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Maternal household crowding during pregnancy and the offspring's risk of schizophrenia

David Kimhy[a,b,*], **Susan Harlap**[c], **Shmuel Fennig**[d], **Lisa Deutsch**[e], **Benjamin G. Draiman**[f], **Cheryl Corcoran**[a,b], **Deborah Goetz**[a,b], **Daniella Nahon**[g], and **Dolores Malaspina**[a,b]

[a] Department of Psychiatry, Columbia University, New York, NY, USA

[b] Department of Medical Genetics, New York State Psychiatric Institute, New York, NY, USA

[c] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

[d] Shalvata Mental Health Center and the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

[e] Hebrew University-Hadassah School of Public Health, Jerusalem, Israel

[f] Department of Social Work, Bar Ilan University, Ramat Gan, Israel

[g] Research Evaluation and Planning Division, Mental Health Services, Ministry of Health, Jerusalem, Israel

Abstract

Background—Animal models of schizophrenia suggest a link between maternal crowding during pregnancy and increased risk of the offspring to develop physiological, developmental, and behavioral abnormalities that are comparable to those observed in schizophrenia. We tested the hypothesis that a similar link is present in humans.

Method—We investigated whether prenatal exposure to household crowding was associated with the risk of schizophrenia in a subcohort of the Jerusalem Perinatal Study (JPS) consisting 11,015 individuals born between 1964 and 1976. During these years mothers participated in face to face interviews in early pregnancy. The prenatal and birth data, including the number of rooms and individuals living in the mothers' household, was cross-linked with the Israel Psychiatric Registry by ministry personnel.

Results—104 schizophrenia cases were identified in the cohort. Offspring who, while in utero, their mother resided in a household with five or more individuals had RR of 1.47 (95% CI: 0.99–2.16, p=0.05) to develop schizophrenia, compared to those whose mother resided with four or fewer individuals. However, when adjusted for paternal age, the RR was reduced to 1.18 (95% CI: 0.76–1.84, p=0.46). The number of rooms in the household and the household crowding during pregnancy did not significantly impact the offspring's risk to develop schizophrenia.

Conclusion—The link between maternal household crowding during pregnancy and the offspring's risk of schizophrenia was explained primarily by the impact of paternal age. The authors discuss the results in view of findings from animal and human studies.

[*] Corresponding author. Department of Psychiatry, Unit 2, Columbia University, 1051 Riverside Drive, New York, NY 10032, USA. Tel.: +1 212 543 6817; fax: +1 212 543 6176. dk553@columbia.edu (D. Kimhy).

Keywords

Schizophrenia; Pregnancy; Crowding; Paternal age; Stress; Infection

The neurodevelopmental hypothesis of schizophrenia posits that schizophrenia results from a disruption in the development of the central nervous system during prenatal and early neonatal life (Weinberger, 1987). Crowding is a well-studied environmental stressor in animal studies, where it has been associated with numerous physiological, developmental, and behavioral abnormalities in offspring. These include structural and functional brain abnormalities (Berger et al., 2002; Clarke et al., 1994; Coe et al., 2003; Creighton and Chevins, 1988; Hayashi et al., 1998; Henry et al., 1995; Kattesh et al., 1980), delayed motor and mental development (Schneider et al., 1999), changes in social, sexual and aggressive behavior (Crump and Chevins, 1989; Dahlof et al., 1977; Harvey and Chevins, 1985), as well as lowered birth weights, and in the females, delayed puberty and altered estrous cycles (Peters, 1986; Harvey and Chevins, 1987). These observations are comparable to observed abnormalities in animal models of schizophrenia (Lipska and Weinberger, 2000). They also parallel some deficits noted in schizophrenia including reduced initiation of social interactions, aberrant dopaminergic and glutamatergic signaling in prefrontal cortex (Castner et al., 2004), exaggerated reactivity to stress (Lipska et al., 1993), stereotypic locomotion (Beauregard and Bachevalier, 1996; Schmajuk, 1987; Hanlon and Sutherland, 2000; Kilts, 2001), abnormalities in hippocampal and mesocorticolimbic system morphology (Lipska et al., 1993; Beauregard and Bachevalier, 1996; Schmajuk, 1987; Hanlon and Sutherland, 2000; Kilts, 2001), as well as deficits in attention, learning, and recognition memory (Kilts, 2001).

