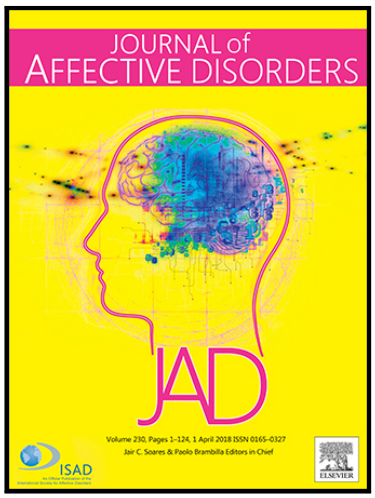

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Highlights:

- Antenatal depression is common and may affect foetal neurodevelopment.
- Increased risk for depression in adult offspring of antenatally depressed mothers.
- High risks for depression and schizophrenia in the offspring with both antenatally depressed mothers and parental severe mental disorder.
- Antenatal depression may potentiate the genetic risk for mental disorders.

Severe Mood Disorders and Schizophrenia in the Adult Offspring of Antenatally Depressed Mothers in the Northern Finland 1966 Birth Cohort: Relationship to Parental Severe Mental Disorder

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Abstract

Background: Maternal antenatal depression may alter offspring neurodevelopment, but long follow-up studies are lacking. We studied the risks for mood disorders and schizophrenia in adult offspring of antenatally depressed mothers, taking account parental severe mental disorders.

Methods: In the general population-based Northern Finland 1966 Birth Cohort with 12 058 children, 13.9 % of the mothers reported themselves depressed at mid-gestation. The offspring were followed 43 years. Severe mood disorders and schizophrenia in the offspring and severe mental disorders in the parents were detected using the Care Register for Healthcare. Maternal smoking during pregnancy, perinatal complications, fathers´ social class, family type at birth, and grand multiparity were considered as confounding variables.

Results: The offspring of antenatally depressed mothers had an elevated risk for depression (adjusted OR 1.5; 95% CI 1.03-2.2), compared to cohort members without maternal antenatal depressed mood. The offspring with maternal antenatal depressed mood and parental severe mental disorder had markedly elevated risks for depression (3.3; 1.8-6.2), and schizophrenia (3.9; 2.0-7.5), compared to the offspring without one or both of these risk factors.

Limitations: Maternal antenatal depressed mood was determined by one question and did not necessarily signify a clinical condition. Data on maternal postnatal mood was not available.

Conclusion: The offspring with maternal antenatal depressed mood and parental severe mental disorder had high risk for depression and schizophrenia. Early interventions in parental severe mental disorder might present an opportunity for decreasing the risk for mood disorders and schizophrenia in the offspring.

Keywords: Antenatal; Bipolar disorder; Depression; Mood disorders; Parental mental disorder; Schizophrenia

Introduction

Depression is one of the leading global causes of burden of disease (Whiteford et al., 2013). Maternal depression during pregnancy is common, affecting 10-17% of mothers, and at least as common as postpartum depression (Evans et al., 2001; Howard et al., 2014). It has long remained understudied in comparison with postnatal depression, but recently interest in antenatal mental health has risen in research and clinical practice. Still, of the mothers with antenatal depression, only 50 % get diagnosed and less than 10% get adequate treatment (Cox et al., 2016). As knowledge increases about the risks in the offspring of antenatally depressed mothers during foetal development, childhood and adolescence (Field, 2011; Gentile, 2017; Stein et al., 2014), the importance of antenatal depression research becomes clearer. The World Psychiatric Association (WPA) has issued a statement (Howard et al., 2017) that calls for improved focus on perinatal mental healthcare.

Maternal depression during pregnancy affects both the mother and the foetus. The offspring of antenatally depressed mothers are found to be at increased risk for perinatal complications, developmental delays, behavioural problems and depression (Field, 2011; Gentile, 2017; Plant et al., 2015; Stein et al., 2014), but long follow-up studies remain scarce. To the authors' knowledge, the only studies with psychiatric follow-up of the offspring of antenatally depressed mothers until middle adulthood are from the general population-based Northern Finland 1966 Birth Cohort (NFBC 1966) (Alaräisänen et al., 2012; Keskinen et al., 2013; Mäki et al., 2004, 2003; Taka-Eilola Née Riekki et al., 2017).

Parental mental disorders are common: up to one in five children have a parent with a mental disorder (Reupert et al., 2013). Mental disorders tend to aggregate in families (Bridge et al., 1997) and spouses have similarities in their psychiatric histories (Galbaud du Fort et al., 1998). Mothers

with a history of personal, familial or spousal mental illness are vulnerable to depression during pregnancy (Coates et al., 2018). Parental mental disorders have been recognized as a risk factor for a variety of psychiatric disorders in the offspring (Rasic et al., 2014). The risk for mental disorders in the offspring related to maternal antenatal depression and other parental mental disorders is probably mediated by both genetic and environmental factors (Schmitt et al., 2014). In our previous study from the NFBC 1966, maternal antenatal depression was associated with an elevated risk for schizophrenia, in the offspring in whom a history of parental psychosis was also present (Mäki et al., 2010). This could be an example of a gene-environment or a gene-gene interaction affecting neurodevelopment of the child (Weinberger, 1995).

The aim of the current study, based on the NFBC 1966, was to determine whether maternal antenatal depressed mood is associated with an elevated risk for depression, bipolar disorder or schizophrenia at ages 16-43 in the offspring, taking account of parental severe mental disorders. Our main interest was in the association of maternal antenatal mood, parental severe mental disorders and the risk for mood disorders in the offspring, as we have already studied schizophrenia in the offspring of antenatally depressed mothers taking account of parental psychosis (Mäki et al., 2010). We also aimed to examine subsequent parental psychiatric disorders in families where mothers had depressed mood during pregnancy. If antenatal depressed mood in association with other parental severe mental disorders results in high risk for severe mental disorders in the offspring, very early interventions in parental severe mental disorder could present an opportunity to reduce mental disorders in the offspring.

