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Cardiometabolic Disorders in the Offspring of Parents With Severe Mental Illness

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ABSTRACT

Objective: The elevated prevalence of cardiometabolic disorders is consistently reported in patients with severe mental illness (SMI). We explored the association between parental SMI and offspring cardiometabolic morbidity. Our hypothesis was that offspring of people with SMI have increased morbidity risk.

Method: The Northern Finland Birth Cohort 1966 is a study of offspring whose date of birth was expected in 1966. The follow-up lasted until 2015 (49 years). The final study sample included 11,175 children. We used parental SMI as the exposure in the study. The following cardiometabolic disorders were used as outcome measures: diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, obesity, and cerebrovascular disorders.

Results: There were 139 (14.7%; hazard ratios [HR] = 1.63; 95% confidence interval [CI] = 1.36–1.94) children of parents with SMI who developed cardiometabolic disorder during follow-up and 957 (9.4%) in the comparison cohort. Statistically significant HRs were found in males (HR = 1.95; 95% CI =1.56–2.44), but not in females (HR = 1.29; 95% CI = 0.96–1.73).

Conclusions: Having a cardiometabolic disorder was associated with male offspring of parents with SMI. Our findings suggest that there is an elevated risk of coronary artery disease, hyperlipidemia, obesity, and hypertension in the male offspring of parents with SMI. Our results suggest that the somatic health of offspring of parents with SMI should also be considered in addition to their mental health in clinical practice.

Key words: schizophrenia, bipolar disorder, depression, metabolic syndrome, offspring, cohort study.

INTRODUCTION

People with severe mental illness (SMI), including schizophrenia, bipolar disorder, and major depressive disorder, tend to have elevated morbidity and mortality rates of chronic diseases compared with the general population. The excess mortality is due primarily to comorbid metabolic and cardiovascular complications (1,2). Recent studies show that individuals with SMI are three to four times more likely to die because of somatic illnesses than the general population (3). Reasons for this include factors relating to having a mental illness, access to health care, life-style factors such as smoking and physical inactivity, and the effects of psychotropic medication (4).

In 1879, Sir Henry Maudsley was the first to observe that the prevalence of diabetes may be increased in the families of schizophrenia patients (5). More recent epidemiological and clinical studies suggest that there is a comorbidity between SMI, metabolic syndrome, and cardiovascular disease risk factors, including systolic blood pressure, triglycerides, low- and high-density lipoprotein, body mass index, waist-to-hip ratio, and type 2 diabetes mellitus. The increased morbidity of people with SMI is mostly due to a higher prevalence of modifiable risk factors, many of which are related to life-style choices, but there may be a common familial pathway leading to a high co-occurrence of somatic disorders and SMI (6). It has been suggested that the increased risk of cardiometabolic disorder may be due, in part, to use of antipsychotics and other psychotropics (7). However, there is increased evidence showing that a diagnosis of SMI itself may be highly correlated with the development of abnormal glucose metabolism. First-episode, antipsychotic-naive patients with schizophrenia have impaired glucose tolerance and higher insulin resistance (8). Furthermore, increased rates of

CI = confidence interval, **CRHC** = Care Register for Health Care, **HR** = hazard ratio, **NFBC1966** = Northern Finland Birth Cohort 1966, **SMI** = severe mental illness

SDC Supplemental Digital Content

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metabolic syndrome have been observed in family members of patients with SMI (9,10).

There have been studies regarding shared loci in schizophrenia or bipolar disorder and cardiometabolic disorders (6,11,12). Subclinical cardiometabolic deregulations and chronic proinflammatory states may occur also among the close relatives of patients with SMI (13). Offspring of people with SMI have an increased risk of developing mental illness (14). Still the co-occurrence of parental SMI and offspring's cardiometabolic disorders are poorly understood. There have been studies showing genetic associations such as the observed relation between maternal mental health during pregnancy, reduced intrauterine growth, and later adult cardiometabolic disease (15,16). Maternal mental disorders are known to be a major cause of complications in pregnancy (17), but few studies have focused on the somatic health outcomes of offspring.