Only two previous studies investigated directly the link between number of household inhabitants and risk of schizophrenia and these yielded conflicting results. Agerbo et al. (2001) found no link between household crowding at age 16 and later incidence of schizophrenia. However, Wahlbeck et al. (2001) reported that the number of siblings in the household at age 7 was related to the schizophrenia risk. This was perhaps distinct from crowding, per se, since the risk was unrelated to the total number of household inhabitants or the number of rooms. A number of methodological issues in these studies may limit the interpretability of their findings with respect to prenatal crowding. First, these assessments were conducted many years after the prenatal period, thus the household data may not reflect the prenatal circumstances. Second, while Wahlbeck et al. (2001) controlled for maternal age, recent data shows that it is actually paternal age which confers the greatest risk of schizophrenia (Malaspina, 2001; Malaspina et al., 2001).

According to the neurodevelopmental hypothesis of schizophrenia, a compromised prenatal and/or early postnatal environment may increase the risk of schizophrenia. As maternal crowding during pregnancy in animal models appear to produce many abnormalities that correspond with deficits associated with schizophrenia, a similar link in humans appears plausible. Such a link in humans has not been studied to date. Thus, the aim of this study is to translate the animal model of pregnancy crowding to the clinical interface by investigating the link between maternal household crowding during pregnancy and the risk of development of schizophrenia in the offspring. Based on data from animal studies, it is hypothesized that offspring, who while in utero their mothers were exposed to higher household crowding, will have higher incidence of schizophrenia. Given previous findings of the impact of paternal age on schizophrenia risk, we will also control the results for paternal age, as well as birth order and socioeconomic status (SES).

1. Method

This study uses data assembled from two independent sources: a population-based research database based on a birth cohort and a national registry of psychiatric disease. The cohort data was obtained from the Jerusalem Perinatal Study—a population-based research file of all births in the greater Jerusalem area from 1964 to 1976. It includes demographic information from birth certificates augmented with data from obstetric and pediatric departments, municipal well-baby clinics, follow-up of vital status, and interviews with some mothers. Its methods have been summarized elsewhere (Harlap et al., 1977; Lichtenberg et al., 1999) and some 80 reports from the study have focused on short- and long-term outcomes. The cohort data were crossed-linked with Israel's national registry of psychiatric disease. The State of Israel maintains a national registry of psychiatric hospitalizations, one of several disease registries used for planning health services, understanding disease etiology, and evaluating measures for prevention. Established in the Ministry of Health in 1950, the Psychiatric Registry receives information about all psychiatric diagnoses, including reports from patients admitted to psychiatric hospitals, psychiatric wards within general hospitals, and psychiatric day-care facilities. The registry's design and methods have been described in detail elsewhere and it has been used for clinical and epidemiologic research in schizophrenia (Harlap et al., 1977; Lichtenberg et al., 1999). In the past decade, studies using the Jerusalem Perinatal Study, linked to other databases in Israel, showed that the offspring' identification numbers, sex, birth dates, and basic demographic information, including parental ages, were more than 99.9% accurate (Lichtenberg et al., 1999; Laor et al., 1997).

In the present study, the Ministry of Health matched a file from the Jerusalem Perinatal Study data to the Psychiatric Registry data using 7-digit identification numbers. These numbers, as well as names and other information that might identify individuals were then removed to create a new, anonymous file limited to psychiatric diagnoses and dates of psychiatric admission. Ministry personnel used a broad definition of schizophrenia (*International Classification of Diseases, 9th Revision; ICD-9*) that included hospital discharge diagnoses of schizophrenia, schizoaffective disorder, schizotypal disorder, delusional disorder, and non-affective psychoses, hereafter considered schizophrenia.

