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# Insulin resistance and lipid levels in the middle-aged offspring of parents with severe mental illness

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ABSTRACT

*Background:* Type 2 diabetes and dyslipidemias co-occur frequently with severe mental illnesses (SMI). However, less is known about serum insulin and lipid levels and prevalence of Insulin Resistance (IR) in offspring with familial risk for SMI.

*Method:* The Northern Finland Birth Cohort 1966 consists of 12,068 mothers, 11,068 fathers, and 12,231 children from the two northernmost provinces in Finland. At age 46 they participated in clinical examination including measurements of glucose, lipids, and IR and answered a questionnaire including information about their nutrition and physical activity. The information on parental SMI was obtained from the Hospital Discharge Register. Parents with SMI were those who had been treated in hospital for any psychiatric disorder during 1969–1982 (ICD-8 codes 290–315). The final study group included 334 (7.3 %) offspring who had a parent with SMI and 4249 (92.7 %) offspring in the comparison group.

*Results:* We did not find increased risk for disturbances in lipid levels, insulin levels, or IR levels between the study group (offspring of either parent with SMI) compared with the comparison group. All offspring, especially female offspring of either parent with SMI, had an increased risk for higher glucose levels and waist circumference. The results remained the same after excluding offspring with SMI.

*Conclusion:* Our findings suggest that offspring of parents with SMI, especially female offspring, have partly increased risk for disturbances in cardiometabolic risk factors. Disturbances in glucose metabolism may have an effect via familial risk of severe mental illness.

## 1. Introduction

People with severe mental illness (SMI) are found to have higher mortality and morbidity rates of chronic diseases than the general population. The excess mortality is mostly due to co-morbid metabolic and cardiovascular complications (Laursen et al., 2013, 2011). The term SMI is widely used across research. However, there is no consistent definition for it (Gonzales et al., 2022). Psychotic and cardio-metabolic disorders both have substantive heritability (Mothi et al., 2015). There might also be a common familial pathway leading to a high co-occurrence of somatic disorders and SMI (Andreassen et al., 2013). This raises the question whether cardio-metabolic risk is increased in relatives of people with familial risk for SMI.

Metabolic syndrome (MetS) is defined as a cluster of metabolic abnormalities that includes hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia (Rochlani et al., 2017). Obesity is a significant risk factor for the development of compensatory hyperinsulinemia and/or insulin resistance (IR). Also, the degree of obesity has been correlated with the degree of IR, which is a key factor for the development of MetS. (Boney et al., 2005; Grundy, 2007) Multiple

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factors appear to predispose to MetS, including for example genetic deficits in insulin signaling pathways, adipose tissue disorders, physical inactivity, mitochondrial dysfunction, individual genetic variability, advancing age, and certain drugs. MetS comprises cardiometabolic risk factors including arterial hypertension, abdominal obesity, elevated triglyceride and glucose levels, and low high-density lipoprotein cholesterol level.(Alberti et al., 2005; Cleeman, 2001; Grundy, 2007) MetS is a useful concept as it identifies patients who have an increased risk for cardiovascular disease and diabetes (Grundy, 2007). Previous studies have suggested metabolic markers that identify insulin-resistant individuals. These metabolic markers insulin concentration and lipid concentrations (McLaughlin et al., 2003). The Quantitative Insulin Sensitivity Check Index (QUICKI) is a simple method calculated from fasting glucose and insulin levels determining insulin sensitivity (Katz et al., 2000). The triglyceride/high-density lipoprotein cholesterol (TG/HDL) ratio can also be used to determine IR (McLaughlin et al., 2003). Peripheral arterial compliance (PAC) is a noninvasive measure used to predict cardiovascular risk in psychiatric patients. People with psychiatric diagnoses are found to have reduced arterial compliance. (Koola et al., 2016).

MetS has been reported to be more prevalent in people with SMI than in the general population (Toalson et al., 2004). Results from first episode drug-naïve (Chen et al., 2016) or medication-free (Cohn et al., 2006) patients with psychotic disorders suggest that a higher frequency of glucose intolerance and/or IR is also associated with psychotic disorders. There are also studies showing impaired glucose tolerance (Fernandez-Egea et al., 2008a; Mukherjee et al., 1989) and increased prevalence of diabetes mellitus type II (Mukherjee et al., 1989) in first-degree relatives of patients with schizophrenia compared to healthy controls. Antipsychotic treatment is associated with metabolic disturbances. However, some antipsychotics, such as aripiprazole, brexpiprazole, ziprasidone, cariprazine, and lurasidone are found to have fewer metabolic side effects. (Pillinger et al., 2020) The objective of this study was to examine cardiometabolic risk factors (serum insulin and lipid levels and prevalence of insulin resistance) in offspring with familial risk for severe mental illness (SMI) and compare them to other members of the Northern Finland Birth Cohort 1966 (NFBC 1966). We hypothesized that the offspring of parents with SMI have increased risk for disturbances in cardiometabolic risk factors.

