

The effects of genetic liability for schizophrenia and maternal smoking during pregnancy on obstetric complications

Lauren M. Ellman^{a,*}, Matti Huttunen^c, Jouko Lönnqvist^{c,d}, Tyrone D. Cannon^{a,b}

^a *UCLA Psychology Department, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563, United States*

^b *University of California-Los Angeles, Department of Psychiatry and Biobehavioral Sciences*

^c *The Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, 00300, Helsinki, Finland*

^d *Department of Psychiatry, University of Helsinki and Helsinki University Central Hospital Department of Psychiatry, University of Helsinki and Helsinki University Central Hospital, P.O. Box 22, Valskariankatu 12, 00014, Helsinki, Finland*

Received 6 October 2006; received in revised form 11 March 2007; accepted 14 March 2007

Available online 1 May 2007

Abstract

The purpose of this study was to determine whether a genetic vulnerability for schizophrenia and/or health-risk behaviors among schizophrenic pregnant women were associated with an increased incidence of obstetric complications (OCs).

Method: A high-risk birth cohort was formed by searching the Finnish Perinatal Register for all births from 1991–2000 with arterial cord pH values below 7.20, an indication of fetal asphyxia. This database was merged with national hospital discharge registries to determine psychiatric morbidity of the mothers and the mothers' first-degree relatives. Mothers were divided into 3 groups: women diagnosed with schizophrenia/schizoaffective disorder ($n=53$), mothers with a first-degree relative with schizophrenia/schizoaffective disorder ($n=590$) and healthy controls ($n=36,895$).

Result: Schizophrenic women had significantly more OCs than mothers with a first-degree schizophrenic relative and controls. These women had significantly increased rates of eclampsia, premature delivery, prenatal hospitalizations, and marginally significant increases in high blood pressure. Offspring of schizophrenic mothers had significantly decreased APGAR scores and birth weight and increased medical complications after birth. In contrast, women with a schizophrenic first-degree relative had no significant increases in OCs compared to controls. Schizophrenic mothers also smoked more than the other groups and smoking was found to mediate the relationship between maternal schizophrenic status and decreased birth weight among offspring.

Conclusions: Maternal schizophrenia during pregnancy leads to an increased risk of OCs, possibly due to engagement in health-risk behaviors during pregnancy, such as smoking, whereas genetic susceptibility to schizophrenia, by itself, does not appear to be related to incidence of OCs.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Schizophrenia; Pregnancy; Obstetric complications; Gene-environment covariation; Behavioral genetics; Health-risk behaviors

Abbreviations: (OC), Obstetric Complications; (Sz), mothers with schizophrenia/schizoaffective disorder; (Fhx), mothers with a first-degree relative with schizophrenia/schizoaffective disorder.

* Corresponding author. Tel.: +1 310 794 9673 (Work); fax: +1 310 794 9740.

E-mail addresses: ellman@psych.ucla.edu (L.M. Ellman), matti.huttunen@konsmoh.inet.fi (M. Huttunen), jouko.lonnqvist@ktl.fi (J. Lönnqvist), cannon@psych.ucla.edu (T.D. Cannon).

1. Introduction

Schizophrenia is a debilitating brain disorder typically with onset in late adolescence/early adulthood (DSM-IV-TR, 2000). Although genetic factors play a substantial role in the etiology of the disorder, with heritability estimates approximating 83% (Cannon et al.,

1998), environmental factors must also play a role. Among the environmental contributors, obstetric complications (OCs) have consistently been associated with schizophrenia (Brown and Susser, 2002; Cannon and Clarke, 2005; Cannon, 1997). Obstetric complications have been defined as the broad class of deviations from a normal course of events and offspring development during pregnancy, labor-delivery, and the early neonatal period (McNeil, 1988). OCs occur at a relatively high frequency, with approximately 20–30% of schizophrenic patients and 5–10% of the overall population having a history of certain OCs, such as those associated with oxygen deprivation (Buka et al., 1993; Cannon, 1997; McNeil, 1988). A question of major importance is whether the effects of OCs depend on (Cannon et al., 1990), covary with (Fish et al., 1992), or are independent of (Lewis and Murray, 1987; Torrey and Yolken, 1995) genetic influences in the etiology of schizophrenia. Determining the correct model is critical for efforts to locate predisposing genes and could have significant implications for prevention efforts.