2. Subjects

There are 11,015 recorded live births in the Jerusalem Perinatal Study file to which the mothers provided information antenatally about household crowding. Interviews with mothers were conducted in the free municipal antenatal clinics, usually in the fourth or fifth month of pregnancy. The mothers attending these clinics tended to be at low risk for a poor obstetric outcome; they excluded some women with preexisting gynecologic or obstetric problems (e.g. sub-fertility) who were more likely to have been referred early in pregnancy to specialist clinics; similarly, they excluded some of the most affluent women, who chose to receive antenatal care privately, and others, typically of lower social status, who may have neglected antenatal care till late in pregnancy. The final birth cohort consisted of 5641 males (51.2%) and 5374 females (48.8%).

3. Statistical analysis

Data was analyzed using SPSS for Windows (version 13). Crowding ratios were calculated by dividing the number of inhabitants in the mother's household by the number of rooms in that household. As offspring born in different years were followed up to different ages, we used Cox proportional hazards model (Cox and Oakes, 1984) to estimate effects of crowding using the Cox regression procedure. Individuals were censored on the last day of follow-up (December 31, 1997) and results are given as rate ratios (RRs) with 95% confidence intervals

(CIs). The categories of crowding were treated as a series of dummy variables (1=present; 0=absent) with 0–0.99 set as the baseline category. In addition, we explored separately the RRs of the variables used to calculate the crowding variable—number of inhabitants and number of rooms in the mother's household. The number of inhabitants in the household was grouped into two categories based on the mean (M=4.18) number of household inhabitants in the cohort: 1–4 individuals (*N*=7288, 66.2%) vs. 5 or more individuals (*N*=3727, 33.8%). Number of rooms were grouped into two categories based on the mean (M=2.37) number of rooms: 1–2 rooms (*N*=6018, 54.6%) vs. 3 or more rooms (*N*=4997, 45.4%). We also explored the impact of a number of other factors that have been hypothesized to impact the risk of schizophrenia in the offspring including paternal age, birth order, and socioeconomic status (SES). We used father's occupation as an SES index. We ranked each occupation according to the mean education of all the fathers with that occupation (in the Jerusalem Perinatal Study) resulting in six ranks, from 1 (high) to 6 (low) and no unknowns.

4. Results

Linkage of the Jerusalem Perinatal Study file to the Psychiatric Registry resulted in 104 individuals (67 males, 37 females) who were common to both databases, and who were diagnosed through December 31, 1997 as having developed schizophrenia (9.4/1000 incidence rate). Table 1 presents the relative risk of the offspring to develop schizophrenia based on household characteristics during the mother's pregnancy.

Offspring who, while in utero, their mother resided with five or more individuals in a household, had RR of 1.47 (95% CI: 0.99–2.16, p=0.05) to develop schizophrenia, compared to those who's mother resided with four or fewer individuals. When adjusted for paternal age, birth order, and SES the RR was reduced to 1.35 (95% CI: 0.74–2.47; p=0.33). In contrast, there was no significant difference (χ^2 =0.01, P=0.97) between offspring who their mother resided in homes with 1–2 rooms compared to those who resided in homes with 3 or more rooms (9.4/1000 vs. 9.5/1000, respectively). Similarly, there was no significant difference in rate of schizophrenia between the four categories of household crowding during mother's pregnancy (χ^2 = 1.40, p=0.70).

We conducted separate analyses to calculate the unique impact of paternal age, birth order, and SES on the link between number of household inhabitants during pregnancy and the offspring' risk of schizophrenia. When adjusted for paternal age only, the RR was reduced to 1.18 (95% CI: 0.76–1.84, p= 0.46), suggesting that paternal age had a sizable impact on the offspring's risk of schizophrenia, above and beyond the number of household inhabitants during the mother's pregnancy. Adjustments for birth order (1.43; 95% CI: 0.77–2.64, p=0.26) and SES (1.32; 95% CI: 0.88–1.99; p=0.18) had relatively smaller impact on this link.