Methods

Subjects of the Northern Finland 1966 Birth Cohort (NFBC 1966)

The NFBC 1966 is an unselected, general population-based sample of 12 058 live-born children www.oulu.fi/nfbc). The cohort includes 96.3 % of live births during 1966 in the two northernmost provinces in Finland. Data on the children, with an estimated date of birth between January 1 and December 31 in the year 1966, was collected beginning during pregnancy, and the cohort has been followed over 40 years. The birth cohort has been described in more details previously (Mäki et al., 2010; Rantakallio, 1969). All NFBC 1966 subjects alive and living in Finland at age 16 years (N=11 017) were included in this study. The data on both maternal antenatal mood and parental severe mental disorders were available for 10 521 cohort members. Background information of the cohort members are reported in Table 1.

Permission to gather data was obtained from the Ministry of Social Affairs and Health. The Ethical Committee of the Northern Ostrobothnia Hospital District in Oulu, Finland has approved the study. An informed consent was obtained from all subjects included in the study.

Maternal depressed mood during pregnancy

The data on maternal mood during pregnancy was gathered at mid-gestation (mainly between the 24th and 28th gestational week during the years 1965-66). The mothers were asked by the interviewing nurse at the antenatal clinic if they felt their mood during pregnancy had been as usual, depressed, or very depressed. Of the mothers, 13.9% rated themselves as depressed (11.8%) or very

depressed (2.1%) during pregnancy (Mäki et al., 2010). In the analyses, these two categories were considered as 'depressed'.

The information regarding the mothers' antenatal mood was available for 10 662 (96.7%) offspring living in Finland at the age of 16 years. Data on the mother's mental disorders prior to, during and immediately after pregnancy, or on psychotropic medication during pregnancy were not available, but national register data on maternal later severe, hospital-treated mental disorders existed from 1972, when the offspring were 5 - 6 years of age, and onward.

Parental severe mental disorders

Data on parental severe, inpatient treated mental disorders were received from the Care Register for Healthcare (CRHC). The CRHC includes patient discharge-diagnoses from all mental and general hospitals, beds in local health centres and private hospitals in the whole country. The cohort members were linked with parental CRHC-data by their individual social security codes. All parents with a mental disorder (ICD-8 codes 290-309) were identified from 1972 until 1984 (between the ages of 5 - 6 and 18 years), when the offspring were of legal age. Data on parental mental disorders were available for 10 521 offspring. Parental mental disorders were considered as severe because they were inpatient ward-treated.

Outcome variables: Mood disorders and schizophrenia in the offspring

All the NFBC 1966 members appearing on the CRHC for mood disorders – depression (ICD-8 2960, 2980, 3004, 709; ICD-9 2961, 2968, 3004, 2969; ICD-10 F32-F33) or bipolar disorder (ICD-8 2961-2969; ICD-9 2962-2967; ICD-10 F30-F31) – or schizophrenia (ICD-8 295; ICD-9 295;

ICD-10 F20) between years 1982-2009 were identified. All case records between 1982-1997 were scrutinized, and diagnoses were validated against DSM-III-R criteria, after which they were rereviewed by a professional panel (Moilanen et al., 2003). Diagnoses during 1998-2009 were based on clinical discharge diagnoses as defined by the physicians responsible for the treatment. The CRHC-diagnoses are found to be relatively reliable (Perälä et al., 2007).

Cumulative incidences of severe mental disorders in the offspring were calculated in cohort groups with and without maternal antenatal depression and with or without parental severe mental disorder. A hierarchy was created in the statistical analysis of the diagnoses; bipolar disorder had priority over unipolar depression, and schizophrenia had priority over all other diagnoses which followed the prevailing practice, meaning that the subject is presented with only the diagnose with a highest priority. Twins (n=258) were excluded from statistical analyses, because they were lacking fathers´ CRHC-data.

Confounding variables

Sex, maternal smoking during pregnancy, perinatal complications, father´s social class, family type in the year 1966, and grand multiparity were taken account as potentially confounding variables. Only the variables, with statistically significant associations (p-value < 0.05), both with maternal antenatal depressed mood and with either severe mood disorder (depression or bipolar disorder) in the offspring, were used in adjustments.

Maternal smoking during pregnancy was considered as a confounding factor (1 = none or the mother stopped before pregnancy, 2 = smoked daily more than one cigarette during the entire duration of pregnancy). Mothers with severe mental disorders tend to smoke during pregnancy more

often than mentally healthy mothers (Goodwin et al., 2017). Smoking during pregnancy elevates risks for antenatal depression (Lancaster et al., 2010) and for obstetric complications (Ellman et al., 2007).

Perinatal complications have been linked to increased risk for mood disorders and schizophrenia in the offspring (Jablensky et al., 2005). Antenatally depressed mothers have a greater risk for preterm birth and low birth weight (Schmitt et al., 2014). Perinatal complications were thus considered as potentially confounding variables (1 = no complications, 2 = low birth weight [<2500g] or short gestational age [<37 weeks], or perinatal brain damage) (Jones et al., 1998; Rantakallio et al., 1987).

Familial factors, such as parental occupation and marital status, are associated with both maternal antenatal depression and elevated risk for depression in the offspring (Fendrich et al., 1990; Lancaster et al., 2010; Lorant et al., 2003). Grand multiparity has been found to be associated with elevated risk for depression in the offspring in the NFBC 1966 (Kemppainen et al., 2000), and in our analysis, it was found also to be associated with maternal antenatal depressed mood ($p < 0.001$). We included *father´s social class in year 1966* (unskilled workers vs. other social classes), *family type in the year 1966* (single vs. two-parent family), and *grand multiparity* (≥ 5 previous live-births) in the adjustments.

Sex of the offspring was not associated statistically significantly with mood disorders in the offspring or with maternal antenatal depression and was thus excluded from the adjustments.

