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Season of birth and Alzheimer's disease: a population-based study in Saguenay-Lac-St-Jean/Québec (IMAGE Project)

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SYNOPSIS The birth distribution of 399 cases of Alzheimer's disease (AD) identified in the region of Saguenay-Lac-St-Jean (Québec) was compared with that of: (*a*) the population currently living in the area; and (*b*) the population born during the same period in the area. AD cases have been recruited since 1986 by the IMAGE Project. Cases and controls were grouped according to the month of birth and according to the day of birth using density estimation. Analyses showed a significant deficit of births in the month of May. We believe these preliminary results deserve further attention and we suggest two possible explanations that could lead to a deficit of AD births at specific periods during the year.

INTRODUCTION

Seasonality of births has been thoroughly investigated in human populations (James, 1990; Lam & Miron, 1991). Various biological and sociocultural factors have been proposed to explain this phenomenon and its variations across populations. However, 'the seasonality of births remains a major unresolved puzzle in empirical demography' (Lam & Miron, 1991).

The relationship between various medical conditions and the date of birth of the affected individuals has also attracted attention for some time (Bailar & Gurian, 1967). This relationship has been investigated in different psychiatric disorders and neurological illnesses; the results, however, have been mainly inconclusive, or remain to be confirmed by further studies (for a review, see Fossey & Shapiro, 1992). The most significant data have been obtained with schizophrenia, for which a seasonality effect, i.e. a slight excess of winter births, is now recognized as a valid observation (Öhlund *et al.* 1991). Many aetiological hypotheses have been put forward to explain this finding (Bradbury & Miller, 1985) although the most cited is that some unknown environmental agent, like a virus, acting at a specific moment of the year, would attack the brain of the foetus or the newborn, leaving a mark that would allow for later development of the disease (Fuller Torrey *et al.* 1988; Kendell & Adams, 1991).

Alzheimer's disease (AD) is characterized by progressive loss of memory and a general deterioration of all cognitive functions, eventually leading to dementia. The role of genetic factors has been clearly established in the aetiology of early-onset familial AD (St Clair, 1994). In late-onset AD, the allele $\epsilon 4$ of apolipoprotein E appears as a major risk factor among both familial and sporadic cases (Saunders *et al.* 1993); however, the exact genetic role remains unclear and environmental components cannot be ruled out as causal factors (Haines, 1991; Gatz *et al.* 1994). As it has been hypothesized for schizophrenia, such an environmental factor could affect the brain of an individual long before he/she develops clinical signs of the disease, possibly with an intensity that fluctuates throughout the year. If such was the case, we would expect a birth distribution

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among individuals with AD that was different from that of the rest of the population.

This hypothesis has recently been investigated in four different studies (Philpot *et al.* 1989; Dysken *et al.* 1991; Henderson *et al.* 1991; Vitiello *et al.* 1991). Philpot and his colleagues found an excess of births in the first trimester of the year for sporadic cases, as opposed to those with a family history of dementia. None of the three other studies was able to reproduce these results, or to find any significant seasonal fluctuations in AD births. We believe that these studies have been inconclusive mainly because of methodological shortcomings.

The IMAGE project is a multidisciplinary research initiative that seeks to elucidate the causes of AD. It has been working on the establishment of a register of AD cases in the region of Saguenay-Lac-St-Jean (SLSJ) in Québec since 1986. It is now possible to use this register as a basis to conduct populational studies in order to avoid the principal biases attributable to the selection of cases in hospital settings. We report on the seasonal distribution of births in the IMAGE Project population-based sample of AD patients and we test the hypothesis of an association between the time of birth of an individual and its future risk of developing AD.

METHOD

Cases

The IMAGE Project has organized an extensive field network to recruit cases of AD in the SLSJ region since 1986 (Gauvreau *et al.* 1988; De Braekeleer *et al.* 1989). The IMAGE diagnostic procedures are based on the NINCDS-ADRDA criteria (McKhann *et al.* 1984) and previously published morphological and morphometric criteria (Tiberghien *et al.* 1993). Currently, the register contains 194 definite cases, 206 probable cases and 211 possible cases. In this study, we worked with 205 probable and 194 definite cases born between 1893 and 1934. One probable case born in 1943 was excluded because the birth period of our control populations did not cover that year. The sample comprises 124 males and 275 females, for a sex ratio of 1:2·2. The places of birth of the cases were documented in 359 instances (90%): 275 cases (69%) were born in the SLSJ area, 75 cases (19%) somewhere else in the province of Québec, while only nine cases (2%) came from outside the province.