Aims of the Study

The objective of this study was to investigate cardiometabolic morbidity risk in offspring of parents with SMI. We explored whether the risk of cardiometabolic morbidity is increased among offspring of parents with SMI compared with offspring of parents without SMI in the Northern Finland Birth Cohort 1966 (NFBC1966). Our hypothesis was that offspring of people with SMI have an increased morbidity risk.

METHODS

Study Design

The NFBC1966 is a prospective follow-up study of offspring who had an expected date of birth in 1966. The data include 12,068 mothers and 12,231 children from the provinces of Lapland and Oulu in Finland (18). There were 171 (1.5%) births in 1965, 61 (0.5%) births in 1967, and 11,999 (98%) births in 1966. The register data were available from 1969 to 2015, when the offspring's age was 49 years. We used personal identification codes given to all citizens and residents of Finland to be able to merge register data to the NFBC1966 data set. Permission to link register data was obtained from the Ministry of Social Affairs and Health. The ethical committee of the Northern Ostrobothnia Hospital District keeps the study under review.

Participants

We excluded 172 (1.4%) stillbirths and 314 (2.6%) twins. We also excluded 474 (3.9%) members of the cohort whose maternal questionnaire information was missing for any variable used in the study. All members of the NFBC1966 who have declined the use of their data have been excluded from the data set (n = 96; 0.8%). Our final study sample included 11,175 children (Figure 1). This included 947 (8.5%) children who had a parent with SMI and 10,228 (91.5%) children in comparison cohort.

Classification of Cardiometabolic Disorders

The following cardiometabolic disorders were our outcome measures: diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, obesity, and cerebrovascular disorders (19). We obtained the identities of individuals with the relevant codes for cardiometabolic disorders from the Care Register for Health Care (CRHC) using inpatient data (since 1969) and outpatient data (since 1998). We identified disorders using *International Classification of Diseases* (ICD) codes: *ICD-8* in 1969 to 1986, *ICD-9* in 1987 to 1995, and *ICD-10* in 1996 to 2015 (Table 1). The earliest recorded diagnosis code in the study period (from 1969 until 2015) was considered the date of onset of the disease.

Parental SMI

We used parental SMI as the exposure in the study. The information of parental SMI was obtained from the CRHC. Parents with SMI were those who had been diagnosed for any hospital-treated psychiatric disorder during 1969–1982 (*ICD-8* codes 290–315) at offspring's 3 to 16 years of age. Parental SMI included all hospital-treated psychiatric disorders excluding mental retardation, sexual deviation, and cephalalgia (*ICD-8* codes 310–315, 302, 30680, and 30698). The most common parental diagnoses were depression and substance use disorders (Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A793). Maternal and paternal SMI were studied separately. The CRHC has a very good accuracy, and it is one of the oldest individual-level hospital discharge registers (20,21).

Confounders

Information about the confounders was collected from the mother by the local midwives using a predefined questionnaire in the antenatal clinics. The questionnaire was completed in the 24th to 28th weeks of gestation. If this was impossible, the questionnaire was completed later during the pregnancy or after the delivery.

Mothers' marital status was dichotomized into two groups: married and others (unmarried, divorced, widowed). Maternal smoking was dichotomized into smokers and nonsmokers. Women who continued smoking in the second trimester were considered as smokers. Place of birth was dichotomized into two categories: urban and rural communities. We also used mothers' educational level as a confounder, and it was categorized into three levels according to the length of education: less than 9 years, 9 to 11 years, and 12 years or more. Sex of the offspring was used as a confounder in analyses of the whole sample. We also used offspring's SMI as a confounder (Table S3, Supplemental Digital Content, http://links.lww.com/PSYMED/A793). Information about offspring's SMI was obtained from CRHC until 49 years of offspring age.

Offspring Life-Style Variables

We used offspring's smoking, alcohol consumption, and physical activity as descriptive variables in Table 2. These data were obtained using a questionnaire at the 46-year follow-up phase. Smoking was dichotomized into two groups: smokers who ever smoked regularly and nonsmokers. Alcohol consumption was divided into three groups: abstainer, moderate, and heavy. Moderate users were offspring who had consumption of maximum 30 g/d for males and 20 g/d for females and heavy users greater than 30 g/d for males and 20 g/d for females. Physical activity was also dichotomized into two groups: active and inactive. Those participating in sports less than once a week were defined as physically inactive and those participating once a week or more often were defined as active (22).

