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Winter birth excess in schizophrenia and in non-schizophrenic psychosis: Sex and birth-cohort differences

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ABSTRACT

Objective: Despite the fact that association between winter birth excess and schizophrenia in the northern Hemisphere is well established, possible sex or birth-cohort differences in this winter birth excess remain unclear. We aimed to evaluate sex and birth-cohort differences in the seasonal birth distribution of patients with schizophrenia or non-schizophrenic psychosis.

Method: The sample included 321 ICD-10 schizophrenia and 294 non-schizophrenic psychosis patients consecutively admitted into a psychiatric hospitalization unit in Granada, southern Spain, during a nine-year period (1998–2006). The distribution of births among the general population born over the same period as the patients was calculated.

Results: Among schizophrenia males ($n=258$), it was possible to demonstrate that the observed proportion of winter birth (December, January or February) was significantly higher than expected. Among schizophrenia females ($n=63$), although proportions were as in males and the effect size of the difference between observed and expected winter births was not lower than for men, only a statistical trend could be demonstrated. Among patients with non-schizophrenic psychosis, the observed proportion of winter birth was significantly higher than expected in women, but not in men. The sex-adjusted proportion of winter birth among schizophrenia patients born in the 1940's (a time period characterized by poor economy and widespread food restrictions because of the Spanish post-civil-war period) was significantly higher than among those born later; a difference that does not occur among patients with a non-schizophrenic psychosis.

Conclusions: Among schizophrenia patients born in winter there appear to be slight sex-differences and strong birth-cohort differences, possibly due to epidemiological factors such as poverty or maternal nutritional deprivation. Epidemiological findings related to winter birth excess among patients with schizophrenia must be identified in longitudinal studies.

1. Introduction

There is an increasing evidence that environmental factors generating brain damage during gestation, such as obstetric complications, viral infections or nutritional deficiencies, increase the risk of schizophrenia later in life. One consequence of this phenomenon may be the extensively replicated association between winter birth excess and schizophrenia in the northern Hemisphere (Torrey et al., 1997). A possible sex difference in this winter birth excess remains unclear. Some authors found that winter–spring excess among patients with schizophrenia is somewhat more pronounced among men than among women (Balestrieri et al., 1997; O'Callaghan et al., 1995); yet others report that seasonal effect is more marked among females (Dassa et al., 1996). Finally, other studies show no or little sex difference (Fouskakis et al., 2004; Suvisaari et al., 2000). Eagles et al. (1995) compared the ratio of winter/spring to summer/autumn births among patients with schizophrenia born between 1900 and 1969, and encountered a highly significant increase in this season-of-birth effect for men but not for women. In contrast, schizophrenia females seem to be more vulnerable to certain environmental factors associated with winter birth excess such as being born in urban areas (O'Callaghan et al., 1995) or maternal dietary insufficiency (Susser and Lin, 1992).

Regarding patients with non-schizophrenic psychoses, the season-of-birth effect has been less investigated. Torrey et al. (1996) report a

Abbreviations: ICD, International Classification of Diseases; OR, odds ratio; CI, confidence intervals.

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winter birth excess for both schizoaffective and bipolar disorder patients, in addition to schizophrenia. However, Fouskakis et al. (2004) find no such effect among patients with non-affective non-schizophrenic psychoses or among patients with schizophrenia. Non-schizophrenic psychoses have generally been considered to be the result of more precipitating stress and fewer familial risk factors (Stephens et al., 1982). Birth in cold months can be considered as an environmental stress factor which may proceed as a "second hit" (after the "first hit" of genetic factors) in the etiology of non-schizophrenic psychosis. On the other hand, Hultman et al. (1999) find that reactive psychosis is associated with maternal age and with large size for gestational age only among females, suggesting that some developmental conditions (as winter birth could be) may increase the risk for non-schizophrenic psychosis among women.

