Early Environmental Factors and Somatic Comorbidity in Schizophrenia and Non-Schizophrenic Psychoses: a 50-Year Follow-Up of the Northern Finland Birth Cohort 1966

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ABSTRACT

Background

We studied the cumulative incidence of physical illnesses, and the effect of early environmental factors (EEFs) on somatic comorbidity in schizophrenia, in non-schizophrenic psychosis and among non-psychotic controls from birth up to the age of 50 years.

Methods

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The sample included 10,933 members of the Northern Finland Birth Cohort 1966, of whom 227 had schizophrenia and 205 had non-schizophrenic psychosis. Diagnoses concerning physical illnesses were based on nationwide registers followed up to the end of 2016 and classified into 13 illness categories. Maternal education and age, family type at birth and paternal socioeconomic status (SES) were studied as EEFs of somatic illnesses.

Results

When adjusted by gender and education, individuals and especially women with non-schizophrenic psychosis had higher risk of morbidity in almost all somatic illness categories compared to controls, and in some categories compared to individuals with schizophrenia. The statistically significant adjusted hazard ratios varied from 1.27 to 2.42 in non-schizophrenic psychosis. Regarding EEFs, single-parent family as the family type at birth was a risk factor for a higher somatic score among men with schizophrenia and women with non-schizophrenic psychosis. Maternal age over 35 years was associated with lower somatic score among women with non-schizophrenic psychosis.

Conclusions

Persons with non-schizophrenic psychoses have higher incidence of somatic diseases compared to people with schizophrenia and non-psychotic controls, and this should be noted in clinical work. EEFs have mostly weak association with somatic comorbidity in our study.

Keywords: Schizophrenia; psychosis; somatic comorbidity; physical illnesses; population-based; cohort study

1. INTRODUCTION

Individuals with psychoses and especially with schizophrenia have increased rates of physical illnesses compared to the general population [1-3]. Cardiovascular morbidity and mortality, and the risk for type 2 diabetes are approximately two- to three-fold higher in schizophrenia compared to the general population, and people with schizophrenia have about 10 to 25 years shorter life expectancy compared to the general population [3-7].

Schizophrenia is associated with increased incidence of cardiovascular disease, stroke and coronary heart disease [4, 8]. Still, these patients receive less antihypertensive and lipid-lowering treatments [9]. Additionally, metabolic syndrome, overweight, hyperglycemia and lipid abnormalities are common in schizophrenia patients [10].
Higher comorbidity is linked to various factors, e.g. the disorder itself and its consequences (e.g. lifestyle), medication use or neglect by the medical profession regarding adequate screening and treatment [10, 11]. Also, those with schizophrenia, bipolar disorder or major depressive disorder are more sedentary and less physically active than non-psychotic controls [11].

The effect of early environmental factors (EEFs), such as maternal age and education, family type and paternal socioeconomic status (SES) at birth, on somatic comorbidity or health in general has been studied in non-psychotic samples [12-15], but not in psychotic samples. Previous studies show that parental SES is associated with offspring health, and low parental education, maternal age and growing up in a single-parent family are risk factors for poor health outcomes [12-17].

Compared to schizophrenia, somatic illnesses in non-schizophrenic psychosis are not well studied. The aim of this study was to evaluate the prevalence of physical illnesses among individuals with schizophrenia, non-schizophrenic psychosis, and non-psychotic controls up to the age of 50 years in the prospective Northern Finland Birth Cohort 1966 (NFBC 1966). We also aimed to analyze potential EEFs’ effects on somatic comorbidity in psychoses. Our hypothesis was that somatic comorbidity is higher in schizophrenia than in non-schizophrenic psychosis or among non-psychotic controls, as studies show that individuals with schizophrenia have lower physical health in general compared to non-psychotic individuals [18, 19]. To our best knowledge, there are only a few previous prospective, unselected birth cohort studies analyzing somatic comorbidities in psychoses. Especially there is a lack of studies comparing somatic comorbidity in schizophrenia and in non-schizophrenic psychosis.