It is particularly critical to determine whether the genes for schizophrenia themselves increase the incidence of OCs, as in the gene-environment covariation model. If this is the case, it would not be clear whether the obstetric influences exert an etiologic effect that is independent of genetic influences, or vice versa. The gene-environment covariation model predicts a relative increase in the number of OCs in individuals carrying the genes for the disorder, regardless of whether they express the illness phenotypically. Support for this model comes from studies that found increased birth complications among schizophrenic mothers (McNeil, 1991; Wrede et al., 1980), but is inconsistent with one study that found no increases in maternal recall of OCs among unaffected siblings of schizophrenic patients (Walshe et al., 2005). Studies that rely on maternal recall of OCs are subject to bias; therefore, it is still unclear whether individuals at high genetic liability for the disorder exhibit increases in OCs (Buka et al., 2000; McIntosh et al., 2002).

Although increased OCs in the offspring of schizophrenic mothers supports the gene-environment covariation model, findings suggest that there also is greater occurrence of health-risk behaviors during pregnancy among these women, including being less likely to receive prenatal care, more likely to be polydrug users, more likely to drink alcohol, and more likely to smoke cigarettes compared to non-schizophrenic controls (Bennedsen, 1998). Many of these health-risk behaviors have been linked with increased incidences of certain OCs. Specifically, maternal smoking during pregnancy

significantly predicts low birth weight, fetal hypoxia, premature delivery, small for gestational age infants, and infant mortality (Delpisheh et al., 2006; Kleinman et al., 1988; Raatikainen et al., 2007; Smith et al., 2006). In fact, one study found that women diagnosed with schizophrenia before the birth of their babies were at especially heightened risk for OCs and that smoking partially mediated these effects (Nilsson et al., 2002). This pattern of results raises the possibility that it is the schizophrenic mother's engagement in health-risk behaviors, rather than her genetic loading for the disorder, that is related to increased incidence of OCs.

The purpose of this study is to determine whether an increased incidence of obstetric complications (OCs) is associated with a family history of schizophrenia and/or maternal smoking during pregnancy among schizophrenic women using prospectively collected obstetric and psychiatric information from national registries in Finland. It was predicted that there would be increased smoking and OCs among schizophrenic women compared with healthy controls and women with a 1st degree schizophrenic relative. In addition, we hypothesized that smoking during pregnancy would mediate the relationship between group status and risk for OCs related to smoking, such as decreased birth weight and premature delivery which have significant associations with smoking during pregnancy in the general population (Delpisheh et al., 2006; Raatikainen et al., 2007; Smith et al., 2006). Lastly, we predicted no significant differences between incidences of OCs among women with a family history of schizophrenia and controls. Women with a first-degree relative with schizophrenia likely have some of the disease-producing genes; therefore, if the genes for schizophrenia were associated with OCs, we would expect an increased frequency of OCs in this group compared with controls.

2. Materials and methods

The institutional review boards at the National Public Health Institute of Finland and from the University of California, Los Angeles, approved this study. To ascertain a sample with a high-risk for obstetric complications, a birth cohort was formed by searching the Finnish Perinatal Register (from the National Research and Development Centre for Welfare and Health/STAKES) for all babies born between the years of 1991 and 2000 with arterial cord pH values below 7.20 ($n=38\ 420$), which is a fair estimate of acute perinatal hypoxia (Silverman et al., 1985; Smith et al., 2004). This inclusion criterion was chosen because perinatal hypoxia has been associated with many OCs,

including the OCs included in this study (Adamson et al., 1995; Heinonen and Saarikoski, 2001; Leuthner and Das, 2004; Moore et al., 1986; Nitsos et al., 2006; Teramo et al., 2004; Unger et al., 1988; Villar et al., 2006), therefore the composition of this high-risk cohort ensured that the groups would include women with a high likelihood of OCs.

Finnish citizens have free access to psychiatric inpatient and outpatient health care. There are 3 national computerized databases that document psychiatric contacts: Hospital Discharge Register, Pension Register, and Free Medicine Register (from the National Research and Development Centre for Welfare and Health/STAKES). Approximately 90% of psychotic patients come into contact with the health care system in one of the aforementioned ways (Lehtinen et al., 1990). Records include primary diagnoses according to the International Classification of Diseases, editions 8–10 (International Classification of Diseases, 1969; International Classification of Diseases, 1977, 2003), but correspond well to DSM-III-R and IV criteria (DSM-III-R, 1987; DSM-IV, 1994). Studies suggest that the national registries have between 92–100% specificity for diagnosing schizophrenia when compared with DSM-III-R criteria (Cannon et al., 1998; Isohanni et al., 1997; Makikyro et al., 1998).