The objective of the present study was two-fold. We aimed first, to evaluate sex differences in the seasonal or monthly birth distribution of patients with schizophrenic or non-schizophrenic psychosis admitted into an acute psychiatric hospitalization unit; and second, to examine the proportion of winter births among schizophrenia patients born during the Spanish post-civil-war period (until 1959) in comparison with those born later. We hypothesized that the proportion of winter births among schizophrenia patients would be greater during the post-war years, a time period characterized by poor economy and widespread food restrictions.

2. Methods

2.1. Participants

We analyzed data from patients with psychosis ($n=615$) consecutively admitted or readmitted during a period of nine years (from 1 January 1998 to 31 December 2006) into one of the two general hospitals in the city of Granada, southern Spain, which serves a catchment area of about 440,000 urban or rural inhabitants. Data collected included socio-demographic variables (sex, date of birth, age at first admission, marital status and residence location), along with diagnoses taken from the discharge summaries made by the treating clinicians, according to the tenth version of the International Classification of Diseases (ICD-10, WHO, 1993). The sample included 321 patients with schizophrenia (ICD-10 code F20); 61 patients with persistent delusional disorder (ICD-10 code F22); 73 patients with schizoaffective disorder (ICD-10 code F25); and 160 patients with other psychotic disorders (ICD-10 codes F21, F23, F28 or F29). Initially, all patients with an ICD-10 psychosis who were admitted during the aforementioned nine-year period ($n=666$) were included in the study. However, 51 patients were excluded because of one of the following reasons: 1) having an age lower than 18 ($n=8$); 2) having no birth date available ($n=4$); and 3) having been born before 1941 ($n=39$), since data on births corresponding to Granada before 1941 were not available from the National Institute of Statistics.

2.2. Assessments and data analysis

We examined associations with season of birth by categorizing subjects into the following four birth groups: winter (December, January or February), spring (March, April or May), summer (June, July or August) and autumn (September, October or November). The expected proportions of births for each season or month were calculated using birth data for the general population of the province of Granada during the same period (from 1941 to 1986), obtained from the Spanish National Institute of Statistics. Since the Spanish post-civil-war period is considered to last until 1959 (Payne, 2000), we analyzed the difference in seasonal birth distribution between patients born from 1941 to 1959 and those born from 1960 to 1986. Within the Spanish post-civil-war, we further analyzed the proportion of winter births from 1941 to 1946, a time period in which famine was quite prevalent (Payne, 2000). In addition, to study trends over time, we broke the sample down by year of birth, into five decades, the last one actually running just six years (from 1980 to 86) as 1986 is the cut-off birth year of our sample.

Firstly, we analyzed birth proportions by season and by month in the whole sample. Secondly, we stratified by sex and then we examined season of birth in patients with schizophrenia and in patients with non-schizophrenic psychosis. And finally we studied the effect of the birth cohort in patients with schizophrenia and in patients with non-schizophrenic psychosis.

Continuous variables and frequencies were respectively compared through t or chi-square tests in bivariate analyses. Logistic regression models were built through a backward selection procedure and the final logistic regression models fit well according to the Hosmer–Lemeshow goodness-of-fit test (Hosmer and Lemeshow, 2000). The strength and direction of the association between the independent and the dependent variables were expressed as odds ratios (ORs), with their 95% confidence intervals (CI).

3. Results

3.1. Birth distribution by seasons and months in the whole sample

The sample included 615 patients with psychosis, aged 18 to 64 (mean age 36.1 ± 10.4 years), 69% of them males (423/615). In the whole sample ($n=615$), the observed proportion of winter birth (December, January or February) was significantly higher than the expected proportion [31% (193/615) vs. 25% (154/615), ($\chi^2=13.17$; df = 1, $P<0.001$)]. Monthly birth distribution is shown in Fig. 1. Among patients with schizophrenia ($n=321$), January showed the highest proportion of births (15%, 49/321). This proportion was significantly higher than expected ($\chi^2=16.16$; df = 1; $P<0.001$) and also higher than the proportion of patients born in the rest of the months (ranging from 6.2% in October to 10.9% in May). Among non-schizophrenia psychotic patients ($n=294$) monthly birth distribution showed January to again be the month in having the highest proportion of births (13.9%, 41/294), significantly higher than expected ($\chi^2=9.49$; df = 1; $P=0.002$).

