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ScienceDirect
Schizophrenia Research 105 (2008) 197–200
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

Twin pregnancy and the risk of schizophrenia ☆

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Received 8 February 2008; received in revised form 21 June 2008; accepted 29 June 2008
Available online 23 August 2008

Abstract

Background: Twins are exposed to intrauterine environments that differ significantly from those of singletons. These diverse environments might alter the risk for schizophrenia in twins and make it difficult to generalize from findings in twins when studying the risk of schizophrenia in the general population. Previous studies report contradictory findings on the risk for schizophrenia in twins.
Methods: We studied the incidence of schizophrenia spectrum disorders, ascertained from Israel's National Psychiatric Registry, in a cohort of 2124 twins and 87,955 singletons. These offspring were followed from their birth in 1964–76 in the Jerusalem Perinatal study. Cox proportional hazards methods were used to compare outcomes over 28–41 years, adjusting for ages of parents.
Results: Twins showed a relative risk [RR] of .84 relative to singletons, with a 95% confidence interval [CI] of (.51–1.4). RRs and CIs for males and females were .68 [.34–1.4] and 1.1 [.55–2.2] respectively. Twins in male–male, female–female or opposite-sex sets showed no significant variation in RRs; furthermore, first- or second-born twins did not differ significantly from each other. Siblings of twins had the same risk of schizophrenia as siblings of singletons.
Conclusion: Twins have the same risk for schizophrenia as the general population.

Keywords: Schizophrenia; Twins; Paternal age; Maternal age

1. Introduction

Comparisons of concordance of conditions in monozygotic versus dizygotic twins have been the basis for estimates of heritability and gene–environment interactions in schizophrenia (Sullivan et al., 2003). The intrauterine environment of twins, however, differs significantly from that of singletons in ways that might be related to the future risk of disease. Twins are exposed to higher levels of steroid hormones such as

☆ Supported by NIH Grants: # 2R01 CA080971 (S. Harlap) and # 1R01 MH059114 (D. Malaspina) and the National Alliance for Research on Schizophrenia and Depression (D. Malaspina, S. Harlap, M. Perrin).
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doi:10.1016/j.schres.2008.06.017

estrogen (Swerdlow et al., 1997), are more likely to be born prematurely, and to weigh less at birth even when born at term (Herruzo et al., 1991). Twins are at increased risk for breech presentation, hypoxia and birth injuries (Bjelic-Radisic et al., 2007). These obstetric complications have been associated with risk of schizophrenia (Byrne et al., 2007). Twins often have different postnatal experiences; parents must provide more resources, and twins may be treated differently in social situations.

The current literature disagrees on whether the incidence of schizophrenia in twins differs from that in the general population, and whether this incidence varies across sets of different zygosity. One study found a 28% increase in the rate of first admissions for schizophrenia in twins compared to the general population, as well as an increased rate in twins for first admission for any psychiatric disorder (Klaning et al., 1996). Another study found no difference in the incidence of psychotic disorders in twins (Kendler et al., 1996). Regarding siblings of twins, a recent report suggested that the rate of schizophrenia in siblings of dizygotic twins was 35% greater than the rate in siblings of singletons, while the rate in siblings of monozygotic twins was not increased. The authors concluded that their results accorded with a hypothetical linkage between genes influencing the rate of dizygotic twinning and those predisposing to schizophrenia (Klaning et al., 2002). We used existing data from a prospective cohort study to test whether the incidence of schizophrenia is higher in twins than in singletons.

2. Methods

We used data from the Jerusalem Perinatal Study, a population-based cohort derived from all 92,408 births in 1964–76 to mothers resident in western Jerusalem. The cohort includes linkages within nuclear families and a 29–41 year follow-up. Core information from the notification of birth was supplemented with other data from multiple sources. The methods and characteristics of the population have been described in previous publications (Harlap et al., 2007), as have the characteristics of fathers of different ages (Harlap et al., 2002). The cohort was linked with Israel's population registry and National Psychiatric Registry; the latter contains a record of all admissions to psychiatric wards and day-facilities and includes the dates of admission and discharge and the discharge diagnosis for each episode, assigned by a board-certified psychiatrist. The diagnoses are coded with the International Statistical Classification of Diseases 10th Revision [ICD-10]. The diagnoses of psychotic disorders have been validated (Weiser et al., 2005).

2.1. Data analysis

SAS 9.1 (SAS Institute Inc, Cary, North Carolina) was used to analyze the data. We assigned a diagnosis of schizophrenia to any person with at least one hospital admission for which the discharge diagnosis was coded with ICD-10 code F20-29, hereafter termed "schizophrenia". The date of onset was taken as the first episode in the psychiatric registry, regardless of the diagnosis at that time. After comparing demographic and other characteristics of singleton and multiple deliveries, we developed Cox proportional hazards models to compare the incidence of schizophrenia in twins versus singletons, running time in days from date of birth until date of diagnosis of schizophrenia or death; survivors were censored on December 31, 2004. Schizophrenia was coded as 1 (if present) or 0. Maternal and paternal ages were included in the models because both have been related to twinning (Tough et al., 2007) and schizophrenia (Malaspina et al., 2001). As has previously been done in this cohort (Malaspina et al., 2001), paternal age was treated as a continuous variable, expressed as deviations from the mean age (30) with unknowns (.8%) assigned to the mean; while maternal age was modeled using two dichotomies 30–34, 35+, versus <30). Other variables considered were mothers' and fathers' places of birth (Israel, other West Asia, North Africa, Europe), social class (based on occupation of father) sex, birth order (1, 2, 3–4, 5+), year of birth, and education of parents (0–8 years, 9+ years). None of these other variables were included in the final models, as they were not related to both schizophrenia and twin status at $p<.05$ or did not alter the crude hazard ratio (HR) for twins by at least 10%.