Controls

In order to generate comparable study groups, controls used in a birth seasonality study should be born in the same period and in the same area as the cases, since the putative deleterious agent could operate at specific moments and places (Bradbury & Miller, 1985; Nonaka & Miura, 1987). Furthermore, when working with elderly cases, it is best to use birth dates of a population of 'survivors', since it has been established that there is a relationship between the month of birth and death (Philpot *et al.* 1989; Dalén, 1990). In this study, we worked with two databases so as to control for these factors. We established our first population of controls with the data obtained from the Ministry of Health and Social Services of Québec through its users' database for universal medicare (the so-called Régie de l'assurance-maladie du Québec (RAMQ) database). This population of controls is composed of all individuals born between 1893 and 1934 and who were living in the SLSJ area as of November 1992, or living in that area at the time of their death between November 1987 and November 1992 ($N = 51170$). The datafile provided by the RAMQ contains the day and month of birth, and the year of birth within a 3-year period, of all individuals. This population can be considered as the population of survivors from which the cases originate; however, it does not allow us to control for place of birth, since the RAMQ database does not have this information. Therefore, we used as another source for the second population of controls a list of all births which took place between 1893 and 1934 in the SLSJ area ($N = 135142$). These data were obtained from the Centre interuniversitaire de recherches sur les populations (SOREP), which has assembled a computerized register of all the catholic parish records of baptisms, marriages and burials that took place in the SLSJ since its foundation in 1842.

Data analysis

We performed two series of independent analyses with our two populations of controls. In the first series, we compared the data for the 399 AD cases with those of the RAMQ database, while

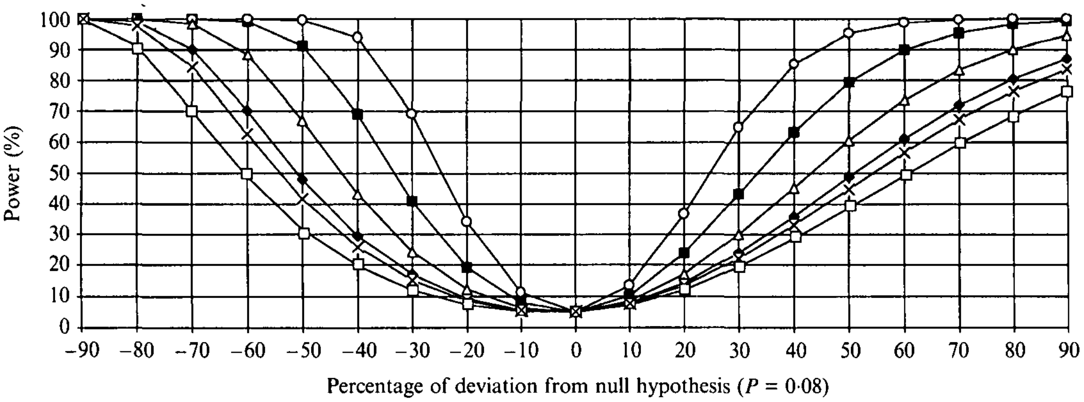

FIG. 1. Power curve for the test of proportion. (■, IMAGE $N = 399$; ○, Dysken $N = 727$; △, Philpot $N = 239$; ◆, Henderson $N = 170$; ×, Vitiello $N = 150$; □, no family history $N = 120$.)

in the second series, we compared the 275 cases born in the SLSJ area with the controls selected throughout the SOREP database.

The distribution of cases according to their year of birth is obviously not uniform: hence, many cases who were born at the beginning of the study period died before they could be recruited by the IMAGE Project while most individuals born at the end of the study period and who will eventually develop AD have not yet manifested clinical signs of the disease. To correct for this, we adjusted the monthly birth distribution in the populations of controls to the yearly birth distribution of the cases according to the following formula (Videbech & Nielsen, 1984):

$$B\mathrm{exp}_m = \sum_i \frac{n_{m,i}}{N_i} . A_i,$$

where

$B\mathrm{exp}_m$	expected births for month m;
i	goes from 1893 to 1933 by 3-year periods;
$n_{m,i}$	number of births for month m during period i;
N_i	total number of births during period i;
A_i	number of AD cases during period i.