3.2. Season of birth by sex stratification

Birth proportions by season season according to sex are shown in Fig. 2.

3.2.1. Patients with schizophrenia

Among patients with schizophrenia ($n=321$), the observed proportion of winter birth was significantly higher than expected (Table 1). Among schizophrenia males ($n=258$), the observed

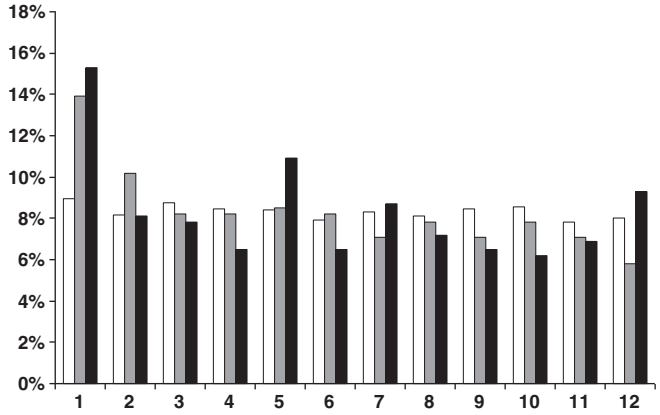

Fig. 1. Birth proportions by months (from January through December, 1 through 12) in general population of the province of Granada (open bars), patients with non-schizophrenic psychosis (gray bars) and patients with schizophrenia (black bars).

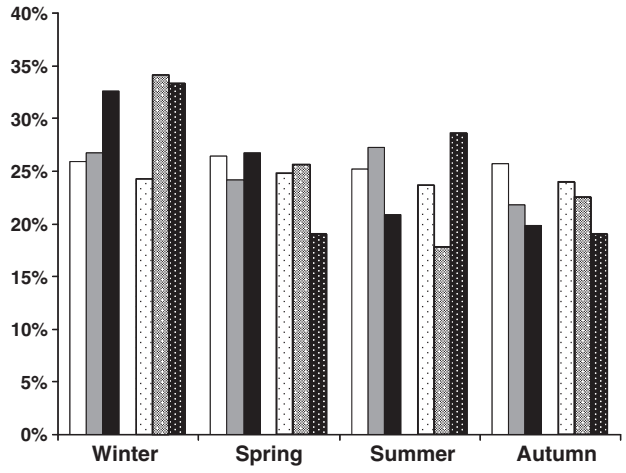

Fig. 2. Birth proportions by season among males of the general population (open bars), with non-schizophrenia psychosis (gray bars) and with schizophrenia (black bars); and among females of the general population (dotted open bars), with non-schizophrenia psychosis (dotted gray bars) and with schizophrenia (dotted black bars).

proportion of winter birth was significantly higher than expected, whereas the observed proportion of autumn birth was significantly lower than expected (Table 1). Among schizophrenia females ($n=63$), the proportions were similar to males; however, due to the smaller sample size, only a statistical trend could be demonstrated (Table 1). Analysis of the monthly birth distribution showed the proportion of January births among schizophrenia males to be higher than among schizophrenia females (16.7% vs. 9.5%) and significantly higher than expected ($\chi^2=16.58$; df = 1; $P<0.001$). Among schizophrenia females, the difference between the observed and expected proportion of births was not significant in any month.

3.2.2. Patients with non-schizophrenic psychosis

Among patients with non-schizophrenic psychosis ($n=294$), the observed proportion of winter births was significantly higher than expected in women, but not in men (Table 1).

3.3. The effect of the birth cohort

Logistic regression, controlling for sex, revealed that the proportion of winter birth was significantly higher in the 1940's than in later decades among schizophrenia patients, but not among patients with a non-schizophrenic psychosis (Table 2).