Statistical Methods

Analyses were performed using SPSS software version 24 and figures using R version 1.2.1335. Descriptive statistics were used to compare the offspring of people with SMI and the comparison group. Comparisons were conducted using cross-tabulation and χ^2 testing. We examined whether offspring of people with SMI had an excess risk of morbidity from cardiometabolic disorders by using the log-rank test for comparison of cumulative incidence curves and Cox regressions for any cardiometabolic disorder together and separately for each disorder. We also did additional analysis (Cox regression for any cardiometabolic disorder) where we excluded offspring with SMI. We also tested the equality of survival distribution for males and females using the log-rank test. Morbidity by cardiometabolic disorders was calculated for sexes. We adjusted the regression model for marital status, mother's education, mother's smoking during pregnancy, offspring with SMI, and infant's residence of birth. For each exposed group (offspring of mothers with SMI, offspring of fathers with SMI, and offspring of either parent or both with SMI) and unexposed group (comparison group), we calculated the hazard ratios (HRs) with 95% confidence intervals (CIs). We also examined if there is a connection between the type of parental SMI and

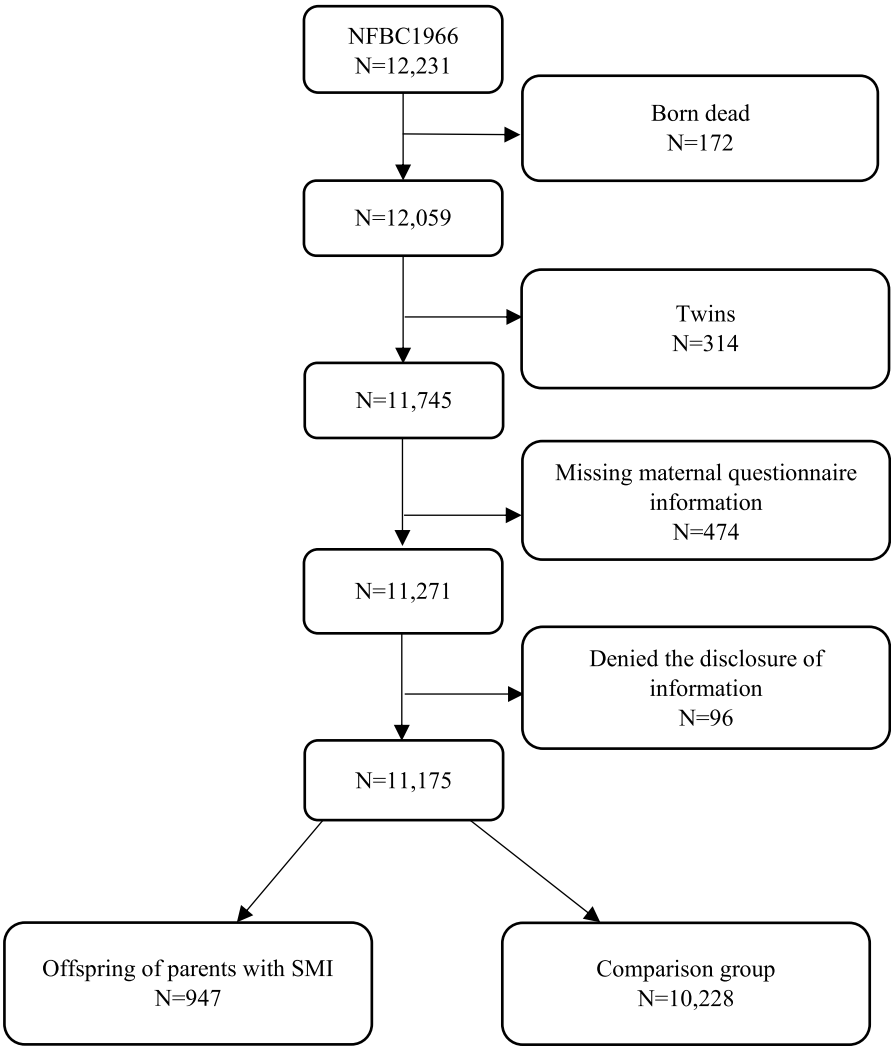

FIGURE 1. Flowchart of the NFBC1966 study design. NFBC1966 = Northern Finland Birth Cohort 1966; SMI = severe mental illness.

offspring having a cardiometabolic disorder using cross-tabulation analysis for both male and female offspring.