The years of birth were grouped in 3-year periods, since we could not obtain the exact year of birth of individuals in the RAMQ file because of ethical considerations. We calculated the number of births per month for the two AD series and for the two adjusted populations of controls. However, the grouping of births by months or trimesters is somewhat arbitrary and may conceal a seasonality effect, as such an effect could cover a period shorter than a calendar month or could overlap 2 contiguous months. To control for this bias, we measured the birth distribution using density estimation (Silverman, 1986). Thus, we considered the day of birth as a continuous variable in the interval 0–365, taking each year as a leap year. We then measured the proportion of births taking place each day for the AD series and for the two populations of controls. For this method, the birth period was considered as a single year. The kernel density estimator allows us to reduce the variance in the birth frequency of each day to an acceptable level while providing a smooth function of the daily proportions of births. The modified density estimator adapted to the data grouped by day gives the following proportion estimator for the day i.

$$\hat{p}_i = \sum_{j=0}^{365} p_j K_h(d_{ij}),$$

where d_{ij} is the minimum distance in days between the day i and the day j considering that the distance between day 1 and day 365 is 2, where $K_h(x)$ is the function allowing calculation of the weight of day j, based on the distance between days i and j, and is given by:

$$K_h(x) = 2\int_x^{x+1} \frac{1}{\sqrt{2\pi}} e^{-\frac{1}{2}(\frac{x}{h})^2} \mathrm{d}x,$$

and where h is the window of the estimator. This parameter can be interpreted as the number of

Table 1. *Monthly frequencies of births among cases, expected frequencies (raw and adjusted) based on control populations distribution and* P *values for the tests of proportion*

	All cases ($N = 399$)	RAMQ population Raw	RAMQ population Adjusted	P	SLSJ cases ($N = 275$)	SOREP population Raw	SOREP population Adjusted	P
Jan.	37	31·94	31·19	0·28	21	22·43	22·05	0·82
Feb.	39	30·49	29·40	0·07	26	20·69	20·58	0·22
Mar.	35	35·35	34·35	0·90	25	25·07	25·17	0·97
Apr.	37	34·75	33·58	0·54	27	25·06	25·44	0·74
May	20	34·97	33·76	**0·01**	14	25·10	25·26	**0·02**
Jun.	29	33·62	33·31	0·44	19	23·79	24·27	0·26
Jul.	33	35·07	36·59	0·54	24	23·93	24·18	0·97
Aug.	31	32·81	35·05	0·47	21	22·54	22·78	0·70
Sep.	32	34·75	35·60	0·53	24	22·93	22·58	0·76
Oct.	40	32·31	33·50	0·24	28	21·45	21·25	0·13
Nov.	32	30·16	29·24	0·60	23	19·66	19·02	0·34
Dec.	34	32·78	33·44	0·92	23	22·35	22·41	0·90

adjacent days used on each side to estimate the frequency of a specific day. We used $h = 15$ for smoothing the sample values and $h = 5$ for the population values. The latter were smoothed because we observed important variations in the frequency of births of adjacent days. We built a 95% interval around the population frequency to use as a visual test in order to compare the population and the sample. The construction of the interval is based on the asymptotic normality of $\hat{p}_i$. The mathematical expectation (the mean) and the variance of this estimator are:

$$E(\hat{p}_i) = \frac{1}{N}\sum_{j=0}^{365} N_j K_h(d_{ij})$$

$$\mathrm{Var}(\hat{p}_i) = \frac{1}{N^2}\sum_{j=0}^{365} N_j^2 K_h^2(d_{ij}) - \frac{2}{N^2}\sum_{j=0}^{365}\sum_{l=j+1}^{365} N_j N_l K_h(d_{ij}) K_h(d_{il}),$$

where N_i is the number of births in the population for day i, $i = 0, 1, \ldots, 365$, and h is the window parameter for the estimation.

Statistical tests

We used the chi-square test to compare the monthly birth distributions observed in the AD series and the expected distributions derived from the populations of controls. The observed proportions of monthly and daily births were also compared with the expected proportions using a test of proportion (Hogg & Craig, 1978).

Before conducting the analyses, the power of the test of proportion was calculated based on our sample size; since all but one of the seasonality studies on AD patients reported so far were unable to reject the null hypothesis, power was also calculated for their sample sizes. All these studies conducted their anlayses on their entire sample as well as on a subgroup composed of sporadic cases. On average, the number of sporadic cases was around 120 and therefore, we calculated power for such a sample size. The power of the test of proportion provides a good indicator of the power of the chi-square test used in the studies. The power curves were generated for a proportion of expected births under the null hypothesis estimated at 0·08 and for alternative hypotheses which are expressed as percentages of the null hypothesis. Sample size is a major concern in seasonality studies, essentially because any seasonal effect that we would be trying to detect, if indeed it existed, would probably only account for a small percentage of cases, or only explain a small fraction of the aetiology for some affected individuals (Bradbury & Miller, 1985; Boyd *et al.* 1986). Fig. 1 shows that in all studies power is very low for detection of such an effect.