## 2. Material and methods

### 2.1. Study design

The NFBC 1966 is a prospective follow-up study of offspring with an expected date of birth in 1966. The data originally includes 12,068 mothers, 11,068 fathers and 12,231 children from the provinces of Lapland and Oulu in Finland. (Nordström et al., 2021) We also applied register data from 1969 until the offspring's age of 46 years. We used personal identification codes given to all citizens and residents of Finland from 1964 to 1968 to merge register data to the NFBC 1966 data set. Permission to link register data was obtained from the Ministry of Social Affairs and Health. The ethical committee of the Northern Finland Ostrobothnia Hospital District is keeping the study under review.

### 2.2. Participants

First, we excluded 326 (2.7 %) twins, since twins do not fulfil the criteria of independent cases. Second, we excluded 6414 (52.4 %) members of the cohort whose cardiometabolic risk factors (HDL, LDL, total cholesterol, triglyceride, glucose, insulin, Quantitative Insulin Sensitivity Check Index (QUICKI), waist circumference) were missing. Third, we excluded 804 (6.6 %) whose background information was missing. Fourth, we excluded 76 (0.6 %) who had a diabetes diagnosis. Fifth, we excluded 28 (0.2 %) members of the cohort who denied the use of their data in research. Our final study group included 4583 offspring

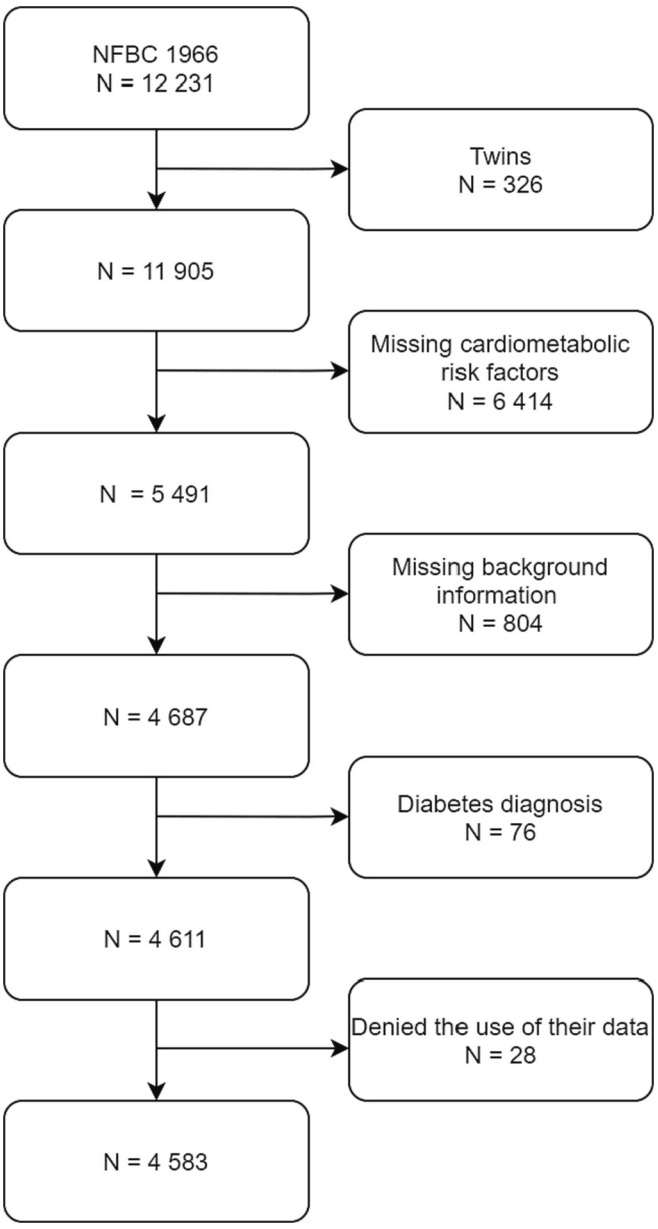


**Fig. 1.** Flowchart of study design.

(Fig. 1). This group included 334 (7.3 %) offspring who had a parent with SMI and 4249 (92.7 %) offspring in the comparison group.