RESULTS

Descriptive Analyses

We divided the characteristics of children and mothers into two groups: the offspring of parents with SMI and the remainder as a comparison cohort (Table 2). In the group of offspring of parents with SMI, mothers were more likely to have smoked during pregnancy and had lower levels of education than mothers in the comparison group. Offspring of parents with SMI also smoked more regularly compared with comparison group. They were also less active. There were 139 (14.7%; HR = 1.63; 95% CI =1.36–1.94) children of parents with SMI who had cardiometabolic disorder during follow-up and 957 (9.4%) in the comparison cohort. In Table 3, we present the difference in morbidity between offspring of parents with SMI and comparison cohort stratified by sex. There was a significantly increased prevalence of hyperlipidemia (5.1% versus 1.7%, $p < .001$) and hypertension (8.5% versus 5.0%, $p = .002$) in the male offspring and coronary artery disease for both male (5.1% versus 2.1%, $p < .001$) and female (2.1% versus 0.7%, $p = .004$) offspring of parents with SMI compared with comparison group.

TABLE 1. List of Offspring Cardiometabolic Disorders and Their *ICD* Codes

	ICD-8 (1969–1986)	*ICD-9* (1987–1995)	*ICD-10* (1996–2015)
Diabetes mellitus	250	250	E10–E14
Coronary artery disease	410–414	410–414	I20–I25
Hyperlipidemia	272	272	E78
Obesity	277.99	278	E65–E68
Hypertension	400–404	401–405	I10–I15
Cerebrovascular disorders	430–438	430–438	I60–I69

ICD = International Classification of Diseases.

Cox Survival Analysis

The results of the cumulative incidences by sex for cardiometabolic morbidity are presented in Figure 2. The difference between males' and females' survival distributions was significant ($p < .001$). The log-rank test indicated that the survival rate was significantly

TABLE 2. Characteristics of Offspring and Their Mothers—Separately in the Offspring of Parents With SMI and Comparison Cohort

	Offspring of Parents With SMI (n = 947)		Comparison Group (n = 10,228)	
	n	%	n	%
Maternal characteristics				
Smoking during pregnancy[a]				
No	758	80.0	8676	84.8
Yes	189	20.0	1552	15.2
Marital status				
Married	901	95.1	9814	96.0
Other	46	4.9	414	4.0
Education level[b]				
<9 y	667	70.4	6773	66.2
9–11 y	247	26.1	2963	29.0
≥12 y	33	3.5	492	4.8
Residence				
Urban	271	28.6	3147	30.8
Rural	676	71.4	7081	69.2
Offspring's characteristics				
Sex				
Male	472	49.8	5252	51.3
Female	475	50.2	4976	48.7
SMI[a]				
No	785	82.9	9,379	91.0
Yes	162	17.1	849	9.0
Physical activity at age of 46 y[b]				
Active	335	68.0	4210	72.7
Inactive	158	32.0	1582	27.3
Missing	454		4436	
Alcohol use at age of 46 y				
Abstainer	51	12.0	573	11.5
Moderate	317	74.4	3732	74.5
Heavy	58	13.6	317	14.0
Missing	521		5221	
Smoking at age of 46 y[b]				
No	220	44.6	3014	52.1
Yes	273	55.4	2776	47.9
Missing	454		4438	

SMI = severe mental illness.

[a] Significant difference between groups, $p < .01$.

[b] Significant difference between groups, $p < .05$.

higher for male offspring of parents with SMI (log-rank test, $p < .001$).

In Table 4, the risk of morbidity in cardiometabolic disorders in offspring of mothers and fathers with and without SMI for all participants is presented. Statistically significantly increased HRs were found in males but not in females. The HRs were 1.66 (95% CI = 1.17–2.36) for male offspring of mothers with SMI, 2.19 (95% CI = 1.68–2.85) for offspring of fathers with SMI; and 1.95 (95% CI = 1.56–2.44) for offspring of either parent with SMI, when using females as the reference group (1.0).