RESULTS

The observed and expected monthly frequencies of births for the two series of analyses are presented in Table 1. For the control populations, values are given before and after adjustment for yearly distribution of cases. The comparison between IMAGE AD cases and the RAMQ controls shows that, from May until September, the observed births are below the expected levels and that this deficit of births

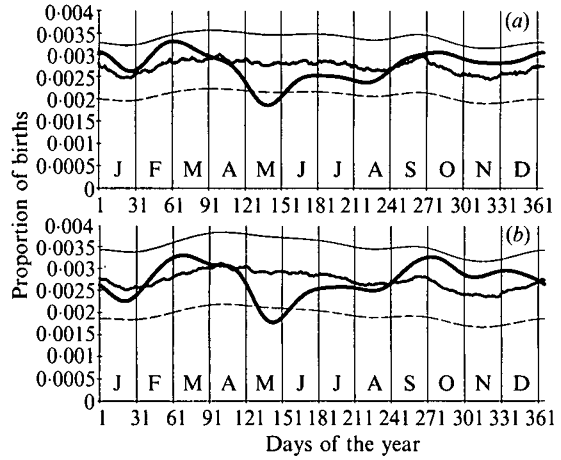

FIG. 2. Daily distribution of births for (*a*) the AD cases and the RAMQ population of controls ($N = 51\,170$); and (*b*) the AD cases born in SLSJ and the SOREP population of controls ($N = 135\,142$) with limits of the rejection region for a test on smoothed proportions with $\alpha = 0{\cdot}05$. Bold curving lines = cases (*a*), $N = 399$, (*b*) $N = 275$; bold jagged lines = population (*a*) RAMQ, (*b*) SOREP; thin horizontal lines = upper and lower limits.

reaches significance in May ($P = 0{\cdot}01$). From January to April and from October until December, the number of births in the AD sample is more important than in the population of controls and February is nearly significant ($P = 0{\cdot}07$). However, the chi-square test is not significant ($\chi^2 = 13{\cdot}46$, df $= 11$, $P > 0{\cdot}10$).

The comparison between the IMAGE AD cases born in the SLSJ area and the SOREP population of controls also shows a significant deficit of births in May ($P = 0{\cdot}02$). The monthly distribution is similar to that obtained in the first analysis, except for January, which displays a slight deficit of births and September where there is small excess. The chi-square test is not significant ($\chi^2 = 10{\cdot}96$, df $= 11$, $P > 0{\cdot}10$).

The smoothed daily proportions of births for the entire sample of cases, as well as for the subgroup of cases born in the SLSJ area, are presented in Fig. 2, with the limits of the rejection region for the test of proportion. To facilitate comparisons, the graphs have been divided in 12 equal parts roughly corresponding to months. Interestingly, it can be noticed that the variations within a single month can be quite important. With the daily distribution, the deficit of births in May remains significant, but the portion of the curve located in the rejection region also includes some days in June.

DISCUSSION

In this study, we have undertaken to compare the monthly and daily distributions of births of AD cases and of populations of controls in order to test the hypothesis of an association between the time of birth and the risk of developing AD. Our data indicate a significant deficit of births in May. The months of June, July and August also have slightly less births in the group of AD patients, as compared with the populations of controls. The deficit of births in May is intriguing and deserves further attention, even though one might argue that, with the number of tests performed, the type I error is inflated.

We believe that the populations of controls used for this study correct for many potential biases: there was a correlation between cases and controls with respect to time and place of birth, and cases were compared with controls who had also survived to the age of greater risk for developing AD. However, since it is likely that a seasonality effect may affect only a subgroup of cases, our sample is still very small for detecting such a phenomenon. Moreover, for sample-size reasons, we had to group together the entire period under study, whereas the factor inducing the seasonal birth effect may only have an influence in certain years, as in the case of epidemics.

The other studies conducted so far on this topic also contain methodological weaknesses that could have led to fallacious results and render comparisons rather awkward. Table 2 summarizes the characteristics of those studies. As mentioned above, sample size is certainly their most serious shortcoming. Fig. 1 indicates that, in order to reach a power of 80% with the sample sizes used in the different studies, the excess or deficit of observed births in a month would have to stand between 35 and 100% of the expected births under the null hypothesis. In comparison, the excess of first trimester births observed among schizophrenic patients when compared with the general population stands between 5 and 15% (Öhlund *et al.* 1991).