### 2.3. Classification for cardiometabolic risk factors

We used IR, serum high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, triglyceride, fasting glucose, fasting insulin, QUICKI, and waist circumference as outcome variables to describe cardiometabolic risk factors. QUICKI was determined according to the equation: QUICKI = 1/[log(I0) + log(G0)], in which I0 is fasting insulin, and G0 is fasting glucose (Katz et al., 2000). Using the WHO cut-off point, IR was defined as the lowest quartile of the QUICKI of the entire study population (Tenerz et al., 2003). IR was also determined from the triglycerides/HDL cholesterol (TG/HDL) ratio. A TG/HDL ratio >3 is a marker of IR (McLaughlin et al., 2003). There were 5 (3.6 %) men and 2 (1.0 %) women who had TG/HDL ratio > 3 in the group of offspring of either with SMI and 92 (5 %) men and 8 (0.3 %) women in the comparison group. Due to the rarity of the events, we made no further analyses for the suggested exposure group. Waist

circumference was measured in a clinical examination at the offspring age of 46 years. Serum lipid, insulin, and glucose levels were measured at the offspring age of 46 years.

### 2.4. Parental SMI

We used either parent with SMI as exposure in the study. The information on parental SMI was obtained from the Hospital Discharge Register, currently called the Care Register for Health Care (CRHC), and kept by THL, the Finnish Institute for Health and Welfare. Parents with SMI were those who had been treated in hospital for any psychiatric disorder during 1969–1982 (ICD-8 codes 290-315) at offspring 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, 30,680, and 30,698). ICD-8 codes of parents included in the parental SMI category are presented in Table 1. The CRHC has a very good accuracy, and it is one of the oldest individual level hospital discharge registers (Sund, 2012).

### 2.5. Confounders

Mother's education level and offspring's place of birth were used as confounders. They have been shown to influence offspring weight (Chen and Escarce, 2010; Lamerz et al., 2005; Shrewsbury and Wardle, 2008). Place of birth was dichotomized into two categories: urban and rural communities. Mother's educational level was categorized into two levels according to the length of education: <9 years and 9 years or more. Maternal smoking during pregnancy may also cause offspring future obesity and that is why it was used as a confounder in this study(Ino, 2010). Maternal smoking was dichotomized into smokers and non-smokers. Those mothers who continued smoking in the second trimester were considered smokers. Information about the confounders was obtained from the mother by local midwives using a pre-defined questionnaire at the antenatal clinics. The questionnaire was filled in from the 24th to 28th gestational week, and if this was impossible, the questionnaire was completed later during the pregnancy or after the delivery.

We also used offspring SMI, physical activity, and nutrition as confounders. Information about the offspring's SMI was obtained from CRHC until 49 years of offspring age. Activity was 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 (Tammelin et al., 2003). Nutrition was dichotomized into two groups according to the amount of fruits, vegetables, and berries used: healthy and unhealthy. Those eating fruits, vegetables, and berries nearly every day or at least once per day were defined as healthy and those eating them more rarely as unhealthy. Information about physical activity and nutrition was obtained from the offspring via a questionnaire at the age of 46 years.

### 2.6. Statistical methods

Analyses were performed using R version 1.4.1106.

Descriptive statistics were used to compare the offspring of either parent with SMI and the comparison group. Comparisons were conducted using cross-tabulation and chi-square testing. Means and 95 % CI were estimated for continuous cardiometabolic risk factors for both offspring of either parent with SMI and the comparison group. Significances for the differences in mean values were calculated using the *t*-test. Log-transformation was performed for triglycerides, glucose level, insulin level, and waist circumference to meet the normality assumption. Drop-out analysis was also utilized as additional analysis by comparing the study population and drop-out population with a chi-square test. Linear regression was used to estimate the association between continuous cardiometabolic risk factors (HDL, LDL, total cholesterol, triglycerides, glucose, insulin, QUICKI, waist circumference) and parental SMI together and separately for both sexes. We did use linear regression modeling because the aim of the study was to model the effects of parental SMI on offspring's cardiometabolic risk factors. Also, while the outcome variables (cardiometabolic risk factors) were measured at age of 46 years and parental SMI at the offspring's age of 3 to 16 years, the models were constructed with parental SMI as exposure. Logistic regression was used to estimate the association between binary IR and parental SMI together and separately for both sexes. Both crude and adjusted (with maternal education, smoking during pregnancy, offspring's place of birth, activity, diet, and SMI) were calculated, and beta coefficients (β) in linear regression, odds ratios (OR) in logistic regression with 95 % confidence intervals (CI) and *p*-values are reported. We also conducted an additional analysis where we excluded offspring with SMI.

**Table 1**
ICD-8 codes of parents included in the parental SMI category.

| Parental SMI | ICD-8 |
|---|---|
| Schizophrenia | 2950–2959, 297 |
| Other psychosis | 299 |
| Bipolar disorder | 29,610–29,640, 2967–2969 |
| Depression | 2960, 2980, 3004, 7902 |
| Substance use disorder excluding 310–315, 302, 30,680 and 30,698 | 291, 303–304 |

### 2.7. Attrition analysis

Supplement Table 1 summarizes the drop-out of the study population. Comparisons were calculated using chi-square testing. Significant differences between the study population and drop-out population were found for a parent with SMI, offspring with SMI, parental education level, maternal smoking, offspring nutrition, offspring activity, and sex of the offspring. In the drop-out population, there were more parents with SMI, and mothers had a lower education level and were more likely to smoke. In the drop-out population, there also were more offspring with SMI and more males.