We also analyzed each cardiometabolic condition separately for male and female offspring (Table S2, Supplemental Digital Content, http://links.lww.com/PSYMED/A793). Statistically significant associations were found for coronary artery disease (HR = 2.20; 95% CI =1.41–3.44), obesity (HR = 2.25; 95% CI =1.07–4.74), hyperlipidemia (HR = 3.21; 95% CI =2.03–5.07), and hypertension (HR = 1.56; 95% CI =1.11–2.19) for male offspring.

In Table S4 (Supplemental Digital Content, http://links.lww.com/PSYMED/A793), the risk of morbidity in cardiometabolic disorders in offspring of mothers and fathers with and without SMI for all participants is presented when excluded offspring with SMI. Most of the significant associations remained significant, with the exception of HRs for male offspring of mothers with SMI.

Type of Parental SMI and Cardiometabolic Disorders in the Offspring

The connection between the type of parental SMI and cardiometabolic disorders in the offspring for males and females is presented in Table 5. When examining the offspring of parents with depression, a significantly increased prevalence of cardiometabolic disorder was observed in male offspring (4.4% versus 2.2%, $p < .001$). A significantly higher prevalence of cardiometabolic disorders for both male (6.3% versus 3.0%, $p < .001$) and female (5.4% versus 3.2%, $p = .014$) offspring was found when examining parental substance use disorder.

DISCUSSION

Main Findings

Our findings suggest that there is an elevated risk of coronary artery disease, hyperlipidemia, obesity, and hypertension in male offspring of parents with SMI. The findings support our hypothesis of higher morbidity from cardiometabolic disorders in offspring of parents with SMI.

Comparison to Earlier Studies

Our findings indicate that offspring of people with SMI are at a significantly increased risk for overall cardiometabolic dysfunction. Our results are partly in line with findings from recent studies looking at associations between cardiometabolic disorders and first-degree relatives of people with SMI (9,10,23–26).

We found six studies focusing on cardiometabolic disease risk in offspring of people with SMI. Most of these studies have focused on diabetes and found an increased prevalence of diabetes in offspring of parents with SMI (9,10,23,25), and two of them had relatively small sample sizes (9,10). One study found no difference in diabetes between offspring of parents with psychotic disorders and a comparison group (26). This finding is similar to ours. In our study, there was no increased prevalence of diabetes in offspring of parents with SMI.

We found two studies that also observed coronary artery disease, hyperlipidemia, or hypertension. In the study by Mothi et al. (24), an increased prevalence of hyperlipidemia and hypertension in first-degree relatives of patients with psychotic disorder was found but no difference when examining coronary artery disease. One study conducted in Finland found no differences in dyslipidemia between the study groups (26). This may be due to the

TABLE 3. Morbidity by Cardiometabolic Disorders in Offspring of Parents With SMI and Comparison Cohort Separately for Male and Female Offspring

Morbidity by Cardiometabolic Disorders	Male Offspring			Female Offspring		
	Offspring of Parents With SMI (n = 472)	Comparison Cohort (n = 5252)		Offspring of Parents With SMI (n = 475)	Comparison Cohort (n = 4979)	
	% (n)	% (n)	χ^2 (p Value)	% (n)	% (n)	χ^2 (p Value)
Diabetes mellitus	4.7 (22)	3.2 (167)	2.53 (.112)	2.1 (10)	1.7 (87)	.14 (0.704)
Coronary artery disease	5.1 (24)	2.1 (110)	15.66 (<.001)	2.1 (10)	0.7 (36)	8.31 (.004)
Hyperlipidemia	5.1 (24)	1.7 (88)	24.49 (<.001)	0.8 (4)	0.8 (39)	N/A
Obesity	2.3 (11)	1.3 (68)	2.69 (.101)	2.5 (12)	1.8 (92)	0.73 (.392)
Hypertension	8.5 (40)	5.0 (263)	9.70 (.002)	5.5 (26)	4.3 (216)	1.06 (.304)
Cerebrovascular disorder	3.0 (14)	1.8 (92)	2.88 (.090)	2.1 (10)	1.5 (77)	0.54 (.462)

SMI = severe mental illness; N/A = not applicable.

inclusion of adolescent participants only. These results are similar in part to ours. We found an increased prevalence for hyperlipidemia and hypertension in male offspring and coronary artery disease in both male and female offspring of parents with SMI.