3. Results

Of the 92,408 offspring in the cohort (91,479 born alive), 90,079 (98%) were traced in Israel's Population Registry. Linkage with Israel's Psychiatric Registry detected 860 cases of schizophrenia, of which 16 were twin offspring and 844 were singletons. Of the twins with schizophrenia, all were in discordant sets and both twins in each set were born alive.

In proportional hazards analysis the unadjusted incidence of schizophrenia was higher in males than in females (RR=1.6, 95% confidence limits=1.4–1.8), offspring of older fathers (1.03, 1.02–1.04 per 10 years increase in father's age) and older mothers aged 30–34

Table 1
Number of people with and without schizophrenia, relative risk (RR) and confidence limits (CL)

	Schizophrenia		Unadjusted analysis			Analysis adjusted for mothers' and fathers' ages		
	+	−	RR	95% CL	*P*	RR	95% CL	*P*
Singletons	844	87,111	1	–	–	1	–	–
Twins	16	2108	.87	(.53, 1.4)	.6	.84	(.51, 1.4)	.5
Males								
Singletons	528	44,768	1	–	–	1	–	–
Twins	8	1084	.70	(.35, 1.4)	.3	.68	(.34, 1.4)	.3
Females								
Singletons	316	42,332	1	–	–	1	–	–
Twins	8	1024	1.1	(.57, 2.3)	.7	1.1	(.55, 2.2)	.8
Twin sets								
Singletons	844	87,111	1	–	–	1	–	–
Male–Male	7	764	1.1	(.51, 2.3)	.8	1.1	(.5, 2.2)	.9
Female–Female	6	704	.96	(.43, 2.1)	.9	.94	(.42, 2.1)	.9
Opposite-sex	3	697	.5	(.16, 1.5)	.2	.46	(.15, 1.4)	.2

(1.3, 1.1–1.6) or 35+ (1.6, 1.3–1.9) versus offspring of mothers aged <30 (reference group). Table 1 shows that the relative risk of schizophrenia in twins was the same as in singletons, and that adjustment for maternal or paternal age did not change the risk. The risk for opposite-sex twins compared to singletons was about half of that in same-sex twins, although the confidence limits included one. The adjusted RR was .46 with a 95% confidence interval of .15–1.4. When the risk for twins from male–male sets was compared to the risk for male singletons, the RR was .86 (.41–1.8). When female singletons were designated as the reference group, the RR for schizophrenia in twins from female–female sets was 1.2, .55–2.7. These relative risks are not significantly different from those in Table 1 where the entire cohort was used as the reference group. The birth order of co-twins did not affect the risk for schizophrenia, nor did discordant birth weights (data not shown). There were 2658 traced singleton siblings of twins, and these also showed no significantly changed risk of schizophrenia as compared to the rest of the population (data not shown).

4. Discussion

In this cohort the incidence of schizophrenia in twins did not differ from that in singletons, nor did it vary across types of twin sets, by the sex of the twins, by birth order within the set, or with discordance in birth weights. These results corroborate those reported by Kendler et al. (1996) in their retrospective study of data from Sweden's registry of twins. In contrast, Klaning et al.'s (1996) analysis of data from Denmark, using the same retrospective methods as the Swedish study, found a 28% increase in risk for schizophrenia in twins as compared to singletons, a higher rate ratio in female twins than in male twins, and in twins from opposite-sex pairs than in twins from same-sex pairs (Klaning et al., 1996). We also observed a higher relative risk in female twins than in male twins, although with overlapping confidence intervals the results were likely to be due to chance. The relative risk for opposite-sex twins in our study was roughly half of the risk in male–male or female–female sets, although here too the confidence intervals overlapped.

The Danish group proposed a possible association between the genetic tendency to conceive dizygotic twins and a genetic vulnerability for schizophrenia (Klaning et al., 2002). Our results lend no support for this hypothesis, as the siblings of twins had the same incidence of schizophrenia as the siblings of singletons. It is not evident why the findings in Denmark diverge from our study and the study from Sweden.

This analysis of prospectively collected data shows that the risk for schizophrenia in singletons and twins are comparable. The findings support assumptions made by the field when estimating risk factors for schizophrenia using data on twins, and also help resolve the discrepancy in the literature.

Role of funding source

None.

Contributors

K. Kleinhaus designed the study, conducted statistical analysis and wrote the first draft of the manuscript. D. Malaspina, S. Harlap, M. Perrin, O. Manor, R. Calderon-Margalit and Y. Friedlander refined the study design and edited the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None of the authors have any actual or potential conflicts of interest.

Acknowledgements

We gratefully acknowledge the participants in the Jerusalem Perinatal Study.

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