## 3. Results

Table 2 summarizes the characteristics of middle-aged offspring and their mothers in the NFBC 1966 divided into two groups: study group (offspring of either parent with SMI) and comparison group (offspring of parents without SMI). Mothers of the study group compared to the comparison group smoked more often during pregnancy, and offspring of the study group had SMI themselves more frequently. Mothers of male offspring of the study grouphad lower education level and smoked more often. Female offspring of the study group had SMI themselves more frequently compared to the comparison group. Comparisons were made using chi-square testing.

Table 3 presents the association between cardiometabolic risk factors and parental SMI together and separately for male and female offspring of either parent with SMI and the comparison group using the *t*-test. Glucose level and waist circumference were associated with all offspring, and glucose level, insulin level and waist circumference with female offspring of either parent with SMI. Glucose level was associated with male offspring of either parent with SMI.

When using linear regression analysis, there were no statistically significant differences in the blood HDL, LDL, total cholesterol, triglycerides, or insulin levels between the offspring of either parent with SMI compared with the comparison group (Table 4). For males and females, the models were adjusted with maternal education, smoking during pregnancy, offspring's place of birth, activity, nutrition, and SMI. For all offspring, models were adjusted with maternal education, smoking during pregnancy, offspring's place of birth, activity, nutrition, SMI, and sex of the offspring. Being offspring of either parent with SMI

**Table 2**
Characteristics of offspring and their mothers – separately in the offspring of either parent with severe mental illness (SMI), and comparison group (offspring of parents without SMI).

| | All offspring | | | Male offspring | | | Female offspring | | |
|---|---|---|---|---|---|---|---|---|---|
| | Offspring of either parent with SMI | Comparison group | | Offspring of either parent with SMI | Comparison group | | Offspring of either parent with SMI | Comparison group | |
| | *N* = 334 | *N* = 4249 | p-value | *N* = 137 | *N* = 1832 | *p*-value | *N* = 197 | *N* = 2417 | p-value |
| | N (%) | N (%) | | N (%) | N (%) | | N (%) | N (%) | |
| Maternal characteristics | | | | | | | | | |
| Education level | | | | | | | | | |
| <9 years | 226 (67.7) | 2662 (62.7) | 0.077 | 98 (71.5) | 1123(61.3) | 0.022[a] | 128 (65.0) | 1539 (63.7) | 0.773 |
| ≥9 years | 108 (32.3) | 1587 (37.3) | | 39 (28.5) | 709 (38.7) | | 69 (35.0) | 878 (36.3) | |
| Smoking during pregnancy | | | | | | | | | |
| Yes | 57 (17.1) | 527 (12.4) | 0.018[a] | 26 (19.0) | 228 (12.4) | 0.039[a] | 31 (15.7) | 299 (12.4) | 0.209 |
| No | 277 (82.9) | 3722 (87.6) | | 111 (81.0) | 1604 (87.6) | | 166 (84.3) | 2118 (87.6) | |
| | 277 (82.9) | | | | | | | | |
| | 277 (82.9) | | | | | | | | |
| Offspring characteristics | | | | | | | | | |
| Place of birth | | | | | | | | | |
| Rural | 243 (72.8) | 2926 (68.9) | 0.155 | 106 (77.4) | 1242 (67.8) | 0.026[a] | 137 (69.5) | 1684 (69.7) | 1.000 |
| Urban | 91 (27.2) | 1323 (31.1) | | 31 (22.6) | 590 (32.2) | | 60 (30.5) | 733 (30.2) | |
| Nutrition | | | | | | | | | |
| Healthy | 268 (80.2) | 3419 (80.5) | 0.977 | 95 (69.3) | 1293 (70.6) | 0.835 | 173 (87.8) | 2126 (88.0) | 1.000 |
| Unhealthy | 66 (19.8) | 830 (19.5) | | 42 (30.7) | 539 (29.4) | | 24 (12.2) | 291 (12.0) | |
| Activity | | | | | | | | | |
| Active | 242 (72.5) | 3131 (73.7) | 0.669 | 94 (68.6) | 1296 (70.7) | 0.667 | 148 (75.1) | 1835 (75.9) | 0.870 |
| Inactive | 92 (27.5) | 1118 (26.3) | | 43 (31.4) | 536 (29.3) | | 49 (24.9) | 582 (24.1) | |
| Severe mental illness (SMI) | | | | | | | | | |
| Yes | 36 (10.8) | 223 (5.2) | <.001[b] | 13 (9.5) | 120 (6.6) | 0.252 | 23 (11.7) | 103 (4.3) | <0.001[b] |
| No | 298 (89.2) | 4026 (94.8) | | 124 (90.5) | 1712 (93.4) | | 174 (88.3) | 2314 (95.7) | |