2. METHODS

2.1. Study Design and Material

This study is based on the population-based, unselected and prospective NFBC 1966 concerning 12 058 live-born children in 1966 in the provinces of Lapland and Oulu [20]. The study design and data of NFBC 1966 have been described in detail elsewhere [20, 21]. The present study population consists of 10 933 individuals being alive at the age of 16 years and living in Finland. They were followed from birth up to the age of 50 years and diagnoses of somatic and psychotic illnesses were coded from age 16 onwards. The NFBC 1966 study design has been approved by The Ethics Committee of the Northern Ostrobothnia Hospital District.

2.2. Identification of psychoses and somatic illnesses

Psychotic and somatic diagnoses were collected from various nationwide registers: The Care Register for Health Care (CRHC) covering all treatment episodes in mental, general and military hospitals, and in the inpatient wards of local health centers nationwide for the period up to 2016;
Register of Specialty Health Care for the period 1998–2016; Register of Primary Health Care Visits in 2011–2013; the registers of the Social Insurance Institution of Finland (including information on reimbursed medicine up to 2005, pensions up to 2000 and sick days up to the end of 1999); and the register of the Finnish Centre for Pensions up to 2013 (data on disability pensions) [22].

2.3. Study population and diagnosis of psychoses

Diagnoses were coded according to the International Classification of Diseases Eighth Revision (ICD-8) before 1987, according to ICD-9 1987–1995, and according to ICD-10 since 1996.

Individuals were classified as having schizophrenia (i.e. disorders of the schizophrenia spectrum: ICD-8: 295; ICD-9: 295, 2954, 2957, 297; ICD-10: F20, F22, F25) or non-schizophrenic psychosis (bipolar disorder with psychotic features, major depressive episode with psychotic features, brief psychosis and other psychosis: ICD-8: 296-299; ICD-9: 298-299, 2961E, 2962E, 2963E, 2964E, 2967; ICD-10: F23-F24, F26, F29, F30.2, F31.2, F31.5, F32.3, F33.3) or no psychosis.

The study population included 432 individuals (237 men, 195 women) with psychosis and 10,501 non-psychotic controls (5352 men, 5149 women), of which 1896 (17.3 %) had a non-psychotic mental, behavioral or neurodevelopmental disorder. In the psychosis population 227 (53 %) had schizophrenia (173 had narrow schizophrenia defined as ICD-10 diagnoses F20.0 to F20.9, 54 had other schizophrenia spectrum disorder), and 205 (47 %) subjects were diagnosed with non-schizophrenic psychosis (72 subjects with a major depressive episode with psychotic features, 24 with bipolar disorder with psychotic features, 109 with brief or undefined psychosis) (Table 1). The diagnostic groups within non-schizophrenic psychosis were not analyzed separately due to the low number of cases.

2.4. Diagnoses of somatic illnesses

Based on information from CRHC, physical illnesses were classified according to ICD-10 Chapters I–XIV and all the diagnoses at age 16 and onwards were considered by transforming ICD-8 and ICD-9 diagnoses to ICD-10 diagnoses. Of the ICD-10, Chapter V Mental and Behavioral Disorders was excluded. Chapters from XIV onwards were excluded because of their nature, as they include, e.g. injuries, poisoning and external causes of morbidity and mortality. The included 13 somatic illness categories are shown in Table 2, and the diagnostic codes used to identify these categories are presented in online supplementary table 1.

2.5. Somatic score

“Somatic score” for each cohort member was calculated based on somatic illness diagnoses. All the diagnoses within one somatic illness category gave a maximum of 1 point and given points from different illness categories were summed. A person may have numerous diagnoses within
any given illness category, but the score for the category remains 1. The score for somatic
diseases ranged from 0 to 13.

2.6. Covariates and early environmental factors for somatic illnesses

Gender and education were analyzed as confounders for somatic illnesses. These were selected
based on earlier studies [1, 18] and our data (please see below, Statistical analyses). Education
data were obtained from the Finnish education register 1997, Statistics Finland and classified as
basic: less than 9 years; secondary: 9–12 years; and tertiary: more than 12 years.