Statistical analysis

The associations between maternal depressed mood during pregnancy, parental severe mental disorder, and severe mood disorders and schizophrenia in the offspring were studied in four separate analyses: Cross tabulations and chi-square-tests were conducted to study the associations between the risk for severe mental disorder in the offspring and 1) maternal antenatal depressed mood, 2) maternal antenatal depressed mood and parental severe mental disorder, 3) maternal antenatal depressed mood and maternal/paternal severe mental disorder separately, and 4) with parental severe mental disorders (neither/one/both parents affected). The associations of the potentially confounding variables with maternal antenatal depressed mood and severe mood disorders in the offspring were also studied by cross tabulations and chi square -tests. Logistic regression analyses, with adjustments for the statistically significant confounding variables, were performed for the analyses 1-3 mentioned above. Regression analyses were not performed for analysis 4 due to the low number of subjects. Crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were measured, but only the adjusted odds ratios and their 95% confidence intervals are presented in this study, since there were little differences between crude and adjusted values. The data were analysed using IBM SPSS Statistics version 24.

In further analysis, the associations between maternal antenatal depressed mood and mothers´ and fathers´ later severe mental disorders (up to 1984) were studied by cross-tabulations and chi-squared -tests.

Data in the present study include all subjects alive and living in Finland at age 16 years. For the cumulative incidences, individual follow-up time was calculated up to the date of first admission

due to the severe mental disorder in question (outcome event) or to the date of censoring (death, emigration, or the end of the follow-up), whichever came first (Figures 1-3).

Results

Maternal antenatal depressed mood and parental severe mental disorders in the NFBC 1966

Of the offspring (cohort members) with data on both maternal antenatal mood and parental severe mental disorders (N = 10 521, 95.5% of the offspring), every seventh (13.9%) had maternal antenatal depressed mood and every tenth (10.2%) had a parent diagnosed with a severe mental disorder during the years 1972-1984 (Table 1). Of the offspring, two per cent (N=231) had had both maternal antenatal depressed mood and parental severe mental disorder, and 0.5% (N=48) had both parents affected with severe mental disorder.

Insert Table 1 here

The risk for severe depression in the offspring (cohort members)

During the follow-up, the total cumulative incidence of severe, hospital-treated depression in the offspring was 2.0% (N = 212) (Table 2). The offspring of antenatally depressed mothers had an elevated risk for depression (adjusted OR 1.5; 95% CI 1.03-2.2), compared to offspring without maternal antenatal depressed mood. The offspring with both maternal antenatal depressed mood and parental severe mental disorder had a markedly higher risk for depression (3.3; 1.8-6.2), compared to offspring with only maternal antenatal depressed mood (1.2; 0.8-1.9) or parental severe mental disorder (1.5; 0.96-2.4). We also looked at the association of antenatal depressed mood with the

outcome in the offspring with maternal or paternal severe mental disorder. Maternal antenatal depressed mood in addition to subsequent maternal severe mental disorder was associated with elevated risk for depression in the offspring (3.6; 1.1-12.0). Among offspring with father´s severe mental disorder, a history of maternal depressed mood during pregnancy was not associated with elevated risk for depression in the offspring (1.8; 0.7-4.6). Looking at the offspring without taking maternal antenatal depressed mood into account, the offspring with both parents affected with severe mental disorder were not at increased risk for depression (p = 0.69), compared to offspring with one or neither of the parents affected (Supplementary Table 2). However, the number of subjects in these groups was rather low, which can bias the findings.

Insert Table 2 here

The risk for severe bipolar disorder in the offspring (cohort members)

The cumulative incidence of severe bipolar disorder in the offspring was 0.5 % (N = 53). The risk for bipolar disorder was not statistically significantly higher in the offspring of antenatally depressed mothers (adjusted OR 1.7; 95% CI 0.9-3.5), than in the offspring without maternal antenatal depressed mood (Table 3). Compared to the offspring without maternal antenatal depressed mood and parental severe mental disorder, the offspring with parental severe mental disorder but without maternal antenatal depressed mood had an elevated risk for bipolar disorder (2.9; 1.4-6.2). The risk for severe bipolar disorder was not significantly higher in the offspring with both maternal antenatal depressed mood and parental severe mental disorder (2.4; 0.6-10.2), than in offspring without one or both of these risk factors, although the number of subjects was low (N = 3). When the parental severe mental disorders were studied separately (maternal and paternal severe mental disorders) and in association with maternal antenatal depressed mood, no associations with

the risk for bipolar disorder in the offspring were found. The offspring with both parents affected with severe mental disorder were at increased risk for bipolar disorder (p = 0.02), compared to offspring with only one or neither of the parents affected (Supplemetary Table 2)

Insert Table 3 here

The risk for any severe mood disorder in the offspring (cohort members)

When considering all mood disorders, the offspring of antenatally depressed mothers had an elevated risk for any severe mood disorder (adjusted OR 1.6; 95% CI 1.1-2.2), compared with offspring without maternal antenatal depressed mood (Supplementary Table 1), but when parental severe mental disorder was taken into account, this association attenuated to non-significant (1.4; 0.95-2.1). Compared to the offspring without maternal antenatal depressed mood and without parental severe mental disorder, the risk for mood disorders was elevated in the offspring with only parental severe mental disorder (1.8; 1.2-2.6), and among offspring with both risk factors (3.2; 1.8-5.7). When maternal and paternal severe mental disorders were studied separately, maternal antenatal depression combined with either parents´ severe mental disorder did not result in elevated risk for any mood disorder in the offspring (Supplementary Table 1).

The risk for schizophrenia in the offspring (cohort members)

The cumulative incidence of schizophrenia in the offspring was 1.3 % (N = 144). Maternal antenatal depressed mood was not associated with an elevated risk for schizophrenia in the offspring (adjusted OR 1.03; 95% CI 0.6-1.7). The offspring with both maternal antenatal depressed

mood and parental severe mental disorder had an elevated risk for schizophrenia (3.9; 2.0-7.5), compared to offspring with only maternal antenatal depressed mood (0.6; 0.3-1.1), or parental severe mental disorder (1.4; 0.8-2.4), or without both of the risk factors (reference group). The offspring with father´s severe mental disorder had over 5-fold risk for schizophrenia, if their mothers had had depressed mood during pregnancy, compared to offspring with only paternal severe mental disorder (reference group) (Table 4). None of the offspring diagnosed with schizophrenia had both parents affected with severe mental disorder (Supplementary Table 2).