[a] Significant difference between groups, $p < 0.05$.
[b] Significant difference between groups, $p < 0.001$.

was associated with higher glucose level and waist circumference. Higher glucose level was associated with male offspring of either parent with SMI, however, the results did not reach statistical significance after adjusting. Female offspring of either parent with SMI were associated with higher glucose level and waist circumference. After excluding offspring with SMI, female offspring of either parent with SMI were associated with higher glucose level and waist circumference (Supplement Table 2).

Logistic regression was used to estimate the association between IR and parental SMI together and separately for both sexes (Table 5). The prevalence of IR was estimated using QUICKI. The cut-off point was defined as the lowest quartile of QUICKI (cut-off: 0.241). For males and females, models were adjusted with maternal education, smoking during pregnancy, offspring's place of birth, activity, diet, and offspring SMI. For all offspring, models were adjusted with maternal education, smoking during pregnancy, offspring's place of birth, activity, diet, offspring SMI, and sex of the offspring. The prevalence of IR estimated by QUICKI did not differ between the subgroups with (26.6 %) or without a parent with SMI (24.9 %). The results did not change after excluding offspring with SMI (Supplement Table 3).

## 4. Discussion

### 4.1. Main findings

Offspring of the study group (either parent with SMI), especially female offspring, had partly increased risk for disturbances in cardiometabolic risk factors. All offspring, especially female offspring of either parent with SMI had increased risk for higher glucose level and waist circumference. The results remained the same after excluding offspring with SMI. We did not find increased risk for disturbances in lipid levels, insulin levels, or IR levels between the study group compared with the comparison group. Mothers of the study group compared to the comparison group smoked more often during pregnancy and offspring of the study group experienced SMI themselves more frequently.

### 4.2. Comparison to other studies

To our knowledge, this is the first study to examine glucose and lipid levels in adult offspring of parents with SMI. The World Health Organization (WHO) defines MetS as a cluster of metabolic abnormalities that include hypertension, central obesity, insulin resistance, microalbuminuria, and atherogenic dyslipidemia(Huang, 2009). MetS has become increasingly relevant due to the exponential increase in obesity worldwide (Rochlani et al., 2017). Obesity increases cardiovascular risk through risk factors such as increased LDL cholesterol, increased plasma triglycerides, low HDL cholesterol, elevated blood glucose, and insulin levels, and high blood pressure (Klop et al., 2013). Knowledge about the role of familial risk of SMI is becoming increasingly important. Our findings suggest that the familial risk of SMI is associated with disturbed glucose metabolism especially in female offspring.

We found one study that investigated the prevalence of insulin resistance and lipid levels in adolescents with familial risk for psychosis in the Northern Finland Birth Cohort 1986 (Koponen et al., 2008). They found no differences in the glucose, insulin and lipid levels, or waist circumference between adolescents with or without familial risk for psychosis, but their focus was on adolescents. A few studies have investigated the prevalence of diabetes being increased in families of people with schizophrenia. Two studies have described an increased prevalence of type 2 diabetes mellitus among first-degree relatives of schizophrenia patients (Fernandez-Egea et al., 2008b; Mukherjee et al., 1989). However, they focused on first-degree relatives and did not include other severe mental illnesses. One found an increased prevalence of impaired glucose tolerance in an oral glucose tolerance test (GTT) in first-degree relatives of patients with schizophrenia compared to healthy controls (Spelman et al., 2007).

The impact of parental SMI on their offspring may vary due to many

**Table 3**
Association between cardiometabolic risk factors and parental severe mental illness (SMI) together and separately for male and female offspring using offspring without a parent with SMI as a comparison group using *t*-test.