The selected EEFs were maternal education and age, family type at birth and paternal SES. These
have been associated with increased risk of psychoses [23-28] and increased risk of somatic
illnesses in non-psychotic samples [12-17]. Data were gathered from the Population Register
Centre and from questionnaires during the mothers’ visits to antenatal clinics at 24–28 weeks
gestation. Data for maternal education was obtained from questionnaires and classified as low: 0–4
years, intermediate: 5–8 years and high education: more than 8 years [29]. Data for maternal age
was obtained from the Population Register Centre and classified as under 20 years, 20–35 years
and over 35 years [29]. Family type at birth was obtained from the questionnaire and based on the
marital status of the mother during pregnancy (married, divorced, widowed or never married). Family type was classified as two-parent families and single-parent families [30]. SES at birth was
obtained from the questionnaire and based on the father’s occupation. SES was classified as high
(classes I and II), low (classes III and IV) and farmers (class V) [30].

2.7. Statistical analyses

The background variables were compared between individuals with schizophrenia, non-
schizophrenic psychosis and controls by using cross-tabulation and the Chi²-exact test. Cox
regression analysis was used to examine the risk of physical illness in schizophrenia and non-
schizophrenic psychosis in comparison to the non-psychotic controls.

Cox regression analyses were done unadjusted and adjusted for gender and education, and
adjusted for EEFs. Additionally, analyses were done in strata by gender as women and men may
have gender differences in health and in symptom reporting [31, 32].

We present the results as adjusted hazard ratios for gender and education (AHRs) with 95 %
confidence intervals (95 % CIs). Unadjusted hazard ratios (HR) are presented if they differ
significantly from AHRs. Cox regression analyses adjusted for EEFs were in line with presented
AHRs. Benjamini-Hochberg procedure was used to correct for multiple comparisons and
Benjamini-Hochberg corrected P-values (BH P-value) are presented.
Differences in the somatic score between individuals with schizophrenia, non-schizophrenic psychosis and controls were examined by using Mann-Whitney’s U test and Kruskal-Wallis H test. Effect of gender and EEFs on somatic score was tested by a one-way analysis of variance, or by the Brown-Forsythe test when group variances within an EEF were not statistically equal. Effect sizes for EEFs were calculated using Hedges’ g and results were interpreted with the following cut-offs: small effect size = 0.2, medium effect size = 0.5 and large effect size = 0.8. Control groups for effect size were high maternal education, maternal age of 20–35 years, high SES and two-parent family. Analyses were performed using IBM SPSS Statistics 24.0.

3. RESULTS

3.1. Characteristics of the sample

The distribution between genders was rather equal, though there were more men than women with schizophrenia (57.7 % vs. 42.3 %). Most individuals have completed secondary education, though tertiary education was more common among non-psychotic controls (25.5 %) than among people with schizophrenia (9.3 %) and non-schizophrenic psychosis (13.2 %). (Table 1.)

3.2. Risk of somatic illnesses in schizophrenia

Diseases of the blood and blood-forming organs (7.9 % in schizophrenia versus 4.0 % in non-psychotic controls, AHR 2.00, 95 % CI 1.25–3.22) and endocrine, nutritional and metabolic diseases (22.5 % vs. 12.7 %, AHR 1.81, 95 % CI 1.36–2.39) were more common among individuals with schizophrenia compared to controls (Table 2). Diseases of the musculoskeletal system and connective tissue were less common in schizophrenia than among controls (37.4 % vs. 48.7 %, AHR 0.68, 95 % CI 0.54–0.84). Adjusted results were in line with unadjusted results except for certain infectious and parasitic diseases in which prevalence was higher in schizophrenia (26.4 % vs. 19.2 %, HR 1.46, 95 % CI 1.13–1.88) in unadjusted analyses.

When analyzed in strata by gender, men with schizophrenia had higher prevalence of diseases of the blood and blood-forming organs, endocrine, nutritional and metabolic diseases and diseases of the genitourinary system. Diseases of the musculoskeletal system and connective tissue were lower compared to the controls (Tables 3 and 4). The unadjusted results were in line with the adjusted results except for diseases of the musculoskeletal system and connective tissue which did not have a statistically significant difference in men with or without schizophrenia in unadjusted analyses.

3.3. Risk of somatic illnesses in non-schizophrenic psychoses

Diseases in multiple somatic illness categories were more common among individuals with non-schizophrenic psychosis compared to non-psychotic controls (Table 2). Diseases of the blood and
blood-forming organs (9.3 % vs. 4.0 %, AHR 2.29, 95 % CI 1.45–3.64) and endocrine, nutritional and metabolic diseases (28.31 % vs. 12.7 %, AHR 2.42, 95 % CI 1.86–3.15) were significantly more prevalent in non-schizophrenic psychosis than in controls (Tables 3 and 4). The unadjusted results were in line with the adjusted results except for the diseases of the musculoskeletal system and connective tissue, which had higher prevalence among individuals with non-schizophrenic psychosis when analyses were done unadjusted (55.1 % vs. 48.7 %, HR 1.26, 95 % CI 1.04–1.52).