Insert Table 4 here

Cumulative incidences of mood disorders and schizophrenia in the offspring (cohort members)

During the follow-up, the cumulative incidences for hospital-treated depression, bipolar disorder and schizophrenia were the highest in the offspring with both maternal antenatal depressed mood and parental severe mental disorder, and the second highest in the offspring with parental severe mental disorder (Figures 1-3). The age at onset for severe depression and for schizophrenia was earlier in adolescence in the offspring with maternal antenatal depressed mood and parental severe mental disorder, compared to all the other risk groups.

Insert Figures 1-3 here

Parental severe mental disorders in families with a history of maternal antenatal depressed mood

Mothers who had antenatal depressed mood were hospital-treated for depression during the years 1972-1984 twice as often as mothers without antenatally depressed mood ($p < 0.001$). The cumulative incidences of schizophrenia ($p < 0.001$), any mood disorder ($p < 0.001$) and substance use disorder ($p = 0.027$) were also higher in mothers with a history of antenatal depressed mood (Supplementary Table 3). Fathers, whose spouses had been antenatally depressed, had been more often hospital-treated for depression ($p = 0.004$), bipolar disorder ($p = 0.026$), any mood disorder ($p = 0.02$), and especially for substance use disorder ($p < 0.001$) during the years 1972-1984, than fathers whose spouses had not had antenatal depressed mood (Supplementary Table 4).

Discussion

In this general population-based birth cohort study with over 10 000 subjects, maternal depressed mood during pregnancy was associated with an elevated risk for severe depression in the offspring. The offspring, whose mothers had antenatal depressed mood and one of the parents had severe mental disorder, had a markedly elevated risk for severe depression and schizophrenia. The combined effect of maternal antenatal depression and parental severe mental disorder was stronger than the risks of the individual risk factors added together, indicating the potentiating effect of maternal antenatal depression. The offspring with one or both parents affected with severe mental disorder had an elevated risk for bipolar disorder.

In the NFBC 43-year follow-up, the cumulative incidences of hospital-treated depression, bipolar disorder and schizophrenia were 2.0%, 0.5%, and 1.5%, respectively. The prevalence of depression is rather low compared to the estimated global point prevalence of 4.7% for major depressive

disorder (Ferrari et al., 2013); however, only hospital inpatient-treated depression was included in the present study. The cumulative incidence of bipolar disorder is line with the Global Burden of Disease-study, where the prevalence of bipolar disorder in Europe was 0.3-0.8% (Ferrari et al., 2011). There is some evidence that the incidence of bipolar disorder might be relatively rare in the Northern Finland (Perälä et al., 2007; Veijola et al., 1996). The cumulative incidence of schizophrenia is relatively high when compared to estimated global lifetime prevalence of 0.4% in schizophrenia (Saha et al., 2005), but there is evidence that the incidence of schizophrenia is relatively high in Northern Finland (Perälä et al., 2007).

In a separate analysis, cumulative incidences of severe mental disorders in the offspring with one parent affected with severe mental disorder were as following: depression 3.5%, bipolar disorder 1.0%, and schizophrenia 2.6%; and in offspring with two parents affected 4.2%, 6.3% and 0%, respectively. These numbers are much lower as compared with meta-analysis by Rasic and colleagues, where the rates of 21% for depression, 7% for bipolar disorder and 8% for schizophrenia in adult offspring of parents with severe mental illness were reported, although those offspring were not all hospital-treated for their mental disorders. The prevalence of mood disorders and schizophrenia were also much lower in offspring with both parents affected with severe mental disorder in the NFBC 1966, when compared to the Danish register study (Gottesman et al., 2010).

Offspring of antenatally depressed mothers

Antenatal depression has previously been associated with foetal over-activity, obstetric complications, and low birth weight, as well as sleep, reactivity, and temperament difficulties in the neonate (Field, 2011; Gentile, 2017; Stein et al., 2014). Developmental delays, behavioural

problems, and externalising and internalising problems during childhood have been reported in the offspring of antenatally depressed mothers (Gentile, 2017; Stein et al., 2014).

Long follow-up studies of mental and behavioural problems in the offspring of antenatally depressed mothers in adolescence and adulthood are still rare, but the results of the studies are quite consistent. In the Avon Longitudinal Study of Parents and Children study (ALSPAC), with 7 944 mother-child dyads, there were associations between maternal antenatal depression and difficulties in attention, emotion, and conduct behaviour in children up to 13 years of age (O'Donnell et al., 2014), and with depression and anxiety up to 18 years of age (Capron et al., 2015; Pearson et al., 2013). In a community-based longitudinal South London Child Development Study of 151 mother-child dyads, maternal antenatal depression was associated with an increased risk for depression (Pawlby et al., 2009) and antisocial outcomes (Hay et al., 2010) in the adolescent offspring, and depression in young adult offspring between ages 18 and 25 (Plant et al., 2015).

To our knowledge, there are no other epidemiological reports than in the NFBC 1966 with long follow-up till middle adulthood of mental health in the offspring of mothers with antenatally depressed mood (for example Mäki et al., 2003, 2004, 2010; Taka-Eilola Née Riekki et al., 2017). In previous reports of the NFBC 1966, the offspring of mothers with antenatally depressed mood had an elevated risk for criminality, especially violent recidivism in adult men (Mäki et al., 2003), and for schizophrenia in the 31-year-old offspring with also parental psychosis (Mäki et al., 2010). The adult offspring of antenatally depressed mothers did not have an elevated risk for schizotypal or affective traits, not even with a parental history of psychosis (Taka-Eilola Née Riekki et al., 2017). Our findings in the present study suggest that the elevated risk for severe depression in the offspring of antenatally depressed mothers, and for schizophrenia in offspring with also parental severe mental disorder, can persist up to over 40 years of age.

The association of maternal antenatal depression with severe mental disorders in the offspring may be mediated through various pathways, such as elevated cortisol levels and inflammation, unhealthy nutrition, reduced maternal responsiveness and sensitivity to the infant, impaired mother-child attachment, maltreatment of the child, conflicts between parents, and later periods of depression (Field, 2011; Gentile, 2017; Pawlby et al., 2009; Stein et al., 2014). These mediating factors could be modified by practical and socio-economical support, and maternal education (Pearson et al., 2013), which can attenuate the effects of antenatal depression on the child (Stein et al., 2014).