To our knowledge, there are no previous studies that have also included depression and substance use disorder in parental SMI diagnosis. We found a significantly increased prevalence of cardiometabolic disorders in male offspring of parents with depression. A significantly increased prevalence of cardiometabolic disorders was also found in male and female offspring of parents with substance use disorder. Previous studies have only focused on psychotic disorders (9,10,23–26). Two of the studies included only patients with schizophrenia (9,10). Van Welie et al. (23) focused on nonaffective psychotic disorders. Mothi et al. (24) and Padmanabhan et al. (25) included schizophrenia, schizoaffective disorder, and bipolar disorder in their study. Mothi et al. suggested that familial risk of cardiometabolic dysfunction exists across psychosis spectrums. One previous study (26) included nonorganic psychoses in their study. Our results indicate that offspring of parents especially with depression and substance use disorder have an increased prevalence of cardiometabolic disorders. Future studies should be conducted studying the relation between parental depression, substance use disorder, and offspring cardiometabolic disorders.

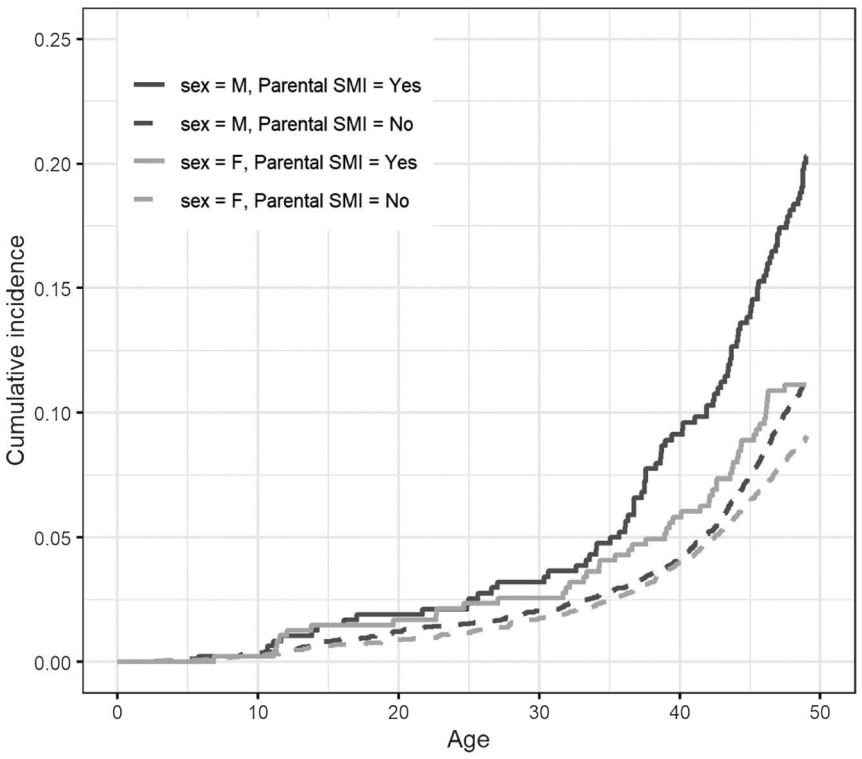

FIGURE 2. Cumulative incidence of cardiometabolic disorders in the offspring of parents with SMI and comparison cohort separately for male and female offspring. F = female; M = male; SMI = severe mental illness.