3.3.1. Patients with schizophrenia

Within the sub-sample of schizophrenia patients, we compared patients born during the post-war period (1941–1959) with those born later (1960–1986) and found that the proportion of schizophrenia patients born in winter was: 1) significantly higher among those born in 1941–1959 than among those born in 1960–1986 [40.5% (45/111) vs. 28.6% (60/210); OR = 1.7; 95% IC: 1.05–2.7; $P=0.030$]; and 2) significantly higher than expected among patients born in the first time period ($\chi^2=15.85$; df = 1; $P<0.001$), but not among those born in the second one ($\chi^2=1.85$; df = 1; $P=0.173$). Controlling for sex, logistic regression showed that having been born in 1941–1959 was significantly associated with winter birth (OR = 1.7; 95% IC: 1.05–2.7; $P=0.030$). In addition, the proportion of schizophrenia patients born in winter was significantly higher among men born in 1941–1959 than among those born later [41.3% (38/84) vs. 27.7% (46/84); OR = 1.8 95% IC: 1.1–3.1; $P=0.026$], a difference that does not occur among women [36.8% (7/21) vs. 31.8% (14/21); OR = 1.2 95% IC: 0.4–3.8; $P=0.70$]. Within the post-war time period, the proportion of schizophrenia patients born in winter during the famine period (1941–1946) was 46.2% (6/13), higher than those born during the rest of the post-war [1947–1959, 39.8% (39/98)] and also higher than in later years [1960–1986, 28.6% (60/210)]. The differences between these proportions were not significant, probably due to the small sub-sample sizes.

The birth cohort effect was not confounded by age, since the mean age of schizophrenia patients was not significantly different within each decade of birth among those who were born in winter than those born in others seasons.

3.3.2. Patients with non-schizophrenic psychosis

In contrast, among patients with a non-schizophrenic psychosis ($n=294$), the proportion of winter births was not significantly different among those born in 1941–1959 than among those born in 1960–1986 [28.0% (23/82) vs. 30.7% (65/212); $P=0.661$]. There was no difference between these proportions when we stratified by sex.

4. Discussion

The main findings of our study were that the proportion of winter births 1) was higher than expected in schizophrenia patients as well as in women (but not in men) with non-schizophrenic psychosis; and 2) was significantly higher during the post-war period among schizophrenia patients, but not among patients with a non-schizophrenic psychosis.

The main strength of this study is the type of sample, which was obtained from the mental health services of a catchment area and is therefore representative of the usual clinical practice. The main

Table 1
Observed and expected seasonal birth distribution according to sex among 321 patients with schizophrenia and among 294 patients with non-schizophrenic psychosis.

Season of birth	Patients with schizophrenia								
	All ($n=321$)			Men ($n=258$)			Women ($n=63$)		
	% (n) observed	% (n) expected	p	% (n) observed	% (n) expected	p	% (n) observed	% (n) expected	p
Winter	32.7 (105)	25.1 (81)	**0.002**	32.6 (84)	25.9 (67)	**0.016**	33.3 (21)	24.3 (15)	0.076
Spring	25.2 (81)	25.6 (82)	0.90	26.7 (69)	26.4 (68)	0.89	19.0 (12)	24.8 (16)	0.25
Summer	22.4 (72)	24.4 (78)	0.44	20.9 (54)	25.2 (65)	0.12	28.6 (18)	23.6 (15)	0.38
Autumn	19.6 (63)	24.8 (80)	**0.028**	19.8 (51)	25.7 (66)	**0.032**	19.0 (12)	24.0 (15)	0.38
Season of birth	Patients with non-schizophrenic psychosis								
	All ($n=294$)			Men ($n=165$)			Women ($n=129$)		
	% (n) observed	% (n) expected	p	% (n) observed	% (n) expected	p	% (n) observed	% (n) expected	p
Winter	29.9 (88)	25.1 (74)	0.060	26.7 (44)	25.9 (43)	0.86	34.1 (44)	24.3 (31)	**0.007**
Spring	24.8 (73)	25.6 (75)	0.79	24.2 (40)	26.4 (44)	0.48	25.6 (33)	24.8 (32)	0.84
Summer	23.1 (68)	24.4 (72)	0.35	27.3 (45)	25.2 (42)	0.53	17.8 (23)	23.6 (30)	0.12
Autumn	22.1 (65)	24.8 (73)	0.42	21.8 (36)	25.7 (42)	0.28	22.5 (29)	24.0 (31)	0.68

Table 2
Proportion of patients born in winter by decade of birth.