In the present study, offspring whose mothers had antenatal depressed mood and a later period of severe mental disorder had a higher risk for depression (adjusted OR 3.6; 95% CI 1.1-12.0), than the offspring with only maternal antenatal depression (1.5; 1.03-2.2) (Table 2). This is consistent with findings, where repeated exposure to maternal depression may partly mediate the effect of antenatal depression to the offspring (Lahti et al., 2017; Pawlby et al., 2009; Stein et al., 2014; van der Waerden et al., 2017). Further, the mothers having depressed mood during pregnancy in the NFBC 1966 may have been depressed prior to pregnancy and/or postnatally, which may enhance the children´s risk for depression.

Parental severe mental disorders

Parental mental disorders are not rare; 14-23 % of children have a parent with mental illness (Rasic et al., 2014; Reupert et al., 2013). In the NFBC 1966, every tenth cohort member had a parent with a severe, hospital-treated mental disorder during their childhood. According to our findings, mothers´ antenatal depressed mood is associated with increased risk for subsequent parental severe mental disorders. As mentioned above, in the present study the mothers with depressed mood during pregnancy may have had a psychiatric disorder prior to or during pregnancy, and the later

maternal psychiatric hospitalisation may associate with the later period of the disorder in question. The paternal severe mental disorder may also be associated with mothers´ underlying severe mental disorder, and not only with antenatal depression, due to shared factors such as assortative mating or environmental factors (Galbaud du Fort et al., 1998; Maes et al., 1998). Also, the fathers´ severe mental disorders may have originated prior to or during the pregnancy at 1966, which may have affected the mothers´ mood.

Parental mental disorders are associated with an elevated risk for a wide range of mental disorders in the offspring (Rasic et al., 2014; Reupert et al., 2013). In the present study, the offspring with only parental severe mental disorder, without maternal antenatal depressed mood, had an elevated risk for bipolar disorder (adjusted OR 2.9; 2.4-6.2), but not for depression (1.5; 0.96-2.4) or schizophrenia (1.1; 0.6-2.1) (Tables 2-4). The offspring, both of whose parents had been affected with severe mental disorder, also had an elevated risk for bipolar disorder, but not for depression or schizophrenia, when compared to offspring with one parent affected. The combined effect of maternal antenatal depressed mood and parental severe mental disorder resulted in a markedly elevated risk for depression (3.3; 1.8-6.2),and schizophrenia (3.9; 2.0-7.5), but not for bipolar disorder (2.4; 0.6-10.2) in the offspring (Tables 2-4). These findings might reflect an example of gene-environment or a gene-gene interaction, where mothers' antenatal depressed mood may act as a potentiating factor (acting *in-utero*) for subjects vulnerable to severe mental disorder due to genetic loading. This interaction can affect foetal neurodevelopment, which may result in vulnerability for mental disorders (Lesch, 2004; Maes et al., 1998; Owen and O'Donovan, 2017; Schmitt et al., 2014).

In the present study, 5.7% of the cohort members (N=600) had a father with hospital-treated mental disorder (Table 1). Of the risk factors included in this study, the combination of maternal antenatal

depressed mood and paternal severe mental disorder resulted in the highest risk for schizophrenia in the offspring, with over 5-fold risk (Table 3), compared to offspring with only paternal severe mental disorder. Anyhow, in these analyses the number of the cohort members was rather low. This finding is consistent with our previous study based on the NFBC 1966 (Mäki et al., 2010), where the risk for schizophrenia was even higher (adjusted OR 14.3; 95% CI 5.9-35.0) in the offspring with maternal antenatal depression and paternal psychosis. It indicates that paternal psychosis is markedly associated with the risk for schizophrenia in the offspring.

Clinical implications

Health care services and research should consider maternal antenatal mood, and in general, both parents' mental health, when evaluating familial risk for mental disorders in the offspring (Solantaus and Salo, 2005). Considering the findings in the present study, it should be further studied whether early interventions in families with maternal antenatal depression and other parental mental disorders could reduce psychiatric illness in the offspring. According to a recent meta-analysis, Cognitive Behavioural Psychotherapy (CBT) and Interpersonal Psychotherapy (IPT) may be beneficial interventions for pregnant women with major depressive disorder (Ravesteyn et al., 2017). Pharmacological treatment can be considered for women with moderate to severe antenatal depression, along with non-pharmacological treatments (McAllister-Williams et al., 2017). Multi-professional co-operation between primary and specialized health care, social services, and child protection services is often needed in managing parental mental health problems. Several intervention programs have been developed for children of parents with mental disorders (Beardslee et al., 2011; Siegenthaler et al., 2012).

Strengths

To the authors´ knowledge, the NFBC 1966 is the first general population -based birth cohort study, where the pregnant mothers´ mood was evaluated as a possible risk factor for later infant adversities. The authors are not aware of any other cohort study, where the incidence of mood disorders and schizophrenia in the offspring of antenatally depressed mothers have been followed for over 40 years. The subjects were representative; all cohort members were born in the same year and in a geographically defined area. Diagnoses of severe mental disorders in the offspring and their parents were received from the nationwide CRHC with relatively reliable diagnoses (Moilanen et al., 2003; Perälä et al., 2007; Poikolainen, 1983). This study adds strength to earlier findings, in which offspring of antenatally depressed mothers are found to have an increased risk for depression, and new information on the elevated risk for depression and schizophrenia in the offspring of antenatally depressed mothers with also parental severe mental disorder.