As mentioned in Table 2, previous studies based case selection on hospital, clinic or medical school referral. With that type of selection, there is a risk that selection would be related to exposure (Hennekens & Buring, 1987). Hence,

Table 2. *Characteristic features of studies on the birth seasonality of Alzheimer's disease*

Study, sample location	Observed variations in births	Sample size	Selection of cases	Correlation cases/controls for			Treatment of time variable
				Period of birth	Place of birth	Survival factor	
Philpot, 1989 London (UK)	Excess of births in first trimester, sporadic cases	239 probable* †FH$^-$ = 119	Hospital and community	Yes	No	Yes	Quarters
Dysken, 1991 Michigan, Ohio, Minnesota (US)	None	727 definite †FH$^-$ = 106	Hospital and medical school	No	No	No	Quarters
Henderson, 1991 Sydney, (Australia)	None	83 probable 87 possible* †FH$^-$ = 118	Hospital	Yes	No	Yes	Quarters
Vitiello, 1991 Maryland (US)	None	150 probable and possible* †FH$^-$ = 103	Research centre	Yes	No	Yes	Months and quarters
IMAGE Québec, (Canada)	Deficit of births in May, all cases	194 definite 205 probable* †FH$^-$ = n/a	General population	Yes	Yes	Yes	Days and months

* Cases classified according to the diagnostic criteria of McKhann *et al.* (1984).
† FH$^-$ = Cases with no family history of dementia among first-degree relatives.

patients born at a certain time of the year (i.e. exposure) could represent a subgroup of the disease with characteristics that would influence the probability of being hospitalized. Moreover, the criteria used for the classification of data following a familial/sporadic distinction contain some flaws: first, since most secondary cases must be identified retrospectively, each group uses a definition of dementia that facilitates such an identification but that prevents uniformity and thus complicates comparisons between studies. Secondly, 'because AD is a prevalent disease in the elderly, there is a possibility of the chance finding of more than one case of AD in first-degree kindreds of advanced age' (Duara *et al.* 1993).

Periods of birth were the same between cases and controls in the studies by Vitiello *et al.* (1991) and Henderson *et al.* (1991) who worked with age-matched controls, as well as in the work by Philpot *et al.* (1989) who used census data allowing adjustment of the age structure of the controls to that of their cases. However, the census data used by Dysken *et al.* (1991) did not allow them to cover the same period of birth as that of the cases. None of these studies was able to control rigorously for place of birth. There was some control over differential survival according to month of birth, Vitiello *et al.* (1991) and Henderson *et al.* (1991) working with age-matched controls and Philpot *et al.* (1989) with census data from 1971. In conclusion, none of these studies actually used a control population that truly represented the population of origin of their cases.

Lastly, in those four studies, the analyses were done with the dates of birth grouped in quarters. Philpot *et al.* (1989) and Dysken *et al.* (1991) also conducted analyses comparing one quarter with the rest of the year. This grouping might increase power (Boyd *et al.* 1986) but it is quite arbitrary and could easily prevent detection of an effect taking place in a shorter period or not following that type of grouping.

We propose two reasons that would explain a deficit of births in May among AD patients, as observed with the IMAGE data. First, an undetermined risk factor could have an effect that would in fact fluctuate over time and have a 'lower' pathological impact in May (or more generally in the late spring and early summer). Consequently, individuals born during that period would be at a smaller risk of developing the disease, or might display a milder form of the disease with for instance a slower rate of development, thus reducing the likelihood of clinical diagnosis during the lifecourse. Secondly, the risk factor would in fact work the opposite way and its pathological impact would be at its peak in the late spring and to some extent in the early summer; the outcome of exposure would then be greater likelihood of death for the foetus or the newborn while the exposure at other periods of the year would lead to the development of AD in later life. This situation would also translate into a deficit of births of AD patients born during a high risk period.

In conclusion, as long as seasonality studies on AD have not improved their methodology and increased their sample size, we believe that a seasonal effect in the distribution of AD births cannot be discarded. We are currently gathering data on the history of epidemics in the SLSJ area for the 1890–1940 period and we have undertaken to correlate it with the time and place of birth of the AD cases. These studies could contribute to the understanding of a deficit of AD births in May and in the early part of the summer.

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