salemi G, Ragonese P, Aridon P, Reggio A, Nicoletti A, Buffa D, et al. Is season of birth associated with multiple sclerosis? *Acta Neurol Scand* 2000;101:381-3.
- 9 Torrey EF, Miller J, Rawlings R, Yolken RH. Seasonal birth patterns of neurological disorders. *Neuroepidemiology* 2000;19:177-85.
- 10 Sadovnick AD, Risch NJ, Ebers GC. Canadian collaborative project on genetic susceptibility to MS, phase 2: rationale and method. Canadian Collaborative Study Group. *Can J Neurol Sci* 1998;25:216-21.
- 11 Rothwell PM, Charlton D. High incidence and prevalence of multiple sclerosis in south east Scotland: evidence of a genetic predisposition. *J Neurol Neurosurg Psychiatry* 1998;64:730-5.
- 12 Branda RF, Eaton JW. Skin color and nutrient photolysis: an evolutionary hypothesis. *Science* 1978;201:625-6.
- 13 Torrey EF, Miller J, Rawlings R, Yolken RH. Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. *Schizophr Res* 1997;28:1-38.
- 14 Acheson ED, Bachrach CA, Wright FM. Some comments on the relationship of the distribution of multiple sclerosis to latitude, solar radiation and other variables. *Acta Psychiat (Scand)* 1960;35(suppl 147):132.
- 15 Holick MF, Smith E, Pincus S. Skin as the site of vitamin D synthesis and target tissue for 1,25-dihydroxyvitamin D3. Use of calcitriol (1,25-dihydroxyvitamin D3) for treatment of psoriasis. *Arch Dermatol* 1987;123:1677-83a.
- 16 Vieth R, Cole DE, Hawker GA, Trang HM, Rubin LA. Wintertime vitamin D insufficiency is common in young Canadian women, and their vitamin D intake does not prevent it. *Eur J Clin Nutr* 2001;55:1901-7.
- 17 Cantorna MT, Hayes CE, DeLuca HF. 1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. *Proc Natl Acad Sci USA* 1996;93:7861-4.
- 18 Van der Mei IA, Ponsonby AL, Dwyer T, Blizzard L, Simmons R, Taylor BV, et al. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. *BMJ* 2003;327:316.
- 19 McGrath JJ, Feron FP, Burne TH, Mackay-Sim A, Eyles DW. Vitamin D3-implications for brain development. *J Steroid Biochem Mol Biol* 2004;89-90:557-60.
- 20 20McLeod JG, Hammond SR, Hallpike JF. Epidemiology of multiple sclerosis in Australia. With NSW and SA survey results. *Med J Aust* 1994;160:117-22.

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Reinstitutionalisation in mental health care: comparison of data on service provision from six European countries

Stefan Priebe, Alli Badesconyi, Angelo Fioritti, Lars Hansson, Reinhold Kilian, Francisco Torres-Gonzales, Trevor Turner, Durk Wiersma

Abstract

Objective To establish whether reinstitutionalisation is occurring in mental health care and, if so, with what variations between western European countries.

Design Comparison of data on changes in service provision.

Setting Six European countries with different traditions of mental health care that have all experienced deinstitutionalisation since the 1970s—England, Germany, Italy, the Netherlands, Spain, and Sweden.

Outcome measures Changes in the number of forensic hospital beds, involuntary hospital admissions, places in supported housing, general psychiatric hospital beds, and general prison population between 1990-1 and 2002-3.

Results Forensic beds and places in supported housing have increased in all countries, whereas changes in involuntary hospital admissions have been inconsistent. The number of psychiatric hospital beds has been reduced in five countries, but only in two countries does this reduction outweigh the number of additional places in forensic institutions and

supported housing. The general prison population has substantially increased in all countries.

Conclusions Reinstitutionalisation is taking place in European countries with different traditions of health care, although with significant variation between the six countries studied. The precise reasons for the phenomenon remain unclear. General attitudes to risk containment in a society, as indicated by the size of the prison population, may be more important than changing morbidity and new methods of mental healthcare delivery.

Introduction

Since the 1950s, deinstitutionalisation has dominated mental healthcare reforms throughout western Europe. Large asylums have been closed or downsized, and the total number of psychiatric hospital beds has

Unit for Social and Community Psychiatry, Queen Mary University of London, Newham Centre for Mental Health, London E13 8SP

Stefan Priebe
professor of social and community psychiatry
Alli Badesconyi
specialist registrar
Trevor Turner
honorary senior lecturer

AUSL Rimini, Italy
I-47900

Angelo Fioritti
medical director

Department of Nursing, University of Lund, Sweden
S-22100

Lars Hansson
professor of psychology
continued over



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