Limitations

The first limitation of the study was, that maternal antenatal depressed mood did not necessarily signify a clinical condition, but it was screened by one structured question 'During this pregnancy, has your mood been as ordinary, depressed or very depressed?', asked by an interviewing nurse during 24^{th}-28^{th} gestation weeks. In another large general population -based birth cohort study, ALSPAC, with about 12 000 mothers having babies in 1991 and 1992 (Evans et al., 2001), maternal mood during pregnancy was identified with the Edinburg Postnatal Depression Scale (EPDS) (Cox et al., 1987). In the year 1965, specific screening tools for antenatal depression, such as the EPDS did not exist. The Beck Depression Inventory was developed at 1961, but it was not yet in clinical or scientific use in Finland at 1965-66 (Beck, 1961). One-item-questionnaires have been shown to

be valid in screening major depression in general population (Blozik et al., 2013). Further, the mothers had met the nurses at their earlier visits at the antenatal clinic, so they were familiar with them. The prevalence of antenatal depressed mood – about 14%- in the NFBC 1966 was in the same range as antenatal depression in earlier reports (Evans et al., 2001; Howard et al., 2014). In fact, it is exactly the same, 13.9%, as reported at 18 weeks pregnancy in ALSPAC (Evans et al., 2001). Depressed mood is a core symptom of depression but may also be a symptom of another clinical condition, such as bipolar disorder or psychosis, which were not identified in the mothers during pregnancy in the present study.

Secondly, the data include only the severe hospital-treated mental disorders, hence the authors are unsure whether the results of the study may be generalized to milder, outpatient-treated mental disorders. However, subjects with non-hospitalised and hospitalised mental disorders can be supposed not to differ systematically, had they maternal antenatal depression or not.

Thirdly, data on maternal use of psychiatric medication and on diagnosed parental mental disorders before and during pregnancy, and in the offspring's early childhood were lacking. Recently, antidepressants have been prescribed increasingly also during pregnancy, but in the middle of 1960's there were far less psychotropic drugs available, and selective serotonin reuptake inhibitors (SSRI) were developed later (Malm, 2012). In another cohort study using national register data in Finland between the years 1996 and 2010, maternal prenatal SSRI exposure was associated with increased rates of depression diagnoses in the young offspring till 14 years of age (Malm et al., 2016).

Fourthly, we did not have data for all potentially confounding factors, such as maternal postnatal depression and outpatient treated depressive periods, or maltreatment of the child (Field, 2011;

Pearson et al., 2013; Stein et al., 2014). In the South London Child Development Study offspring experience of child maltreatment was found to mediate the association between exposure to maternal depression in pregnancy and depression the offspring in early adulthood (Plant et al., 2015).

Conclusion

In this study, based on the NFCB 1966 with over 40 years' follow-up, the risk for severe depression and schizophrenia was elevated in offspring with maternal antenatal depressed mood and parental severe mental disorders, and for bipolar disorder in offspring both of whose parents had been affected with severe mental disorder. The findings highlight the importance of both parents' mental health as potential treatment targets to reduce severe mental disorders in the offspring. The perinatal period presents a good opportunity for early interventions in parental mental illness because of the frequent health care contacts associated with pregnancy and childbirth.

Perinatal mental health has recently seen a rise in interest in research and in clinical practice. Still, screening, diagnostics and treatment of perinatal depression are not efficient enough (Cox et al., 2016; Ko et al., 2012). Mothers should be asked about their depressive symptoms during pregnancy and postnatally, and families with severe mental disorders should be taken in special concern. Health care providers should also have intervention programmes for treatment of perinatal depression. The World Health Organization has published a manual for the psychosocial management of perinatal depression (World Health Organization, 2015) for all primary care workers worldwide.

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Disclosure of interest

The authors declare that they have no competing interests

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Conflict of Interest

The authors declare that they have no competing interests.

Contributors

Authors TT-E and PM had the main responsibility for interpreting data, planning the tables and figures, and searching the literature. Statistician JK had the main responsibility for statistical analyses. All authors took part in writing the manuscript and have seen and accepted the first draft of the manuscript.

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Table 1. Background data of the offspring in the Northern Finland 1966 Birth Cohort

Variable	Total offspring, N (%)
Maternal depressed mood during pregnancy	
No	9 059 (86.1%)
Yes	1 462 (13.9%)
Parental severe mental disorder	
No	9 452 (89.8%)
Yes	1 069 (10.2%)
- Maternal severe mental disorder	459 (4.4%)
- Paternal severe mental disorder	658 (7.0%)
- Both parents	48 (0.5%)
Maternal smoking during pregnancy	
No	8 939 (86.0%)
Yes	1 458 (14.0%)
Perinatal complications in the Offspring*	
No	9 761 (92.8%)
Yes	760 (7.2%)
Grand multiparity	
No	9 281 (88.2%)
Yes	1 240 (11.8%)
Father's social class year 1966	
Other	7 962 (78.7%)
Unskilled (IV)	2 158 (21.3%)
Family type year 1966	
Two-parent	10 136 (96.5%)
Single-parent	372 (3.5%)
Offspring:	
Gender	
Male	5 395 (51.3%)
Female	5 126 (48.7%)
Outcome variables: Severe hospital-treated mental disorders in the Offspring during follow-up till over 40 years of age	
Depression	212 (2.0%)
Bipolar disorder	53 (0.5%)
Schizophrenia	144 (1.4%)

*Low birth weight [<2500g] or short gestational age [<37 weeks] or perinatal brain damage

Table 2. Cumulative Incidence and Risk of Severe Depression in the Offspring of Antenatally Depressed Mothers by Maternal Mood During Pregnancy and Presence of Parental Severe Mental Disorders[c] in the Northern Finland 1966 Birth Cohort.

Variable		Severe Depression in the Offspring (cohort members)				
		No		Yes		
		N	%	N	%	OR[b] (95% CI)
Total offspring[a]	(N = 10 521)	10 319	98.0	212	2.0	
Maternal mood during pregnancy						
As usual	(N = 9 059)	8 889	98.1	170	1.9	1.0 (Ref)
Depressed	(N = 1 462)	1 420	97.1	42	2.9	**1.5 (1.03-2.2)**
Maternal depressed mood during pregnancy / Parental severe mental disorder[c]						
No/No	(N = 8 221)	8 075	98.2	146	1.8	1.0 (Ref)
Yes/No	(N = 1 231)	1 203	97.7	28	2.3	1.2 (0.8-1.9)
No/Yes	(N = 838)	814	97.1	24	2.9	1.5 (0.96-2.4)
Yes/Yes	(N = 231)	217	93.9	14	6.1	**3.3 (1.8-6.2)**
Maternal depressed mood during pregnancy / Maternal severe mental disorder[c]						
No/Yes	(N = 348)	341	98.0	7	2.0	1.0 (Ref)
Yes/Yes	(N = 111)	104	93.7	7	6.3	**3.6 (1.1-12.0)**
Maternal depressed mood during pregnancy / Paternal severe mental disorder[c]						
No/Yes	(N = 523)	505	96.6	18	3.4	1.0 (Ref)
Yes/Yes	(N = 135)	127	94.1	8	5.9	1.8 (0.7-4.6)

[a] Data include subjects alive and living in Finland at age 16 year and with data on all variables.
[b] Odds Ratio (OR) adjusted for maternal smoking during pregnancy, perinatal risk (brain damage, low gestational age or low birth weight), grand multiparity, father's social class 1966, and family type 1966.
[c] Parental severe mental disorders during 1972-1984.
Statistically significant differences are in **bold**.