| | Offspring of either parent with SMI | | Comparison group | | T-value | p-value |
|---|---|---|---|---|---|---|
| | Mean | 95 % CI[a] | Mean | 95 % CI[a] | | |
| All offspring | | | | | | |
| High-density lipoprotein (HDL) cholesterol (mmol/l) | 1.52 | [1.48, 1.57] | 1.55 | [1.54, 1.57] | −1.33 | 0.183 |
| Low-density lipoprotein (LDL) cholesterol (mmol/l) | 3.46 | [3.36, 3.56] | 3.45 | [3.42, 3.48] | 0.08 | 0.939 |
| Total cholesterol (mmol/l) | 5.31 | [5.21, 5.40] | 5.34 | [5.31, 5.37] | −0.67 | 0.504 |
| Triglyceride (mmol/l) | 1.26 | [1.18, 1.34] | 1.24 | [1.22, 1.27] | 0.43 | 0.672 |
| Glucose (mmol/l) | **5.57** | **[5.50, 5.64]** | **5.46** | **[5.44, 5.48]** | **3.10** | **0.006** |
| Insulin (U/l) | 9.95 | [9.11, 10.79] | 9.27 | [9.08, 9.47] | 1.67 | 0.122 |
| Quantitative insulin sensitivity check index (QUICKI)[b] | 0.27 | [0.26, 0.27] | 0.27 | [0.27, 0.28] | 1.95 | 0.052 |
| Waist circumference (cm) | **93.05** | **[91.57, 94.54]** | **91.24** | **[90.84, 91.64]** | **2.39** | **0.020** |
| Male offspring | | | | | | |
| High-density lipoprotein (HDL) cholesterol (mmol/l) | 1.37 | [1.31, 1.43] | 1.40 | [1.38, 1.41] | −0.94 | 0.348 |
| Low-density lipoprotein (LDL) cholesterol (mmol/l) | 3.73 | [3.57, 3.89] | 3.74 | [3.70, 3.79] | −0.14 | 0.892 |
| Total cholesterol (mmol/l) | 5.49 | [5.32, 5.65] | 5.56 | [5.52, 5.61] | −0.85 | 0.396 |
| Triglyceride (mmol/l) | 1.44 | [1.30, 1.58] | 1.49 | [1.45, 1.53] | −0.34 | 0.732 |
| Glucose (mmol/l) | **5.77** | **[5.67, 5.87]** | **5.67** | **[5.64, 5.71]** | **2.02** | **0.043** |
| Insulin (U/l) | 10.02 | [9.09, 10.96] | 10.29 | [9.94, 10.65] | −0.67 | 0.501 |
| Quantitative insulin sensitivity check index (QUICKI)[b] | 0.26 | [0.25, 0.27] | 0.27 | [0.26, 0.27] | −1.81 | 0.071 |
| Waist circumference (cm) | 98.00 | [96.25, 99.75] | 97.19 | [96.65, 97.72] | 0.95 | 0.341 |
| Female offspring | | | | | | |
| High-density lipoprotein (HDL) cholesterol (mmol/l) | 1.63 | [1.57, 1.69] | 1.67 | [1.66, 1.69] | −1.38 | 0.17 |
| Low-density lipoprotein (LDL) cholesterol (mmol/l) | 3.26 | [3.14, 3.39] | 3.23 | [3.20, 3.26] | 0.51 | 0.612 |
| | 5.18 | | 5.17 | | 0.13 | 0.898 |
| Total cholesterol (mmol/l) | | [5.07, 5.30] | | [5.14, 5.21] | | |
| Triglyceride (mmol/l) | 1.14 | [1.04, 1.23] | 1.06 | [1.04, 1.08] | 1.31 | 0.191 |
| Glucose (mmol/l) | **5.42** | **[5.33, 5.52]** | **5.30** | **[5.28, 5.33]** | **2.89** | **0.004** |
| Insulin (U/l) | **9.90** | **[8.63, 11.18]** | **8.50** | **[8.29, 8.71]** | **2.14** | **0.034** |
| Quantitative Insulin Sensitivity Check Index (QUICKI)[b] | 0.28 | [0.27, 0.28] | 0.28 | [0.28, 0.28] | 1.32 | 0.188 |
| Waist circumference (cm) | **89.62** | **[87.54, 91.69]** | **86.73** | **[86.22, 87.23]** | **2.90** | **0.004** |

Significances for the means were calculated using *t*-test. Log-transformation was performed for triglyceride, glucose, insulin, and waist circumference to meet the normality assumption.
Significant results are bolded.
[a] Confidence Interval.
[b] QUICKI = 1/[log(I0) + log(G0)], in which I0 is fasting insulin, and G0 is fasting glucose normanormality assumption.

intervening factors such as the characteristics of the illness, support system, and environment. The length of the parental psychiatric disorder may also affect the child; for example, if the psychiatric disorder is chronic and enduring, the child is at greater risk of developing problems themselves as they grow up (Singleton, 2007) Offspring of parents with SMI are found to be at risk for psychiatric symptoms and disorders. Somatic illnesses are often comorbid with psychiatric illnesses, hence the impact of parental SMI on offspring may be partly due to the psychological effects of the parental SMI (Agnafors et al., 2019). Parents with SMI are at increased risk for having a lower education level compared to healthy parents. Lower educational attainment is associated with lower socioeconomic status and poorer physical health, which may affect offspring. (Cutler and Lleras-Muney, 2006; Frissen et al., 2015).