We also assessed whether the sex of the offspring influenced the link between number of household inhabitants during pregnancy and later development of schizophrenia. The crude RR was 1.43 (CI: 0.88–2.32, p=0.15) for males and 1.50 (CI: 0.78–2.88, p=0.22) for females. After adjustment for paternal age, birth order, and SES the RR was 1.31 for males (CI: 0.61–2.85, p=0.49) and 1.40 for females (CI: 0.51–3.78, p=0.51). Adjustment for paternal age alone resulted in RR of 1.28 for males (CI: 0.73–2.23, p=0.39) and 1.01 for females (CI: 0.48–2.12, p=0.98).

5. Discussion

This is the first epidemiological study assessing the link between maternal household crowding during pregnancy and the offspring's risk of schizophrenia. The results do not support our hypothesis of an association between elevated maternal household crowding during pregnancy

and an increased risk for the offspring to develop schizophrenia. While offspring whose mothers resided in a household with 5 or more inhabitants had 47% higher risk to developed schizophrenia (compared to those who resided with 4 or less), this finding was explained primarily by the impact of the paternal age. These results are consistent with the growing literature demonstrating the significant impact of paternal age on the offspring's risk of schizophrenia (Tsuchiya et al., 2005; Sipos et al., 2004; El-Saadi et al., 2004; Zammit et al., 2003; Byrne et al., 2003; Dalman and Allebeck, 2002; Brown et al., 2002). The number of rooms in the mother's household during pregnancy and the household crowding per se did not have a significant impact on the offspring's risk to develop schizophrenia. Additionally, birth order and father's SES at birth (his occupation ranked by mean education) had limited impact on the offspring's risk of schizophrenia, beyond the impact of paternal age and number of inhabitants in the household during pregnancy.

Our findings raise a question about the nature of the association between paternal age, crowding, and schizophrenia. As paternal age advances, family sizes typically increase. While maternal crowding during pregnancy is significantly associated with schizophrenia risk in the offspring, our data show that a portion of the association is due to the independent relationships of paternal age and schizophrenia. However, the exact mechanisms of this link currently remain speculative. Our findings are discrepant with results from animal studies showing a link between maternal crowding during pregnancy and offspring's abnormalities. One potential explanation is that no previous animal studies assessed jointly the impact of paternal age and maternal crowding during pregnancy on development of offspring's abnormalities. Such study might clarify the relative impact of paternal age and pregnancy crowding in animals. Another explanation may be rooted in the fact that in contrast to animals in studies, humans typically have opportunities to temporarily exit potentially crowded home environments and thus regulate their stress levels. Other models have been proposed to explain the putative association between schizophrenia and crowding. Torrey and Yolken (1998) suggested that exposure to infectious agents through household crowding might account for this association. A number of studies found a link between schizophrenia and exposure to infections during prenatal development (Brown et al., 2004; Limosin et al., 2003; McGrath et al., 1994). However, other studies failed to replicate this link (Erlenmeyer-Kimling et al., 1994; Selten et al., 1999; Westergaard et al., 1999). Data on our cohort's prenatal exposure to infectious agents was not available. Thus, we could not exclude the possibility that later development of schizophrenia was influenced by prenatal or neonatal exposure to infectious agents.