When analyzed in strata by gender, men with non-schizophrenic psychosis had significantly higher prevalence of diseases of the blood and blood-forming organs (7.5 % vs. 2.7 %, AHR 2.89, 95 % CI 1.42–5.90) than male controls. Women with non-schizophrenic psychosis had significantly higher prevalence of endocrine, nutritional and metabolic diseases (37.4 % vs. 14.1 %, AHR 2.89, 95 % CI 2.07–4.02) compared to female controls. Disease prevalence was statistically significantly higher in various disease categories as seen in tables 3 and 4. Unadjusted results were in line with adjusted results except for diseases of the digestive system among women with non-schizophrenic psychosis where prevalence was higher compared to female controls when analyzed unadjusted (70.7 % vs. 60.1 %, HR 1.31, 95 % CI 1.03–1.66).

3.4. The risk of somatic illness in schizophrenia compared to non-schizophrenic psychoses

Compared to non-schizophrenic psychosis, individuals with schizophrenia had less diseases of the nervous system (24.2 % vs. 34.1 %, AHR 0.66, 95 % CI 0.46–0.94), diseases of the skin and subcutaneous tissue (22.5 % vs. 31.7 %, AHR 0.66, 95 % CI 0.46–0.96), diseases of the musculoskeletal system and connective tissue (37.4 % vs. 55.1 %, AHR 0.56, 95 % CI 0.42–0.74) and diseases of the genitourinary system (32.6 % vs. 43.4 %, AHR 0.69, 95 % CI 0.50–0.93).

3.5. Somatic score

When both sexes were examined together, the median number of somatic diseases from different somatic illness categories was three among people with schizophrenia, four among people with non-schizophrenic psychosis and three among non-psychotic controls (Figure 1). The difference in somatic score in people with non-schizophrenic psychosis compared to both schizophrenia (U = 26 917, P = .005) and non-psychotic controls (U = 825 117, P < .001) was statistically significant. The difference of the distribution of somatic diseases between people with schizophrenia and non-psychotic controls (U = 1 104 804, P = .06) was non-significant.

The median somatic score was three among men with schizophrenia and among controls, and four among men with non-schizophrenic psychosis. The median somatic score was four among women with schizophrenia, five among women with non-schizophrenic psychosis and three among control females. Women with non-schizophrenic psychosis had statistically significantly higher median somatic scores compared to men with non-schizophrenic psychosis (U= 6520, P = .003).
3.6. Early environmental factors of somatic illness

Online supplementary table 2 describes the median and mean somatic scores among different EEFs according to sex and psychotic illness group. Among women with schizophrenia and men with non-schizophrenic psychosis, none of the EEFs predicted the somatic score. Single-parent family as the family type at birth was a risk factor for higher somatic score among men with schizophrenia, (Median somatic score = 5 in single-parent family versus 3 in two-parent family, \( P = 0.01, \) Hedges’ \( g = 0.86 \)) and among women with non-schizophrenic psychosis (Median somatic score = 7 vs. 5, \( P = 0.03, \) Hedges’ \( g = 0.87 \)). Among women with non-schizophrenic psychosis, maternal age higher than 35 years was associated with lower somatic score (Median somatic score = 3 vs. 5, \( P = .03, \) Hedges’ \( g = 0.76 \)) compared to the reference group of mothers (age 20–35). Among controls, high maternal education and high SES statistically significant predictors of lower somatic score among both men and women. Among control women, young maternal age was also a statistically significant predictor of higher somatic score. Effect sizes among statistically significant predictors varied from 0.002 to 0.22, so despite the statistical significance, EEFs were weak predictors for somatic illness among controls in our study population.