Groups were formed by searching these three registers for all women with an ICD-9 code of 295, thereby diagnosed with schizophrenia and/or schizoaffective disorder. The perinatal database then was merged with psychiatric databases and control subjects were selected based on having no psychiatric diagnoses in the psychiatric registries. Mothers were divided into 3 groups: women diagnosed with schizophrenia/schizoaffective disorder (*Sz*, $n=53$), mothers with a first-degree relative with schizophrenia/schizoaffective disorder (*Fhx*, $n=590$) and healthy controls (without psychiatric morbidity and/or a family history of psychiatric morbidity $n=36,895$). First-degree relatives were defined as mothers, fathers, and siblings. All of the psychotic women in this study were diagnosed with schizophrenia or schizoaffective disorder before the birth of their babies. Women diagnosed after the birth of their baby were excluded from the study in order to isolate women that had a greater likelihood of being symptomatic during pregnancy. Sample characteristics are displayed in Table 1.

2.1. Obstetric variables

Beginning in 1990, all births (including still births) in Finland were recorded in a computerized perinatal registry, which includes systematically acquired medical information pertaining to the pregnancies and births of

Table 1
Demographic characteristics of sample by group status

Characteristic Category	Schizophrenic/ schizoaffective mothers ($N=53$)	Mothers with first-degree schizophrenic relative ($N=590$)	No diagnosis ($N=36,895$)
Baby's sex	Male	54.72%	53.82%
	Female	45.28%	46.18%
Marital status	Married	58.49%	63.73%
	Unmarried	37.74%	34.32%
	Divorced	0.00%	0.08%
	Widowed	3.77%	1.87%
Mother's age	Mean (SD)	33.87(5.71)	29.22 (5.29)
	Earlier deliveries	Mean (SD) 0.93(1.82)	1.00(1.63)

individuals in the population. In Finland, approximately 90% of pregnant women attend outpatient clinics at least once a month. During these visits, a personal pregnancy data card, which includes medical information pertaining to the visit, is completed by the physician. Similarly, labor and delivery information is collected during the mother's stay in hospital. Obstetric data included in the perinatal registry have greater than 95% agreement with medical records and are considered reliable and valid (Gissler et al., 1995; Teperi, 1993).

One minute APGAR scores, birth weight (grams), premature delivery (earlier than 37 weeks), eclampsia, prenatal hospital admission due to unknown reasons, smoking during pregnancy, neonatal treatment 7 days after birth (0 indicated no treatment and 1 indicated treatment), treatment at hospital due to high blood pressure, and bleeding during pregnancy were used in this study.

Smoking during pregnancy was defined as smoking at any time during the course of pregnancy. An APGAR score is a measure of the newborn derived at by scoring the heart rate, respiratory effort, muscle tone, skin color, and response to a catheter in the nostril (rated from 0–10, 10 indicating perfect health). Eclampsia is defined as convulsions occurring with pregnancy-associated high blood pressure.

2.2. Statistical analyses

Statistical analyses were conducted using SAS version 8.2 software (SAS, Inc., Cary, N.C.). One-way ANOVA's determined significant differences in maternal age ($f=99.86$, $df=2$, $p<0.0001$) and parity ($f=34.05$, $df=2$, $p<.0001$) among the 3 comparison groups (see Table 1); therefore maternal age and parity

were controlled for in all regression and logistic regression analyses. Chi-square tests and post-hoc chi-square tests were estimated to examine whether groups differed in smoking status during pregnancy. Logistic regression (for dichotomous dependent variables) and multiple regression analyses (for normally distributed continuous dependent variables) were conducted to ascertain whether group status significantly predicted OCs, net of maternal age and parity. All analyses using measures of the newborn also controlled for the baby's gender.

To test whether smoking mediated the relationship between group status and OCs, smoking during pregnancy was added as a covariate to the above models, to determine whether inclusion of this variable eliminated the effects of group status on OCs. As described by Barron and Kenny (1986), a mediation variable changes the relationship between the antecedent and outcome variable and must be significantly associated with the antecedent and outcome variables. Specifically, for smoking to mediate the relationship between schizophrenic status and OCs: 1. Schizophrenic status must be significantly associated with the OC 2. Schizophrenic status must be associated with smoking during pregnancy and 3. Addition of smoking during pregnancy to a model must remove the significant effect of schizophrenic status on OCs.

3. Results

Table 2 displays percentages, means, chi-squares, and ANOVA results for all obstetric variables by group status. Results indicated no significant overall differences between the 3 groups with respect to smoking ($\chi^2=4.0372$, $df=2$, $p=0.1328$), however post-hoc com-

parisons revealed a significant difference in smoking between Sz and controls ($\chi^2=4.0239$, $df=1$, $p=0.0449$) and a marginal difference between Sz and Fhx ($\chi^2=3.3717$, $df=1$, $p=0.0663$). The significant difference in smoking between Sz and controls meets the second condition for a mediation variable. There was no significant difference in smoking between Fhx and controls, indicating that this effect was limited to those who expressed the disorder phenotypically.