Conversely, maternal psychological stress during pregnancy may also impact the offspring's risk of schizophrenia (Huttunen and Niskanen, 1978). Huizink and colleagues (2003, 2004) found an association between increased maternal stress during pregnancy and restless temperament, as well as delays in motor and mental development in infants at ages 3 and 8 months. Follow-up assessments at age 27 months found a link between maternal anxiety during pregnancy and restless temperament and increase in behavioral problems (Gutteling et al., 2005). Such motor, behavioral, and developmental difficulties correspond with deficits associated with schizophrenia. These studies controlled for a number of confounding variables including SES, maternal age, birth weight, gestational age, and biomedical risks during pregnancy. Similarly, children whose mothers experienced high levels of anxiety during pregnancy exhibited higher rates of behavioral and emotional problems at 47 and 81 months of age after controlling for obstetric risks, psychosocial disadvantage, and postnatal anxiety and depression (O'Connor et al., 2003). In the present study, the numbers of inhabitants in a household and household crowding represent crude and indirect indices of psychological stress. Other physical characteristics of the residence may also influence the inhabitants' level of stress including the size of the rooms, their structure and settings, the quality of the construction, the nature of the residence (apartment vs. house), the floor level, as well as the quality of life in the neighborhood. Thus, we could also not exclude the possibility that later development of

schizophrenia in the offspring may be influenced by other indexes of maternal psychological stress during pregnancy.

When examined by sex, the impact of paternal age on the link between number of household inhabitants during pregnancy and the offspring's risk of schizophrenia was not significant. Malaspina et al. (2001) found that each decade of paternal age changed the offspring RR by 1.40 (95% CI, 1.21–1.59) for males and 1.26 (95% CI, 1.07–1.48) for females. However, as the CIs in these 2 estimates overlap, the difference between the sexes may have been caused by chance. A similar trend have been reported by Sipos et al. (2004) who found offspring RR increased by 1.65 (95% CI, 1.32–2.06) for males and 1.40 (95% CI, 1.03–1.89) for females for every 10 years of paternal age in a population based cohort study with over 700,000 subjects. However, they found no statistically marked difference in the association between paternal age and schizophrenia by sex (p=0.20, for interaction).

The limitations of our study should be acknowledged–our data on number of inhabitants and number of rooms per residence are based on the mothers' self reports–thus, they may not represent the actual characteristics of the household and may potentially confound the link between crowding and schizophrenia. Another potential limitation, which will be remedied with the completion of our study in several years, is the lack of information on family psychiatric history. Byrne et al. (2003) reported that paternal age had a significant impact on offspring's risk of schizophrenia after controlling for family psychiatric history. This finding is consistent with Malaspina et al. (2001) who proposed that the paternal age effect is caused by de-novo point mutations arising in paternal germ cells, leading to stronger influence of paternal age in sporadic cases than in familial ones. Similarly, we did not adjust the data for the impact of obstetric complications. Dalman and Allebeck (2002) found that adjusting to obstetric complications had little impact on the link between paternal age and offspring's risk of schizophrenia.

The strengths of this study are its use of prospectively acquired data on household crowding and potential confounding factors, and that it provided a continuous follow-up of schizophrenia cases. Future research should assess the potential contribution of different types of maternal psychological stressors on offspring's risk of schizophrenia. Furthermore, animal studies (Bhatnagar et al., 2005; Bethus et al., 2005) suggest that maternal stress may have a differential impact depending on the sex of the offspring—future studies should assess this impact as a potential source of heterogeneity in schizophrenia. Finally, paternal age has been found to have a robust impact on risk of schizophrenia. Future investigations should assess the impact of paternal age in relationship to other variables that have been linked to increased risk of schizophrenia including urbanicity and immigration. In conclusion, this study contributes the growing literature regarding the impact of paternal age on offspring's risk of schizophrenia. It indicates that increased maternal household crowding during pregnancy did not significantly increase the offspring's risk of developing schizophrenia beyond the impact of paternal age.