In previous research, parental mental illness has been connected to marital distress and poor family relationships. Offspring having a parent with mental illness are at high risk for the development of psychological symptoms like depression and anxiety as well as poor social functioning. This risk may continue throughout the lifespan. (Sell et al., 2021) Divorce and parental separation are damaging to offspring, as the child may have poorer health (Anderson, 2014). Previous studies show health disparities between rural and urban communities. Access to and use of health information are critical to health outcomes in individuals. Better health information access and use help individuals improve knowledge, increase the use of health services, adopt healthier behavioral patterns, reduce health care costs, and therefore promote health. (Eng et al., 1998; Kelley et al., 2016) Rural residents may have lower access to the use of certain health information sources compared to urban residents (Chen et al., 2019).

### 4.3. Strengths and limitations

Our study had several strengths. The NFBC1966 has a prospective cohort setting and good participation rates (above 50 % after 46 years of follow-up). It is a large population-based birth cohort that comprises nearly 97 % (12,231) of all children born in northern Finland in 1966, with systematically collected high-quality data from pregnancy onwards. (Nordström et al., 2021) We had the possibility to study the long-term effect of parental SMI on offspring glucose and lipid levels until the offspring age of 46 years. In addition, the parental SMI was based on

**Table 4**
Association between cardiometabolic risk factors and parental severe mental illness (SMI) together and separately for male and female offspring using offspring without a parent with SMI as a reference group.

| | Crude | | | Adjusted[a] | | |
|---|---|---|---|---|---|---|
| | β | 95 % CI[b] | p-value | β | 95 % CI[b] | p-value |
| All offspring | | | | | | |
| High-density lipoprotein (HDL) cholesterol (mmol/l) | −0.022 | [−0.074, 0.012] | 0.160 | −0.020 | [−0.074, 0.006] | 0.095 |
| Low-density lipoprotein (LDL) cholesterol (mmol/l) | 0.052 | [−0.099, 0.107] | 0.939 | 0.051 | [−0.086, 0.112] | 0.799 |
| Total cholesterol (mmol/l) | −0.052 | [−0.136, 0.068] | 0.510 | −0.051 | [−0.125, 0.076] | 0.632 |
| Triglyceride (mmol/l) | 0.028 | [−0.042, 0.066] | 0.666 | 0.026 | [−0.041, 0.061] | 0.704 |
| Glucose (mmol/l) | **0.012** | **[0.007, 0.031]** | **0.002** | **0.011** | **[0.008, 0.030]** | **0.001** |
| Insulin (U/l) | 0.032 | [−0.009, 0.118] | 0.093 | 0.032 | [−0.014, 0.110] | 0.132 |
| Quantitative Insulin Sensitivity Check Index (QUICKI)[c] | −0.003 | [−0.010, 0.000] | 0.054 | −0.003 | [−0.010, 0.000] | 0.069 |
| Waist circumference (cm) | **0.008** | **[0.004, 0.035]** | **0.017** | **0.007** | **[0.005, 0.033]** | **0.009** |
| Male offspring | | | | | | |
| High-density lipoprotein (HDL) cholesterol (mmol/l) | −0.030 | [−0.088, 0.028] | 0.316 | −0.030 | [−0.089, 0.027] | 0.290 |
| Low-density lipoprotein (LDL) cholesterol (mmol/l) | 0.083 | [−0.174, 0.152] | 0.892 | 0.083 | [−0.176, 0.151] | 0.878 |
| Total cholesterol (mmol/l) | −0.086 | [−0.244, 0.093] | 0.382 | −0.086 | [−0.246, 0.092] | 0.37 |
| Triglyceride (mmol/l) | −0.045 | [−0.104, 0.073] | 0.732 | −0.045 | [−0.108, 0.068] | 0.653 |
| Glucose (mmol/l) | **0.010** | **[0.001, 0.039]** | **0.044** | 0.010 | [−0.001, 0.037] | 0.071 |
| Insulin (U/l) | 0.053 | [−0.068, 0.139] | 0.501 | 0.052 | [−0.078, 0.127] | 0.637 |
| Quantitative Insulin Sensitivity Check Index (QUICKI)[c] | −0.004 | [−0.014, 0.002] | 0.133 | −0.004 | [−0.014, 0.002] | 0.176 |
| Waist circumference (cm) | 0.010 | [−0.010, 0.030] | 0.342 | 0.010 | [−0.012, 0.028] | 0.432 |
| Female offspring | | | | | | |
| High-density lipoprotein (HDL) cholesterol (mmol/l) | −0.028 | [−0.097, 0.014] | 0.143 | −0.028 | [−0.093, 0.017] | 0.177 |
| Low-density lipoprotein (LDL) cholesterol (mmol/l) | 0.063 | [−0.090, 0.156] | 0.600 | 0.063 | [−0.091, 0.156] | 0.606 |
| Total cholesterol (mmol/l) | 0.062 | [−0.114, 0.129] | 0.900 | 0.062 | [−0.112, 0.132] | 0.874 |
| Triglyceride (mmol/l) | 0.032 | [−0.021, 0.104] | 0.191 | 0.032 | [−0.033, 0.091] | 0.362 |
| Glucose (mmol/l) | **0.007** | **[0.007, 0.035]** | **0.004** | **0.007** | **[0.004, 0.032]** | **0.010** |
| Insulin (U/l) | 0.040 | [−0.006, 0.151] | 0.069 | 0.040 | [−0.017, 0.139] | 0.124 |
| Quantitative Insulin Sensitivity Check Index (QUICKI)[c] | −0.003 | [−0.012, 0.002] | 0.152 | −0.003 | [−0.011, 0.003] | 0.255 |
| Waist circumference (cm) | **0.010** | **[0.010, 0.051]** | **0.004** | **0.010** | **[0.006, 0.046]** | **0.012** |