The initial models, without including smoking as a covariate, suggested that maternal schizophrenic status compared with control status was significantly associated with a multitude of prenatal complications, meeting the first condition for mediation. Specifically, schizophrenic status compared to control status was associated with a 57.05 times increase in eclampsia ($\chi^2=51.96$, $df=1$, $p<.0001$), a 2.17 times increase in prenatal hospital treatment ($\chi^2=7.09$, $df=1$, $p=0.0077$), a 3.43 times increase in premature delivery ($\chi^2=5.55$, $df=1$, $p=0.018$), and a marginal 2.05 times increase in maternal hospital treatment for high blood pressure ($\chi^2=2.71$, $df=1$, $p=0.099$), independent of maternal age and parity (see Table 3). Similarly, maternal schizophrenic status compared to control status was significantly associated with a series of neonatal complications among offspring, including a 173.46 gram decrease in birth weight ($t=-2.17$, $df=1$, $p=0.03$), a 0.78 decrease in APGAR scores ($t=-3.39$, $df=1$, $p=0.0007$), and a 4.74 times increase in neonatal medical treatment 7 days after delivery ($\chi^2=28.32$, $df=1$, $p<.0001$), controlling for maternal age, parity, and infant's gender. In contrast, having a first-degree relative with schizophrenia had no significant effect on any of the obstetric variables compared to controls. Lastly, there was no effect of group status on vaginal bleeding, which may have been

Table 2
Means and percentages of obstetric complications by group status

Characteristic	Category	Schizophrenic/ schizoaffective mothers (<i>N</i> =53)	Mothers with first-degree schizophrenic relative (<i>N</i> =590)	No diagnosis (<i>N</i> =36,895)	Analysis	
					<i>F</i> , <i>df</i> , <i>p</i>	χ^2 , <i>df</i> , <i>p</i>
Smoking during pregnancy	Percentage	25.00%	15.24%	15.04%		4.04, 2, 0.13
Birth weight	Mean (SD)	3377.36 (757.96)	3550.84 (619.58)	3548.54 (590.69)	2.22, 2, 0.11	
1-minute APGAR	Mean (SD)	7.09 (2.48)	7.84 (1.67)	7.91 (1.67)	6.80, 2, 0.001	
Premature delivery	Percentage	7.55%	1.69%	1.97%		8.73, 2, 0.01
Eclampsia	Percentage	3.77%	0.00%	0.05%		131.47, 2, <.0001
Prenatal hospitalization	Percentage	33.96%	17.97%	17.52%		9.9596, 2, 0.007
Neonatal medical treatment within 1 week after birth	Percentage	33.96%	10.00%	8.62%		44.20, 2, <.0001
Vaginal bleeding	Percentage	0.00%	1.02%	1.06%		0.58, 2, 0.75
Maternal high blood pressure	Percentage	11.32%	4.75%	5.20%		4.27, 2, 0.12

Table 3
Effects of group status on OCs: results from regression and logistic regression analyses

Characteristic	Model 1				Model 2: adding smoking			
	Sz vs. controls		Fhx vs. controls		Sz vs. controls		Fhx vs. control	
	Parameter estimate	95% CI	Parameter estimate	95% CI	Parameter estimate	95% CI	Parameter estimate	95% CI
Birth weight	-173.47*	-330.51, -16.43	-12.36	-59.85, 35.13	-102.54	-259.59, 54.51	-1.69	-49.51, 46.14
1-minute APGAR	-0.78***	-1.23, -0.33	-0.06	-0.20, 0.08	-0.68**	-1.13, -0.22	-0.06	-0.20, 0.08
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Premature delivery	3.43*	1.23, 9.57	0.78	0.42, 1.47	3.32*	1.20, 9.34	0.80	0.43, 1.51
Eclampsia	57.05***	11.94, 272.58	0.00	<0.001, >999.999	28.03**	3.36, 233.50	0.00	<0.001, >999.999
Prenatal hospitalization	2.17**	1.23, 3.84	0.96	0.78, 1.19	2.20**	1.24, 3.90	0.95	0.76, 1.17
Neonatal medical treatment within 1 week after birth	4.74***	2.67, 8.40	1.09	0.83, 1.43	4.44***	2.48, 7.97	1.06	0.80, 1.41
Vaginal bleeding	0.00	<0.001, >999.999	0.89	0.39, 2.00	0.00	<0.001, >999.999	0.92	0.41, 2.06
High blood pressure	2.05†	0.87, 4.84	0.88	0.60, 1.30	2.16††	0.92, 5.11	0.84	0.565, 1.25

Table 3 displays parameter estimates and odds ratios for all multiple regression and logistic regression analyses. Ninety-five percent confidence intervals also are displayed. Model 1 examined the effects of group status on OCs, after controlling for maternal age and parity. Model 2 examined whether smoking during pregnancy mediated the effects of group status on OCs by adding smoking as a covariate. Model 2 also controlled for maternal age and parity.