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References

Agerbo E, Torrey EF, Mortensen PB. Household crowding in early adulthood and schizophrenia are unrelated in Denmark: a nested case–control study. Schizophr Res 2001;47:243–246. [PubMed: 11278141]

Beauregard M, Bachevalier J. Neonatal insult to the hippocampal region and schizophrenia: a review and a putative animal model. Can J Psychiatry 1996;41:446–456. [PubMed: 8884034]

Berger MA, Barros VG, Sarchi MI, Tarazi FI, Antonelli MC. Long-term effects of prenatal stress on dopamine and glutamate receptors in adult rat brain. Neurochem Res 2002;27:1525–1533. [PubMed: 12512957]

Bethus I, Lemaire V, Lhomme M, Goodall G. Does prenatal stress affect latent inhibition? It depends on the gender Behav Brain Res 2005;58(2):331–338.

Bhatnagar S, Lee TM, Vining C. Prenatal stress differentially affects habituation of corticosterone responses to repeated stress in adult male and female rats. Horm Behav 2005;47:430–438. [PubMed: 15777808]

Brown AS, Schaefer CA, Wyatt RJ, Begg MD, Goetz R, Bresnahan MA, Harkavy-Friedman J, Gorman JM, Malaspina D, Susser ES. Paternal age and risk of schizophrenia in adult offspring. Am J Psychiatry 2002;159:1528–1533. [PubMed: 12202273]

Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, Babulas VP, Susser ES. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry 2004;61:774–780. [PubMed: 15289276]

Byrne M, Agerbo E, Ewald H, Eaton WW, Mortensen PB. Parental age and risk of schizophrenia: a case–control study. Arch Gen Psychiatry 2003;60:673–678. [PubMed: 12860771]

Castner SA, Goldman-Rakic PS, Williams GV. Animal models of working memory: insights for targeting cognitive dysfunction in schizophrenia. Psychopharmacology 2004;174:111–125. [PubMed: 15205882]

Clarke AS, Wittwer DJ, Abbott DH, Schneider ML. Long-term effects of prenatal stress on HPA axis activity in juvenile rhesus monkeys. Dev Psychobiol 1994;27:257–269. [PubMed: 7926279]

Coe CL, Kramer M, Czeh B, Gould E, Reeves AJ, Kirschbaum C, Fuchs E. Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. Biol Psychiatry 2003;54:1025–1034. [PubMed: 14625144]

Cox, DR.; Oakes, D. Analysis of Survival Data. Chapman & Hall; London, England: 1984.

Creighton JA, Chevins PF. Stressful crowding during pregnancy advances onset of offspring adrenocortical rhythm. Exp Biol 1988;48:57–62. [PubMed: 3268429]

Crump CJ, Chevins PF. Prenatal stress reduces fertility of male offspring in mice, without affecting their adult testosterone levels. Horm Behav 1989;23:333–343. [PubMed: 2793076]

Dahlof LG, Hard E, Larsson K. Influence of maternal stress on offspring sexual behaviour. Anim Behav 1977;25:958–968. [PubMed: 564150]

Dalman C, Allebeck P. Paternal age and schizophrenia: further support for an association. Am J Psychiatry 2002;159:1591–1592. [PubMed: 12202282]

El-Saadi O, Pedersen CB, McNeil TF, Saha S, Welham J, O'Callaghan E, Cantor-Graae E, Chant D, Mortensen PB, McGrath J. Paternal and maternal age as risk factors for psychosis: findings from Denmark, Sweden and Australia. Schizophr Res 2004;67:227–236. [PubMed: 14984882]

Erlenmeyer-Kimling L, Folnegovic Z, Hrabak-Zerjavic V, Borcic B, Folnegovic-Smalc V, Susser E. Schizophrenia and prenatal exposure to the 1957 A2 influenza epidemic in Croatia. Am J Psychiatry 1994;151:1496–1498. [PubMed: 8092342]

Gutteling BM, de Weerth C, Willemsen-Swinkels SH, Huizink AC, Mulder EJ, Visser GH, Buitelaar JK. The effects of prenatal stress on temperament and problem behavior of 27-month-old toddlers. Eur Child Adolesc Psychiatry 2005;14:41–51. [PubMed: 15756515]