Significant results are bolded.
[a] All offspring djusted with maternal education, smoking during pregnancy, offspring's place of birth, activity, nutrition, and SMI, sex of offspring. Males and females adjusted with maternal education, smoking during pregnancy, offspring's place of birth, activity, nutrition, and SMI.
[b] Confidence Interval.
[c] QUICKI = 1/[log(I0) + log(G0)], in which I0 is fasting insulin, and G0 is fasting glucose.

**Table 5**
Association between insulin resistance (IR) and parental severe mental illness (SMI) together and separately for male and female offspring using offspring without a parent with SMI as a reference group.

| | Crude | | | Adjusted | | |
|---|---|---|---|---|---|---|
| | OR | 95 % CI[b] | *p*-value | OR[a] | 95 % CI[b] | p-value |
| All offspring | | | | | | |
| IR | 1.09 | [0.85, 1.40] | 0.484 | 1.07 | [0.83, 1.36] | 0.590 |
| Male offspring | | | | | | |
| IR | 1.01 | [0.69, 1.45] | 0.971 | 0.97 | [0.66, 1.40] | 0.861 |
| Female offspring | | | | | | |
| IR | 1.22 | [0.85, 1.72] | 0.259 | 1.17 | [0.81, 1.66] | 0.381 |

[a] Odds Ratio. All offspring adjusted with maternal education, smoking during pregnancy, offspring's place of birth, activity, and diet, offspring with SMI, and sex of offspring. Males and females adjusted with maternal education, smoking during pregnancy, offspring's place of birth, activity, and diet, offspring with SMI.
[b] Confidence Interval.

data from the nationwide register, which has high quality (Sund, 2012). We were also able to use a relatively large sample size and had the possibility to use multiple confounders including maternal smoking during pregnancy and socio-economic factors. In addition, some of the data were measured in a clinical examination, which increases the validity of the measures compared to self-reported data. Last, we were able to conduct a drop-out analysis.

The present study has a few limitations. Some of the collected information was collected via questionnaire and this may have caused information bias in the study results. We were also not able to study parental SMI before pregnancy, during pregnancy, or in the infancy of the offspring from 1966 until 1968 due to a lack of data. Since the CRHC did not have complete registration of personal identification codes before 1969, there is a two to three-year gap in parental diagnoses. Third, we had no information on childhood glucose or lipid levels, so it was not possible to study the developmental period more. The evaluation of IR by QUICKI relying on mathematical modeling of fasting plasma glucose and insulin concentration may also be a limitation. However, QUICKI has been shown to be an accurate index of insulin sensitivity in adults(Katz et al., 2000). In addition, adiponectin has a strong association with IR, and measurements of adiponectin levels may be useful in future research (st. Clair and Ballantyne, 2007). The sample sizes in offspring of either parent with SMI and the comparison group are lopsided, which can also be considered as a limitation. The sample size differences between the drop-out population and the study population can also be considered as a serious limitation. Attrition rates were very high and the population between the groups is distinct. In the drop-out population, there were more parents with SMI, and mothers had a lower education level and poorer lifestyle factors regarding smoking. In the drop-out population, there also were more offspring with SMI and more males. Last, there was a relatively high amount of missing data for measured cardiometabolic risk factors among offspring mainly due to nonattendance at the clinical examination ($n = 6414$; 52.5 %).

## 5. Conclusions

We conclude that offspring of parents with SMI, especially female offspring, have partly increased risk for disturbances in cardiometabolic risk factors. Disturbances in glucose metabolism may have an effect via familial risk of severe mental illness.

## Declaration of competing interest

None.

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*Role of the funding source*

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.01.013.

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