Decade of birth	Schizophrenia		Non-schizophrenic psychosis	
	% (n)	OR[a] (95% CI)	% (n)	OR[b] (95% CI)
1941–49	54.5 (18/33)	1 (Ref.)	38.5 (10/26)	1 (Ref.)
1950–59	34.6 (27/78)	0.42 (0.18–0.98)	23.2 (13/56)	0.50 (0.18–1.39)
1960–69	23.9 (28/117)	0.25 (0.11–0.57)	32.6 (30/92)	0.79 (0.32–1.96)
1970–79	33.8 (26/77)	0.41 (0.18–0.96)	33.0 (29/98)	0.82 (0.33–2.06)
1980–86	37.5 (6/16)	0.48 (0.14–1.52)	18.8 (6/32)	0.41 (0.12–1.40)

a. The Hosmer–Lemeshow goodness-of-fit test showed that the sex-adjusted logistic model was appropriate ($\chi^2 = 1.82$; df = 5, $p = 0.87$).
b. The Hosmer–Lemeshow goodness-of-fit test showed that the sex-adjusted logistic model was appropriate ($\chi^2 = 6.16$; df = 7, $p = 0.52$).

limitations are the relatively small sample size, the cross-sectional design and the fact that diagnoses were taken from charts recorded by different treating clinicians whose inter-rater reliability had not been assessed.

4.1. Season of birth by sex stratification

A higher than expected proportion of winter births was observed among patients with schizophrenia. Most of the studies which have examined the relationship between birth seasonality in schizophrenia and family history for this disorder, report that schizophrenia patients who had a negative family history for the disease were more likely to show a winter birth excess than those with a positive family history (Torrey et al., 1997). This pattern suggests that environmental factors may have greater etiological impact than genetic factors on the birth-season effect among schizophrenia patients.

Although the proportions of winter births of persons with schizophrenia in our sample (Table 1) were similar in both sexes, the higher than expected proportion was statistically significant among men whereas only a statistical trend could be demonstrated among women, due to the smaller sample size. Nevertheless, the effect size of the difference between observed and expected winter births was not lower for women (0.19) than for men (0.15), although this difference is not statistically significant. Some studies have found that schizophrenia males born in winter have an early onset of the illness and no family history of psychosis (Chen et al., 1996), as well as having an urban-birth location (O'Callaghan et al., 1995). Winter birth excess may be the expression of several factors related to neuro-developmental processes, in which males could be more vulnerable to suffering obstetric complications and prenatal insults in the second trimester due to slower cerebral maturation in utero (Van Os and Selton, 1998) and to having structural brain abnormalities (Chen et al., 1996). These findings may lead researchers to surmise that the winter birth effect may be more pronounced in men than in women, as reported by some previous authors (Balestrieri et al., 1997; O'Callaghan et al., 1995), but this is not confirmed in our study or in two previous ones (Fouskakis et al., 2004; Suvisaari et al., 2000).