† $p = .099$, †† $p = 0.078$, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.0001$

due to the very low incidence of this OC in the overall sample (see Table 2).

To test the third condition of mediation, smoking during pregnancy was entered into each regression and logistic regression model. Results replicated the initial findings for eclampsia, prenatal hospital treatment, premature delivery, vaginal bleeding, prenatal treatment at hospital for high blood pressure, 1-minute APGAR scores, and neonatal medical treatment 7 days after delivery, indicating an absence of mediation effects of smoking on these OCs (see Table 3). However, smoking was found to mediate the relationship between schizophrenic status and decreased birth weight, such that there was no longer a significant association between schizophrenic status and birth weight when smoking was included in the model ($t = 1.28$, $df = 1$, $p = 2.007$) (see Table 3).

4. Discussion

This is the first study to demonstrate in a prospective design that schizophrenic women had significantly more obstetric complications than mothers with a genetic vulnerability for schizophrenia and controls. Specifically, schizophrenic mothers had more complications during pregnancy, with increased rates of eclampsia, prenatal hospitalizations, high blood pressure during pregnancy, and preterm delivery. In addition, offspring

of these women had significantly more difficulties than offspring of the other two comparison groups, with decreased APGAR scores and birth weight and increased rates of neonatal medical treatments. In contrast, women with a genetic liability for schizophrenia had no significant increases in OCs compared to controls. These findings argue against the gene-environment covariation model, which predicts increases in OCs among mothers with a genetic liability for schizophrenia. Because women with a schizophrenic first-degree relative likely have some of the disease-producing genes, if the gene-environment covariation model were correct, there would be increased OCs among this group, which was not observed.

Findings also indicated that schizophrenic mothers smoked more than the other two groups and smoking mediated the relationship between schizophrenic status and decreased birth weight. This finding is especially important given that there have been conflicting results pertaining to increased incidence of low birth weight babies among schizophrenic mothers (Bennedsen, 1998; McNeil, 1991; Sacker et al., 1996). Nevertheless, smoking was not found to mediate the relationship between schizophrenic status and premature delivery. One possibility is that the mediational effects of smoking on gestational length were obscured by using a dichotomous variable (term/preterm) versus a continuous estimation of gestational length, which were not

available. Another possibility is that other factors, such as increased maternal stress, health-risk behaviors not measured in this study, and/or increased genetic liability for the disorder masked the effects of smoking on premature delivery among cases. Future studies are necessary to unravel the potential contributors linking schizophrenic status and decreased gestational length.

The present study also found that schizophrenic mothers were significantly older than the other comparison groups and increased maternal age has been associated with a variety of OCs (Cogswell and Yip, 1995; Feldman et al., 2000; Lu and Halfon, 2003). Differences in parity also were found among groups, however there was only a trend difference between schizophrenic women and controls, with schizophrenic women tending to have more previous deliveries than controls, which is typically associated with fewer OCs (Cogswell and Yip, 1995; Feldman et al., 2000; Lu and Halfon, 2003). The present study controlled for these variables in analyses to focus on the study hypotheses; however, differences in maternal age highlight the necessity for future studies to consider how maternal characteristics may influence risk of OCs.

Overall, the results of this study raise the possibility that increases in all OCs among schizophrenic mothers may be mediated by health-risk behaviors that were not examined in this study, such as poor nutrition, limited prenatal care, decreased prenatal vitamin use, neuroleptic use, and substance abuse. There has been a paucity of large, case controlled studies examining the use of neuroleptic medications during pregnancy on risk of OCs, although the available studies have reported mixed findings (reviewed in Iqbal et al., 2003; Patton et al., 2002). Conversely, discontinuation of neuroleptic use during pregnancy has been associated with a worsening of symptoms, often leading to psychotic episodes in relatively asymptomatic women (reviewed in McNeil et al., 1984; Miller, 1997), which can have multiple consequences for prenatal health, including increased stress, poor nutrition, poor self-care, and other risky behaviors (Miller, 1997). Unfortunately, data on medication use and other health-risk behaviors were not available for the women used in this study.

It also is possible that schizophrenic pregnant women experience increased anxiety and stress during pregnancy, which has been associated with a series of OCs, such as shortened gestational length (Dunkel-Schetter, 1998; Wadhwa et al., 2001). No studies have systematically examined whether schizophrenic pregnant women experience augmented stress during pregnancy, however there is some data suggesting that the pregnancies of schizophrenic women are more

likely to be unplanned and a result of coerced sexual encounters (Miller, 1997; Miller and Finnerty, 1996). In addition, some schizophrenic women will lose custody of their child after delivery due to active psychotic states, which may augment psychotic symptomatology during pregnancy and/or pregnancy-related anxiety (Miller, 1997). Additional exploration into the potentially distinct experiences of schizophrenic pregnant women would be useful to determine factors that could increase the risk of OCs.