4. DISCUSSION

4.1. Main findings

The main finding in our study was that people with non-schizophrenic psychosis had increased risk of several somatic illnesses when compared to schizophrenia or non-psychotic controls. People with non-schizophrenic psychosis had more diseases of the skin, and nervous, genitourinary and musculoskeletal system than people with schizophrenia. Especially women with non-schizophrenic psychosis had a higher risk of somatic comorbidities. EEFs had a very small effect among non-psychotic individuals. Among men with schizophrenia and women with non-schizophrenic psychosis, single-parent family as the family type at birth was a significant risk factor for higher somatic comorbidity. Among women with non-schizophrenic psychosis, maternal age higher than 35 years at birth seemed to be a protective factor against somatic illnesses.

4.2. Comparison with earlier studies

Some previous studies show that somatic comorbidity is common among patients with depressive disorder and that the prevalence of somatic illnesses is more common in patients with bipolar disorder than among patients with schizophrenia [33-35]. People with schizoaffective disorder have a higher risk of metabolic syndrome than people with schizophrenia or other non-affective psychoses [36]. It may be that especially depressive symptoms increase the risk of metabolic...
syndrome and somatic illnesses via unhealthy lifestyle, medication, and co-occurring biological mechanisms (e.g. hypercortisolism) [35, 36]. These may be some of the reasons behind our findings of higher risk of somatic comorbidity among non-schizophrenic psychoses, as suggested by some previous literature [11]. In addition, persons with non-schizophrenic psychoses, especially those with affective psychosis, may have more personality problems or impulsiveness that associate to, e.g. smoking and alcohol use and somatic problems relating to those [37]. Persons with non-schizophrenic psychoses may also seek medical help more often compared to persons with schizophrenia. Thus, there may be some undiagnosed somatic comorbidities in the schizophrenia group [38].

Women with non-schizophrenic psychosis had a higher risk of somatic comorbidities in our sample. Some studies have found evidence that women experience multiple comorbidities in schizophrenia and psychosis [6, 33], and they are more ready to report illness and to seek help than men [39, 40]. Women have more morbidity burden at all ages, and they experience the negative side-effects of antipsychotics (e.g. weight gain, diabetes, and cardiovascular risks) more than men [31, 32, 41, 42].

Diseases of the blood and blood-forming organs and disorders of the immune mechanism were more prevalent in subjects with psychosis compared to non-psychotic controls. One explanation for this could be altered development of the immune system, which has been linked to development of psychosis and other psychiatric disorders [43, 44].

Our study shows an association between endocrine, nutritional and metabolic diseases and psychoses, the finding being consistent with previous studies that have shown associations especially between metabolic syndrome, diabetes and thyroid dysfunction and psychoses [45-47]. Several studies have suggested that schizophrenia is associated with increased incidence of cardiovascular disease and coronary heart disease [9, 48], but also contrary results have been found [6, 49]. In our study, there was higher prevalence of diseases of the circulatory system only among men with non-schizophrenic psychosis. This could be because of the relatively young age of our study population, as the risk for cardiovascular diseases increases with age [50].

In our study, diseases of the musculoskeletal system and connective tissue were less common in men with schizophrenia than among controls. Studies have shown that there is a reduced risk of musculoskeletal diseases in schizophrenia and in schizoaffective patients [33, 51]. This may be due to pain insensitivity to chronic pain, as people with schizophrenia have decreased or altered pain perception [52] and the lack of pain might leave physical diseases undiagnosed.

4.3. Early environmental factors and somatic illnesses
The only significant predictors of somatic illnesses among individuals with psychosis were family type at birth and maternal age.

It has been shown that children living in single-parent families have poorer health than children living with two biological parents [14, 53]. Our study results support this finding partially as single-parent family was a risk factor of somatic illnesses among men with non-schizophrenic psychosis and women with schizophrenia.

Studies show that offspring born to mothers younger than age 25 or older than 35 have worse outcomes with respect to, e.g. self-rated health and the number of diagnosed conditions as adults than those born to mothers aged 25–34 [12]. Our results are contrary, as higher maternal age was associated with lower somatic comorbidity among women with non-schizophrenic psychosis.

4.4. Limitations

Regarding somatic illnesses, our sample may include mainly the patients who have primarily been in hospital care because the outpatient data from primary health care is available only from 2011 onwards and from specialized outpatient care from 1998 onwards. Thus, we may have missed some of the less severe somatic diagnoses and some psychosis cases treated solely as outpatients before 1998. On the other hand, in earlier days most psychosis cases were hospitalized [22], and Finnish national registries have been found to be reliable sources for case detection in severe psychotic disorders [54, 55]. The limitations also include the lack of clinical details and generalizability of the results to populations other than Northern Europe. The study was not designed for the purpose of looking back at data.