Concerning non-schizophrenic psychosis, we found a higher than expected proportion of winter births only among women. It is known that among patients requiring hospitalization, the proportion of a diagnosis of schizophrenia among men tends to be much higher than among women, probably because there is a higher tolerance of schizophrenia women in the home setting (Chen et al., 1996), or because women with schizophrenia may suffer from a less severe form of the illness with a better course and global outcome than men. In addition, among patients with non-schizophrenic psychosis, women also show better functioning over time, more frequent periods of good functioning and periods of recovery, less likelihood of a uniformly poor outcome, and fewer and shorter hospitalizations (Grossman et al., 2006). The protective effect of estrogens is known to reduce psychotic activity (Riecher-Rossler et al., 1994). We could speculate that the women in our sample diagnosed with non-schizophrenic psychosis may correspond, in some proportion, to an attenuated form of schizophrenia. On the other hand, the finding that the birth-season effect for schizophrenia in men is similar to that for non-schizophrenic psychosis in women, suggest that similar prenatal neurodevelopmental stressors may produce different neuropsychiatric sequelae in males and females. Some prenatal and perinatal factors such as multiparity, bleeding during pregnancy (which is often a sign of placental insufficiency) and small size for gestational age have been associated (Hultman et al., 1999) with increased risk for schizophrenia among males, but not among females. These findings of Hultman et al. (1999) suggest that, among schizophrenia patients, males may be more vulnerable to the environmental stressors. But that study also finds that reactive psychosis was associated with maternal age and with large size for gestational age only among females, suggesting that some developmental conditions (as winter birth could be) may increase the risk for non-schizophrenic psychosis among women.

Our results of a similar winter birth excess in men and women with schizophrenia are in line with Fouskakis et al. (2004), but differ from these authors in that the winter birth excess is found in women with non schizophrenic psychosis but not in men.

4.2. The effect of the birth cohort

We found that the proportion of winter birth was significantly higher in the 1940's among schizophrenia patients, but not among patients with a non-schizophrenic psychosis. Similarly, Suvisaari et al. (2000) show that seasonal variation of births among schizophrenia patients born in the 1950's was markedly higher than among patients born in the 1960's, and suggest that the intensity of the factor causing the winter excess of births in schizophrenia may be decreasing.

Specifically, we found that schizophrenia patients born during the Spanish post-civil-war (1941–1959) were more likely to have been born in winter than patients born in later decades, a difference that significantly occurred only among men. Since winter birth among schizophrenia males has been associated with a history of obstetric complications (Takagai et al., 2006), the improvement in maternity welfare and obstetric care in the last few decades could partially explain this decrease in winter birth among schizophrenia males. Maternal nutritional deficiency may also play a role in the higher proportion of winter birth in schizophrenia during the post-war in comparison with those born later. A higher risk of developing schizophrenia has been associated with marked prenatal nutritional deprivation (Susser and Lin, 1992), low maternal weight (Done et al., 1991) and maternal iron deficiency (Insel et al., 2008). In addition, vitamin D deficiency has been associated with increased vulnerability to infections as well as increased risk of schizophrenia (Kinney et al., 2010; McGrath et al., 2010). The fact that vitamin D deficiency is more prevalent in winter and in high latitudes could help explain the association between schizophrenia and winter birth and also the increased prevalence of schizophrenia at higher latitudes (Kinney et al., 2009, 2010; McGrath and Brown, 2011) despite the protective effects of better prenatal healthcare and nutrition found in more developed countries that are concentrated at higher latitudes, according to the meta-analysis by Kinney et al. (2009). Due to the fact that the production of vitamin D depends mainly on the action of sunlight on the skin, malnourished pregnant women may be particularly vulnerable to hypovitaminosis D during the winter months, since they are unable to compensate the lack of sunlight exposure through dietary intake.

Susser and Lin (1992) found that birth cohorts exposed to severe food deprivation during the Dutch Hunger winter of 1944–45 were associated with an increase in schizophrenia for women but not for men. These authors suggest that women could be more vulnerable to specific interacting causes, such as infection or genetic factors. Nevertheless, it has been demonstrated that vitamin D supplementation during the first

year of life was associated with reduced risk of schizophrenia in males but not in females (McGrath et al., 2004).

In conclusion, among schizophrenia patients born in winter there appear to be slight sex-differences and strong birth-cohort differences, possibly due to epidemiological factors such as poverty or maternal nutritional deprivation. Epidemiological findings related to winter birth excess among patients with schizophrenia seem to be linked among themselves and must therefore be identified in longitudinal studies in order to improve our knowledge of the etiology of this complex illness.

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