Hanlon FM, Sutherland RJ. Changes in adult brain and behavior caused by neonatal limbic damage: implications for the etiology of schizophrenia. Behav Brain Res 2000;107:71–83. [PubMed: 10628731]

Harlap S, Davies AM, Grover NB, Prywes R. The Jerusalem perinatal study: the first decade 1964–73. Isr J Med Sci 1977;13:1073–1091. [PubMed: 591301]

Harvey PW, Chevins PF. Crowding pregnant mice affects attack and threat behavior of male offspring. Horm Behav 1985;19:86–97. [PubMed: 4038967]

Harvey PW, Chevins PF. Crowding during pregnancy delays puberty and alters estrous cycles of female offspring in mice. Experientia 1987;43:306–308. [PubMed: 3556526]

Hayashi A, Nagaoka M, Yamada K, Ichitani Y, Miake Y, Okado N. Maternal stress induces synaptic loss and developmental disabilities of offspring. Int J Dev Neurosci 1998;16:209–216. [PubMed: 9785117]

Henry C, Guegant G, Cador M, Arnauld E, Arsaut J, Le Moal M, Demotes-Mainard J. Prenatal stress in rats facilitates amphetamine-induced sensitization and induces long-lasting changes in dopamine receptors in the nucleus accumbens. Brain Res 1995;685:179–186. [PubMed: 7583244]

Huizink AC, Robles de Medina PG, Mulder EJ, Visser GH, Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. J Child Psychol Psychiatry 2003;44:810–818. [PubMed: 12959490]

Huizink AC, Mulder EJ, Buitelaar JK. Prenatal stress and risk for psychopathology: specific effects or induction of general susceptibility. Psychol Bull 2004;130:115–142. [PubMed: 14717652]

Huttunen MO, Niskanen P. Prenatal loss of father and psychiatric disorders. Arch Gen Psychiatry 1978;35:429–431. [PubMed: 727894]

Kattesh HG, Kornegay ET, Knight JW, Gwazdauskas FG, Thomas HR, Notter DR. Glucocorticoid concentrations, corticosteroid binding protein characteristics and reproduction performance of sows and gilts subjected to applied stress during mid-gestation. J Anim Sci 1980;50:897–905. [PubMed: 7390944]

Kilts CD. The changing roles and targets for animal models of schizophrenia. Biol Psychiatry 2001;50:845–855. [PubMed: 11743940]

Laor A, Stevenson DK, Shemer J, Gale R, Seidman DS. Size at birth, maternal nutritional status in pregnancy, and blood pressure at age 17: population based analysis. BMJ 1997;315:449–453. [PubMed: 9284660]

Lichtenberg P, Kaplan Z, Grinshpoon A, Feldman D, Nahon D. The goals and limitations of Israel's psychiatric case register. Psychiatr Serv 1999;50:1043–1048. [PubMed: 10445652]

Limosin F, Rouillon F, Payan C, Cohen JM, Strub N. Prenatal exposure to influenza as a risk factor for adult schizophrenia. Acta Psychiatr Scand 2003;107:331–335. [PubMed: 12752028]

Lipska BK, Weinberger DR. To model a psychiatric disorder in animals: schizophrenia as a reality test. Neuropsychopharmacology 2000;23:223–239. [PubMed: 10942847]

Lipska BK, Jaskiw GE, Weinberger DR. Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: a potential animal model of schizophrenia. Neuropsychopharmacology 1993;9:67–75. [PubMed: 8397725]

Malaspina D. Paternal factors and schizophrenia risk: de novo mutations and imprinting. Schizophr Bull 2001;27:379–393. [PubMed: 11596842]

Malaspina D, Harlap S, Fennig S, Heiman D, Nahon D, Feldman D, Susser ES. Advancing paternal age and the risk of schizophrenia. Arch Gen Psychiatry 2001;58:361–367. [PubMed: 11296097]

McGrath JJ, Pemberton MR, Welham JL, Murray RM. Schizophrenia and the influenza epidemics of 1954, 1957 and 1959: a southern hemisphere study. Schizophr Res 1994;14:1–8. [PubMed: 7893616]