There are multiple limitations of this study. One limitation is that a high-risk sample was chosen to form a population of women with an increased incidence of OCs (mothers with hypoxic births); however, this design may limit the generalizability of our findings to low-risk populations. In addition, we only examined 1 health-risk behavior during pregnancy. As mentioned previously, schizophrenic women are at risk for many health-risk behaviors that could portend increases in OCs; therefore, further exploration into the role of these behaviors on OCs is necessary. Lastly, other variables that may be associated with schizophrenic status, such as other health-risk behaviors, psychoactive medication use, and increased psychosocial stress should be examined as possible mediators between schizophrenic status and increased OCs.

5. Role of the funding source

Funding for this study was provided by a gift from Garen and Shari Staglin.

6. Contributors

Lauren M. Ellman wrote the manuscript, analyzed the data, and primarily determined the idea for the study. Matti Huttunen and Jouko Lönnqvist handled all of the aspects of the study that were carried out in Finland, including registry searches and explanation of the databases. In addition, both authors contributed their ideas in the construction of the manuscript. Tyrone D. Cannon participated in every part of the study, including idea formation, statistical analyses, and interaction with collaborators in Finland.

Acknowledgment

This research was supported by a gift to the UCLA Foundation from Garen and Shari Staglin. The authors wish to thank Theodor van Erp, Katherine Karsgodt, and Antti Tanskanen for their contributions.

References

- Adamson, S.J., Alessandri, L.M., Badawi, N., Burton, P.R., Pember-ton, P.J., Stanley, F., 1995. Predictors of neonatal encephalopathy in full-term infants. *BMJ* 311 (7005), 598–602.