TABLE 4. Morbidity by Cardiometabolic Disorders in Offspring of Mothers and Fathers With and Without SMI for All Participants and Separately for Males and Females

	Morbidity by Cardiometabolic Disorders							
	Yes		No					
	n	%	*n*	%	HR	95% CI	Adjusted HR[a]	95% CI
All								
Offspring of mothers with SMI	56	14.1	340	85.9	**1.55**	**1.19–2.03**	**1.43**	**1.09–1.86**
Offspring of fathers with SMI	94	16.0	493	84.0	**1.74**	**1.41–2.15**	**1.58**	**1.28–1.96**
Offspring of either parent with SMI	139	14.7	808	85.3	**1.63**	**1.36–1.94**	**1.48**	**1.24–1.77**
Comparison group	957	9.4	9271	90.6	1.00		1.00	
Male offspring								
Offspring of mothers with SMI	33	16.7	165	83.3	**1.66**	**1.17–2.36**	**1.47**	**1.04–2.10**
Offspring of fathers with SMI	61	21.0	229	79.0	**2.19**	**1.68–2.85**	**2.19**	**1.68–2.85**
Offspring of either parent with SMI	88	18.6	384	81.4	**1.95**	**1.56–2.44**	**1.77**	**1.41–2.22**
Comparison group	543	10.3	4709	89.7	1.00		1.00	
Female offspring								
Offspring of mothers with SMI	23	11.6	175	88.4	1.44	0.95–2.19	1.34	0.88–2.05
Offspring of fathers with SMI	33	11.1	264	88.9	1.30	0.91–1.85	1.18	0.83–1.69
Offspring of either parent with SMI	51	10.7	424	89.3	1.29	0.96–1.73	1.19	0.89–1.59
Comparison group	414	8.3	4562	91.7	1.00		1.00	

SMI = severe mental illness; HR = hazard ratio; CI = confidence interval.

Statistically significant results are set in bold.

[a] Adjusted HR for offspring SMI, mother's marital status, mother's education, mother's smoking during pregnancy, and offspring's residence of birth.

Most previous studies focused only on healthy offspring and excluded offspring with SMI from their study (9,10,23–25). One study did not exclude offspring with SMI from their study (26). Offspring of people with SMI have an increased risk of developing mental illness themselves and therefore have an increased risk of cardiometabolic disorders (14). In our study, we first included offspring with SMI in the analyses and then did additional analyses in which we excluded them. Our findings of a higher risk of cardiometabolic disorders in offspring of parents with SMI remained statistically significant when offspring with SMI were excluded.

Comparison to Genetic Research and Familial Factors

Psychotic and metabolic disorders both have substantive heritability (24). Results from large studies have suggested partly overlapping genetic architecture for cardiovascular risk factors and schizophrenia (6) Our observations of increased cardiometabolic disorders indicate the possibility that cardiometabolic disorders, and SMI may share risk factors that are familial. This could be due to common risk factors, such as genetic architecture, environmental factors, and epigenetic interactions (24). There is an increasing literature regarding shared loci in schizophrenia or bipolar disorder and cardiometabolic disorders (12,27). Diabetes is a polygenic disorder (25) with a high

TABLE 5. Comparison Between the Type of Parental SMI and Offspring Having a Cardiometabolic Disorder in Male and Female Offspring

	Male Offspring Cardiometabolic Disorder			Female Offspring Cardiometabolic Disorder		
	Yes (*n* = 631)	No (*n* = 5093)		Yes (*n* = 465)	No (*n* = 4986)	
Parental SMI	% (*n*)	% (*n*)	χ^2 (*p* Value)	% (*n*)	% (*n*)	χ^2 (*p* Value)
Schizophrenia	1.4 (9)	0.4 (19)	10.72 (.001)	0.0 (0)	0.5 (24)	N/A
Other psychosis	0.3 (2)	0.3 (17)	N/A	0.4 (2)	0.3 (14)	N/A
Bipolar disorder	0.3 (2)	0.2 (8)	N/A	0.0 (0)	0.3 (14)	N/A
Depression	4.4 (28)	2.2 (107)	12.31 (<.001)	3.7 (17)	2.7 (129)	1.48 (.224)
Substance use disorder	6.8 (43)	3.0 (147)	25.79 (<.001)	5.4 (25)	3.2 (156)	6.01 (.014)
Any other	2.9 (18)	2.6 (133)	0.12 (.721)	2.6 (12)	2.7 (135)	0.03 (.872)
Any psychiatric disorder	13.9 (88)	7.5 (384)	29.61 (<.001)	11.0 (51)	8.5 (424)	2.94 (.086)

SMI = severe mental illness; N/A = not applicable.

prevalence of polygenic psychiatric disorders, particularly major depressive disorder and schizophrenia (28,29). However, identifying causal loci for psychiatric disorders has proven to be challenging (30). Future genetic research should be conducted to explore the genetic pathway between SMI and cardiometabolic disorders.