Table 3. Cumulative Incidence and Risk of Bipolar Disorder in the Offspring of Antenatally Depressed Mothers by Maternal Mood During Pregnancy and Presence of Parental Severe Mental Disorders[c] in the Northern Finland 1966 Birth Cohort.

Variable		Bipolar Disorder in the Offspring (cohort members)				
		No		Yes		
		N	%	N	%	OR[b] (95% CI)
Total offspring[a]	(N = 10 521)	10 468	99.5	53	0.5	
Maternal mood during pregnancy						
As usual	(N = 9 059)	9 018	99.5	41	0.5	1.0 (Ref)
Depressed	(N = 1 462)	1 450	99.2	12	0.8	1.7 (0.9-3.5)
Maternal depressed mood during pregnancy / Parental severe mental disorder[c]						
No/No	(N = 8 221)	8 190	99.6	31	0.4	1.0
Yes/No	(N = 1 231)	1 222	99.3	9	0.7	2.0 (0.9-4.4)
No/Yes	(N = 838)	828	98.8	10	1.2	**2.9 (1.4-6.2)**
Yes/Yes	(N = 231)	228	98.7	3	1.3	2.4 (0.6-10.2)
Maternal depressed mood during pregnancy / Maternal severe mental disorder[c]						
No/Yes	(N = 348)	342	98.3	6	1.7	1.0 (Ref)
Yes/Yes	(N = 111)	109	98.2	2	1.8	0.8 (0.1-8.2)
Maternal depressed mood during pregnancy / Paternal severe mental disorder[c]						
No/Yes	(N = 523)	516	98.7	7	1.3	1.0 (Ref)
Yes/Yes	(N = 135)	134	99.3	1	0.7	0.7 (0.1-6.0)

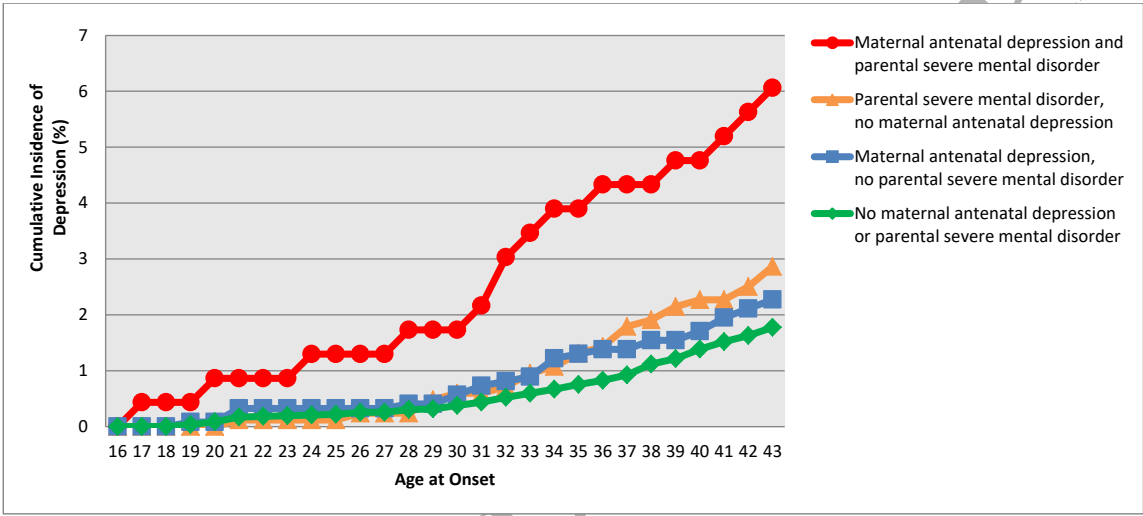
[a] Data include subjects alive and living in Finland at age 16 year and with data on all variables.
[b] Odds Ratio (OR) adjusted for maternal smoking during pregnancy, perinatal risk (brain damage, low gestational age or low birth weight), grand multiparity, father's social class 1966, and family type 1966.
[c] Parental severe mental disorders during 1972-1984.
Statistically significant differences are in **bold**.

Table 4. Cumulative Incidence and Risk of Schizophrenia in the Offspring of Antenatally Depressed Mothers by Maternal Mood During Pregnancy and Presence of Parental Severe Mental Disorders[c] in the Northern Finland 1966 Birth Cohort.