O'Connor TG, Heron J, Golding J, Glover V, ALSPAC Study Team. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. J Child Psychol Psychiatry 2003;44:1025–1036. [PubMed: 14531585]

Peters AR. Hormonal control of the bovine oestrous cycle: II. Pharmacological principles. Br Vet J 1986;142:20–29. [PubMed: 3947928]

Schmajuk NA. Animal models for schizophrenia: the hippocampally lesioned animal. Schizophr Bull 1987;13:317–327. [PubMed: 3616522]

Schneider ML, Roughton EC, Koehler AJ, Lubach GR. Growth and development following prenatal stress exposure in primates: an examination of ontogenetic vulnerability. Child Dev 1999;70:263–274. [PubMed: 10218255]

Selten JP, Brown AS, Moons KG, Slaets JP, Susser ES, Kahn RS. Prenatal exposure to the 1957 influenza pandemic and non-affective psychosis in The Netherlands. Schizophr Res 1999;38:85–91. [PubMed: 10463456]

Sipos A, Rasmussen F, Harrison G, Tynelius P, Lewis G, Leon DA, Gunnell D. Paternal age and schizophrenia: a population based cohort study. BMJ 2004;329:1070. [PubMed: 15501901]

Torrey EF, Yolken RH. At issue: is household crowding a risk factor for schizophrenia and bipolar disorder? Schizophr Bull 1998;24:321–324. [PubMed: 9718626]

Tsuchiya KJ, Takagai S, Kawai M, Matsumoto H, Nakamura K, Minabe Y, Mori N, Takei N. Advanced paternal age associated with an elevated risk for schizophrenia in offspring in a Japanese population. Schizophr Res 2005;76:337–342. [PubMed: 15949666]

Wahlbeck K, Osmond C, Forsen T, Barker DJ, Eriksson JG. Associations between childhood living circumstances and schizophrenia: a population-based cohort study. Acta Psychiatr Scand 2001;104:356–360. [PubMed: 11722316]

Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987;44:660–669. [PubMed: 3606332]

Westergaard T, Mortensen PB, Pedersen CB, Wohlfahrt J, Melbye M. Exposure to prenatal and childhood infections and the risk of schizophrenia: suggestions from a study of sibship characteristics and influenza prevalence. Arch Gen Psychiatry 1999;56:993–998. [PubMed: 10565498]

Zammit S, Allebeck P, Dalman C, Lundberg I, Hemmingson T, Owen MJ, Lewis G. Paternal age and risk for schizophrenia. Br J Psychiatry 2003;183:405–408. [PubMed: 14594914]

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Table 1

Incidence of schizophrenia in offspring by characteristics of the mother's household during her pregnancy

Household characteristics	Number of cases and population	Crude relative risk (RR)		Adjusted relative risk (RR)	
		RR (95% CI)	*p*	RR (95% CI)	*p*
Crowding (inhabitants per room)					
0–0.99	9/1174	1.00= reference	–	1.00= reference	–
1–1.99	48/4778	1.29 (0.63–2.63)	0.48	1.17 (0.57–2.40)	0.66
2–2.99	22/2655	0.98 (0.46–2.15)	0.98	0.83 (0.38–1.82)	0.64
3 or more	25/2304	1.28 (0.60–2.74)	0.52	0.91 (0.41–2.03)	0.82
Number of rooms					
1–2	57/5961	1.00= reference	–	100=reference	–
3 or more	47/4950	1.11 (0.75–1.63)	0.60	1.04 (0.70–1.53)	0.86
Number of inhabitants					
1–4	59/7229	1.00= reference	–	1.00= reference	–
5 or more	45/3682	1.47 (0.99–2.16)	0.05	1.35 (0.74–2.47)	0.33

Adjusted RR—variables adjusted for paternal age (continuous), birth order (continuous), and SES (categorical).