Environmental factors, such as poor health habits and decreased access to or compliance with medical care, could also affect the prevalence of cardiometabolic disorders among offspring (24). The prevalence among nonaffected offspring is less clear but could include caretaker burden or even social network phenomena (31,32). Also, studies of relatives of people with psychosis have reported higher social, economic, and social distress (24). Parents with SMI may have different parenting styles and consequently have potentially profound impacts on offspring health (33).

Behavioral factors, such as physical activity, smoking, and alcohol consumption, are associated with cardiometabolic dysfunction. A low level of physical activity increases the risk of obesity, elevated blood pressure, and insulin resistance (34–36). Previous studies have also indicated that smoking is associated with cardiometabolic disorders (37). When examining the link between alcohol intake and cardiometabolic disorders, moderate alcohol consumption has been suggested to have both beneficial and unfavorable effects on insulin sensitivity and cardiovascular complications. Alcohol intake has been suggested to increase insulin sensitivity in a positive linear association and blood pressure in a J-shaped association (38,39). In our study, there was no significant difference between offspring of parents with SMI and comparison cohort in alcohol consumption. However, offspring smoked more regularly compared with comparison cohort.

Sex Differences

To our knowledge, this is the first study to explore sex differences in morbidity of cardiometabolic disorders in the offspring of parents with SMI. We found that male offspring had an increased risk of cardiometabolic disorders. We examined separately if offspring had a mother or a father with SMI. Male offspring of fathers with SMI had the highest risk of developing cardiometabolic disorder.

Although there are no studies regarding sex difference in the offspring of parents with SMI, there are studies that have focused on sex differences in the co-occurrence of cardiometabolic disorders and SMI. One study observed higher triglycerides and lower high-density lipoprotein levels in males, and greater fat mass and more abdominal obesity in females with schizophrenia (40). The study also reported no sex differences in metabolic syndrome among young people, but differences emerged among older people. Another more recent study found an increased prevalence of metabolic syndrome in males than in females with bipolar disorder (41). Depression has also been associated with obesity and metabolic syndrome, with a higher risk in males than in females (42).

Strengths

Our study has several strengths. First, there was a long follow-up time of the offspring from birth to age 49 years.

Second, the data were prospectively collected. The follow-up started during pregnancy. We were able to use multiple confounders including maternal smoking during pregnancy and socioeconomic factors. The sample size was relatively large. The risk group and comparison group were born in the same area of Finland and in the same year. Statistical analyses used in the study were suitable for this kind of epidemiological study. Another strength is the high quality of the register data (CRHC) (20). It is obligatory for all healthcare providers, both public and private, in Finland to report the cause(s) of use (*ICD* diagnoses) of healthcare services at discharge. A further strength is the additional analyses conducted with exclusion criteria of offspring with SMI, which did not change the results significantly.

Limitations

The current study should be interpreted in the view of several limitations. First, the cases of cardiometabolic disorders included in the study were the most severe cases, as they were clinically treated; as a result, it is likely that only a minority of the cases were included in the present study. Second, some of the maternal information was collected via questionnaire, which may have caused some information bias in the study results. However, these data were collected prospectively. Third, we were not able to study parental SMI before pregnancy, during pregnancy, or in the infancy of the offspring from 1966 until 1968. This is due to lacking data because the CRHC did not have complete registration of personal identification codes before 1969. This means that there was a 2- to 3-year gap on parental diagnoses. Fourth, there was a substantial amount of missing data on life-style variables at the 46-year follow-up phase. However, we have not used these variables as confounders because they are more descriptive variables.

CONCLUSIONS

With our birth cohort setting, we were able to study the relation between parental SMI and offspring cardiometabolic morbidity. Our findings suggest that there is an elevated risk of coronary artery disease, hyperlipidemia, obesity, and hypertension in the male offspring of parents with SMI. Furthermore, the hypothesis of higher morbidity from cardiometabolic disorders in offspring of parents with SMI is supported by our findings. Our results suggest that the somatic health of offspring of parents with SMI should also be considered in addition to their mental health in clinical practice (43).

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