Variable		Schizophrenia in the offspring (cohort members)				
		No		Yes		
		N	%	N	%	OR[b] (95% CI)
Total offspring[a]	(N = 10 521)	10 377	98.6	144	1.4	
Maternal mood during pregnancy						
As usual	(N = 9 059)	8 939	98.7	120	1.3	1.0 (Ref)
Depressed	(N = 1 462)	1 438	98.4	24	1.6	1.03 (0.6-1.7)
Maternal depressed mood during pregnancy / Parental severe mental disorder[c]						
No/No	(N = 8 221)	8 116	98.7	105	1.3	1.0 (Ref)
Yes/No	(N = 1 231)	1 219	99.0	12	1.0	0.6 (0.3-1.1)
No/Yes	(N = 838)	823	98.2	15	1.8	1.4 (0.8-2.4)
Yes/Yes	(N = 231)	219	94.8	12	5.2	**3.9 (2.0-7.5)**
Maternal depressed mood during pregnancy / Maternal severe mental disorder[c]						
No/Yes	(N = 348)	338	97.1	10	2.9	1.0 (Ref)
Yes/Yes	(N = 111)	107	96.4	4	3.6	1.1 (0.3-4.4)
Maternal depressed mood during pregnancy / Paternal severe mental disorder[c]						
No/Yes	(N = 523)	518	99.0	5	1.0	1.0 (Ref)
Yes/Yes	(N = 135)	127	94.1	8	5.9	**5.4 (1.7-17.4)**

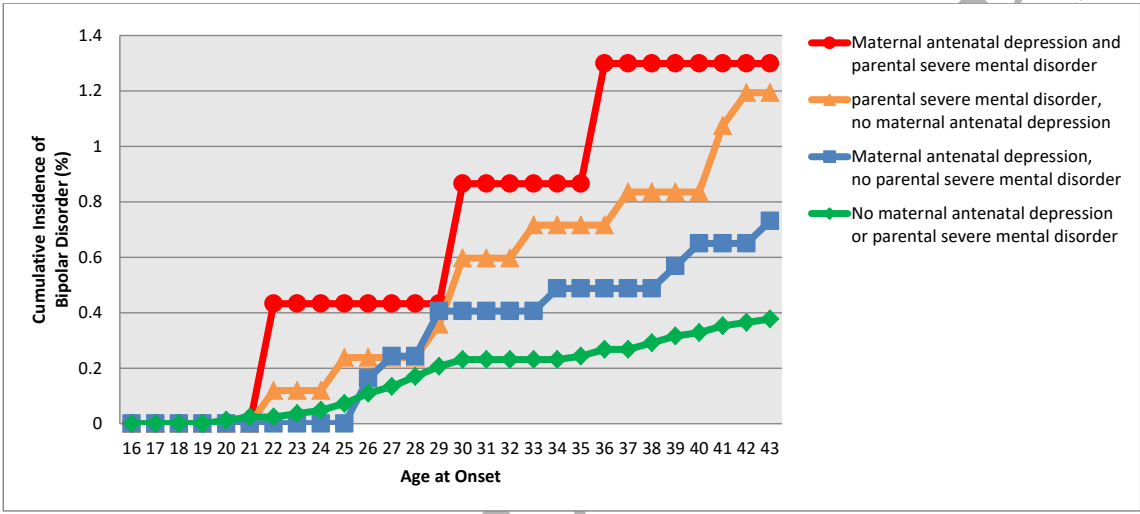
[a] Data include subjects alive and living in Finland at age 16 year and with data on all variables.
[b] Odds Ratio (OR) adjusted for maternal smoking during pregnancy, perinatal risk (brain damage, low gestational age or low birth weight), grand multiparity, father's social class 1966, and family type 1966.
[c] Parental severe mental disorders during 1972-1984.
Statistically significant differences are in **bold**.

Figure 1. Cumulative Incidences of Severe, Hospital-treated Depression in the Offspring with and without Antenatally Depressed Mothers and with and without Parental Severe Mental Disorder during 1972-1984 in the NFBC 1966[a].



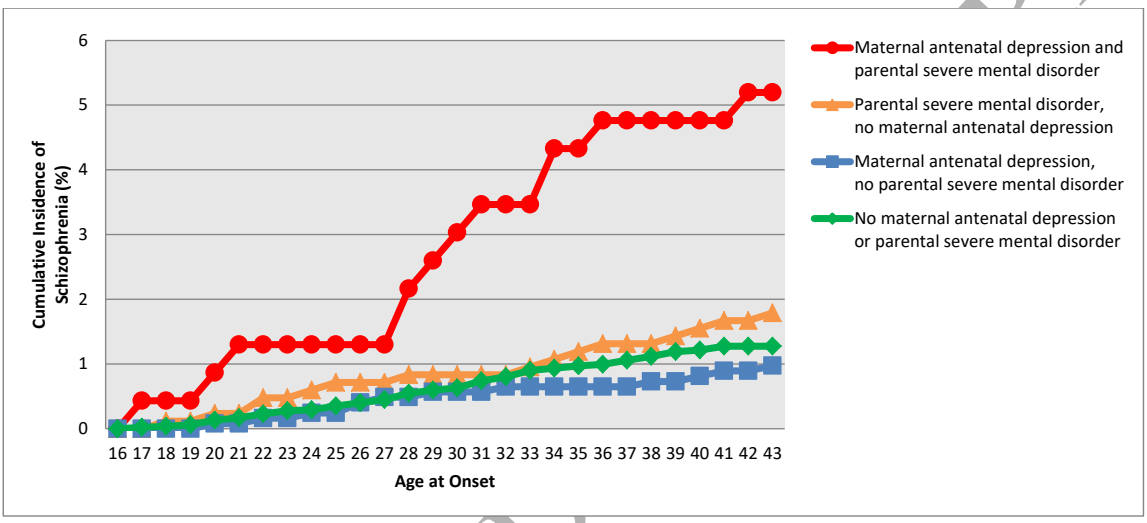
[a]Data include all subjects alive and living in Finland at age 16 years. Individual follow-up time was calculated up to the date of first admission due to severe depression or to the date of censoring (death, emigration, or the end of the follow-up), whichever came first.

Figure 2. Cumulative Incidences of Bipolar Disorder in the Offspring with and without Antenatally Depressed Mothers and with and without Parental Severe Mental Disorder during 1972-1984 in the NFBC 1966[a].



[a]Data include all subjects alive and living in Finland at age 16 years. Individual follow-up time was calculated up to the date of first admission due to bipolar disorder or to the date of censoring (death, emigration, or the end of the follow-up), whichever came first.

Figure 3. Cumulative Incidences of Schizophrenia in the Offspring with and without Antenatally Depressed Mothers and with and without Parental Severe Mental disorder during 1972-1984 in the NFBC 1966[a].



[a]Data include all subjects alive and living in Finland at age 16 years. Individual follow-up time was calculated up to the date of first admission due to bipolar disorder or to the date of censoring (death, emigration, or the end of the follow-up), whichever came first.