- Baron, R.M., Kenny, D.A., 1986. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J. Pers. Psychol.* 51 (6), 1173–1182.
- Bennedsen, B.E., 1998. Adverse pregnancy outcome in schizophrenic women: occurrence and risk factors. *Schizophr. Res.* 33 (1–2), 1–26.
- Brown, A.S., Susser, E.S., 2002. In utero infection and adult schizophrenia. *Ment. Retard. Dev. Disabil. Res. Rev.* 8 (1), 51–57.
- Buka, S.L., Tsuang, M.T., Lipsitt, L.P., 1993. Pregnancy/delivery complications and psychiatric diagnosis. A prospective study. *Arch. Gen. Psychiatry* 50 (2), 151–156.
- Buka, S.L., Goldstein, J.M., Seidman, L.J., Tsuang, M.T., 2000. Maternal recall of pregnancy history: accuracy and bias in schizophrenia research. *Schizophr. Bull.* 26 (2), 335–350.
- Cannon, T.D., 1997. On the nature and mechanisms of obstetric influences in schizophrenia: a review and synthesis of epidemiologic studies. *International Review of Psychiatry* 9, 387–397.
- Cannon, M., Clarke, M.C., 2005. Risk for schizophrenia—broadening the concepts, pushing back the boundaries. *Schizophr. Res.* 79 (1), 5–13.
- Cannon, T.D., Mednick, S.A., Parnas, J., 1990. Antecedents of predominantly negative-and predominantly positive—symptom schizophrenia in a high-risk population. *Arch. Gen. Psychiatry* 47 (7), 622–632.
- Cannon, T.D., Kaprio, J., Lonnqvist, J., Huttunen, M., Koskenvuo, M., 1998. The genetic epidemiology of schizophrenia in a Finnish twin cohort: a population-based modeling study. *Arch. Gen. Psychiatry* 55, 67–74.
- Cogswell, M.E., Yip, R., 1995. The influence of fetal and maternal factors on the distribution of birthweight. *Semin. Perinatol.* 19 (3), 222–240.
- Delpisheh, A., Kelly, Y., Rizwan, S., Brabin, B.J., 2006. Socio-economic status, smoking during pregnancy and birth outcomes: an analysis of cross-sectional community studies in Liverpool (1993–2001). *J. Child. Health Care* 10 (2), 140–148.
- DSM-III-R, 1987. *Diagnostic and Statistical Manual of Mental Disorders (IV)*, Vol. Third Edition-Revised. American Psychiatric Association, Washington D.C.
- DSM-IV, 1994. *Diagnostic and Statistical Manual of Mental Disorders (IV)*, Vol. Fourth Edition. American Psychiatric Association, Washington D.C.
- DSM-IV-TR, 2000. *Diagnostic and Statistical Manual of Mental Disorders (IV-TR)*, Vol. Fourth Edition. American Psychiatric Association, Washington D.C. Text Revision.
- Dunkel-Schetter, C., 1998. Maternal stress and preterm delivery. *Prenat. Neonat. Med.* 3, 39–42.
- Feldman, P.J., Dunkel-Schetter, C., Sandman, C.A., Wadhwa, P.D., 2000. Maternal social support predicts birth weight and fetal growth in human pregnancy. *Psychosom Med* 62 (5), 715–725.
- Fish, B., Marcus, J., Hans, S.L., Auerbach, J.G., Perdue, S., 1992. Infants at risk for schizophrenia: sequelae of a genetic neurointegrative defect. A review and replication analysis of pandysmaturation in the Jerusalem Infant Development Study. *Arch. Gen. Psychiatry* 49 (3), 221–235.
- Gissler, M., Teperi, J., Hemminki, E., Merilainen, J., 1995. Data quality after restructuring a national medical registry. *Scand. J. Soc. Med.* 23 (1), 75–80.
- Heinonen, S., Saarikoski, S., 2001. Reproductive risk factors of fetal asphyxia at delivery: a population based analysis. *J. Clin. Epidemiol.* 54 (4), 407–410.
- International Classification of Diseases, E. R. I.-. (1969). Geneva, Switzerland: World Health Organization.
- International Classification of Diseases, N. R. I.-. (1977). Geneva, Switzerland: World Health Organization.
- International Classification of Diseases, N. R. I.-. (2003). Geneva, Switzerland: World Health Organization.
- Iqbal, M.M., Rahman, A., Husain, Z., Mahmud, S.Z., Ryan, W.G., Feldman, J.M., 2003. Clozapine: a clinical review of adverse effects and management. *Ann. Clin. Psychiatry* 15 (1), 33–48.
- Isohanni, M., Makikyro, T., Moring, J., Rasanen, P., Hakko, H., Partanen, U., Koiranen, M., Jones, P., 1997. A comparison of clinical and research DSM-III-R diagnoses of schizophrenia in a Finnish national birth cohort. Clinical and research diagnoses of schizophrenia. *Soc. Psychiatry Psychiatr. Epidemiol.* 32 (5), 303–308.
- Kleinman, J.C., Pierre Jr, M.B., Madans, J.H., Land, G.H., Schramm, W.F., 1988. The effects of maternal smoking on fetal and infant mortality. *Am. J. Epidemiol.* 127 (2), 274–282.
- Lehtinen, V., Joukamaa, M., Jyrkinen, E., Lahtela, K., Raitasalo, R., Maatela, J., Aromaa, A., 1990. Need for mental health services of the adult population in Finland: results from the Mini Finland Health Survey. *Acta Psychiatr. Scand.* 81 (5), 426–431.
- Leuthner, S.R., Das, U.G., 2004. Low Apgar scores and the definition of birth asphyxia. *Pediatr. Clin. North Am.* 51 (3), 737–745.
- Lewis, S.W., Murray, R.M., 1987. Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. *J. Psychiatr. Res.* 21 (4), 413–421.
- Lu, M.C., Halfon, N., 2003. Racial and ethnic disparities in birth outcomes: a life-course perspective. *Matern. Child Health J.* 7 (1), 13–30.
- Makikyro, T., Isohanni, M., Moring, J., Hakko, H., Hovatta, I., Lonnqvist, J., 1998. Accuracy of register-based schizophrenia diagnoses in a genetic study. *European Psychiatry* 13 (2), 57–62.
- McIntosh, A.M., Holmes, S., Gleeson, S., Burns, J.K., Hodges, A.K., Byrne, M.M., Dobbie, R., Miller, P., Lawrie, S.M., Johnstone, E.C., 2002. Maternal recall bias, obstetric history and schizophrenia. *Br. J. Psychiatry* 181, 520–525.
- McNeil, T.F., 1988. Obstetric factors and perinatal injuries. In: Tsuang, M.T., Simpson, J.C. (Eds.), *Handbook of schizophrenia. Nosology, epidemiology and genetics*, Vol. 3. Elsevier Science Pub. Co., New York, pp. 319–343.
- McNeil, T.F., 1991. Obstetric complications in schizophrenic parents. *Schizophr. Res.* 5 (2), 89–101.
- McNeil, T.F., Kaij, L., Malmquist-Larsson, A., 1984. Women with nonorganic psychosis: factors associated with pregnancy's effect on mental health. *Acta Psychiatr. Scand.* 70 (3), 209–219.
- Miller, L.J., 1997. Sexuality, reproduction, and family planning in women with schizophrenia. *Schizophr. Bull.* 23 (4), 623–635.
- Miller, L.J., Finnerty, M., 1996. Sexuality, pregnancy, and childrearing among women with schizophrenia-spectrum disorders. *Psychiatr. Serv.* 47 (5), 502–506.
- Moore, L.G., Brodeur, P., Chumbe, O., D'Brot, J., Hofmeister, S., Monge, C., 1986. Maternal hypoxic ventilatory response, ventilation, and infant birth weight at 4,300 m. *J. Appl. Physiol.* 60 (4), 1401–1406.
- Nilsson, E., Lichtenstein, P., Cnattingius, S., Murray, R.M., Hultman, C.M., 2002. Women with schizophrenia: pregnancy outcome and infant death among their offspring. *Schizophr. Res.* 58 (2–3), 221–229.
- Nitsos, I., Rees, S.M., Duncan, J., Kramer, B.W., Harding, R., Newnham, J.P., Moss, T.J., 2006. Chronic exposure to intra-amniotic lipopolysaccharide affects the ovine fetal brain. *J. Soc. Gynecol. Investig.* 13 (4), 239–247.
- Patton, S.W., Misri, S., Corral, M.R., Perry, K.F., Kuan, A.J., 2002. Antipsychotic medication during pregnancy and lactation in women with schizophrenia: evaluating the risk. *Can. J. Psychiatry* 47 (10), 959–965.

- Raatikainen, K., Huurinainen, P., Heinonen, S., 2007. Smoking in early gestation or through pregnancy: a decision crucial to pregnancy outcome. *Prev. Med.* 44 (1), 59–63.
- Sacker, A., Done, D.J., Crow, T.J., 1996. Obstetric complications in children born to parents with schizophrenia: a meta-analysis of case-control studies. *Psychol. Med.* 26 (2), 279–287.
- Silverman, F., Suidan, J., Wasserman, J., Antoine, C., Young, B.K., 1985. The Apgar score: is it enough? *Obstet. Gynecol.* 66 (3), 331–336.
- Smith, J.R., Franc, D.T., Carter, N.S., Zamora, D., Planck, S.R., Rosenbaum, J.T., 2004. Susceptibility of retinal vascular endothelium to infection with *Toxoplasma gondii* tachyzoites. *Invest. Ophthalmol. Visual Sci.* 45 (4), 1157–1161.
- Smith, G.C., Shah, I., White, I.R., Pell, J.P., Crossley, J.A., Dobbie, R., 2006. Maternal and biochemical predictors of spontaneous preterm birth among nulliparous women: a systematic analysis in relation to the degree of prematurity. *Int. J. Epidemiol.* 35 (5), 1169–1177.
- Teperi, J., 1993. Multi method approach to the assessment of data quality in the Finnish Medical Birth Registry. *J. Epidemiol. Community Health* 47 (3), 242–247.
- Teramo, K.A., Hiilesmaa, V.K., Schwartz, R., Clemons, G.K., Widness, J.A., 2004. Amniotic fluid and cord plasma erythropoietin levels in pregnancies complicated by preeclampsia, pregnancy-induced hypertension and chronic hypertension. *J. Perinat. Med.* 32 (3), 240–247.
- Torrey, E.F., Yolken, R.H., 1995. Could schizophrenia be a viral zoonosis transmitted from house cats? *Schizophr. Bull.* 21 (2), 167–171.
- Unger, C., Weiser, J.K., McCullough, R.E., Keefer, S., Moore, L.G., 1988. Altitude, low birth weight, and infant mortality in Colorado. *JAMA* 259 (23), 3427–3432.
- Villar, J., Carroli, G., Wojdyla, D., Abalos, E., Giordano, D., Ba'aqeel, H., Farnot, U., Bergsjö, P., Bakketeig, L., Lumbiganon, P., Campodonico, L., Al-Mazrou, Y., Lindheimer, M., Kramer, M., 2006. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? *Am. J. Obstet. Gynecol.* 194 (4), 921–931.
- Wadhwa, P.D., Culhane, J.F., Rauh, V., Barve, S.S., Hogan, V., Sandman, C.A., Hobel, C.J., Chicz-DeMet, A., Dunkel-Schetter, C., Garite, T.J., Glynn, L., 2001. Stress, infection and preterm birth: a biobehavioural perspective. *Paediatr. Perinat. Epidemiol.* 15 (Suppl 2), 17–29.
- Walshe, M., McDonald, C., Taylor, M., Zhao, J., Sham, P., Grech, A., Schulze, K., Bramon, E., Murray, R.M., 2005. Obstetric complications in patients with schizophrenia and their unaffected siblings. *Eur. Psychiatr.* 20 (1), 28–34.
- Wrede, G., Mednick, S.A., Huttunen, M.O., Nilsson, C.G., 1980. Pregnancy and delivery complications in the births of an unselected series of Finnish children with schizophrenic mothers. *Acta Psychiatr. Scand.* 62 (4), 369–381.