Neither psychiatric nor somatic medication were included in our data, and as medication might have some adverse effects on one’s health, it causes study bias. Due to follow-up up to middle age, the generalizability of the results to older age groups is limited. The relatively young age of the participants at the end of the follow-up and the low number of cases in some of the somatic illness groups are limitations.

Somatic score is a rough measure and may cause bias as it gives the same somatic score regardless of how many diagnoses one has within one somatic illness category. It does not describe the severity of illnesses nor the severity of one’s condition. Somatic score has not been used before.

4.5. Conclusion
Our results suggest that people with non-schizophrenic psychosis show a greater occurrence of somatic diseases compared to non-psychotic controls, and this should be noted by medical professionals. Further studies are warranted to investigate somatic comorbidities and their causes in non-schizophrenic psychosis and longitudinal studies on risk factors of somatic comorbidities in schizophrenia and non-schizophrenic psychosis during lifespans are needed.

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Conflicts of interest: Authors declare none.

Supplementary Material:
For supplementary material accompanying this paper, visit cambridge.org/EPA.

The data that support the findings of this study are available from the Northern Finland Cohorts (www.oulu.fi/nfbc) for research purposes with a study plan.

Figure 1. Distribution of somatic score among people with schizophrenia (n=227), non-schizophrenic psychosis (n=205) and non-psychotic controls (n=10501).
Table 1. Gender, education and early environmental factors in individuals with schizophrenia, non-schizophrenic psychosis and no psychosis in the NFBC1966 cohort.

|                      | Schizophrenia n=227 | Non-schizophrenic psychosis n=205 | No psychoses n=10501 |
|----------------------|----------------------|------------------------------------|-----------------------|
|                      | n                   | %                                 | n                     | %                      |
| **Gender**           |                      |                                    |                       |                        |
| Men                  | 131                 | 57.7                              | 106                   | 51.7                   |
| Women                | 96                  | 42.3                              | 99                    | 48.3                   |
| **Education**        |                      |                                    |                       |                        |
| Basic (≤ 9 years)    | 68                  | 30.0                              | 51                    | 24.9                   |
| Secondary (10-12 years) | 138            | 60.8                              | 127                   | 62.0                   |
| Tertiary (over 12 years) | 21               | 9.3                               | 27                    | 13.2                   |
| **Mother’s education** |                      |                                    |                       |                        |
| Low (0-4 years)      | 14                  | 6.2                               | 18                    | 8.8                    |
| Intermediate (5-8 years) | 125             | 55.1                              | 123                   | 60.0                   |
| High (≥ 9 years)     | 88                  | 38.8                              | 64                    | 31.2                   |
| **Mother’s age at birth** |                       |                                    |                       |                        |
| <20 years            | 18                  | 7.9                               | 18                    | 8.8                    |
| 20-35 years          | 172                 | 75.8                              | 158                   | 77.1                   |
| >35 years            | 37                  | 16.3                              | 29                    | 14.1                   |
| **Paternal socioeconomic status at birth** |                       |                                    |                       |                        |
| High (I-II)          | 21                  | 9.3                               | 8                     | 3.9                    |
| Low (III-IV)         | 170                 | 74.9                              | 153                   | 74.6                   |
| Farmers (V)          | 35                  | 15.4                              | 44                    | 21.5                   |
| **Family type at birth** |                      |                                    |                       |                        |
| Two parent family    | 213                 | 93.8                              | 193                   | 94.1                   |
| Single-parent family | 14                  | 6.2                               | 12                    | 5.9                    |
Table 2. Somatic comorbidity in men and women with schizophrenia, non-schizophrenic psychoses and non-psychotic controls.

| Somatic disease                                      | Schizophrenia (n=227) | Non-schizophrenic psychoses (n=205) | Non-psychotic controls (n=10501) | BH p-value |
|-----------------------------------------------------|------------------------|-------------------------------------|----------------------------------|------------|
|                                                     | n    | %    | AHR 95% CI   | n     | %    | AHR 95% CI   | n     | %    | AHR 95% CI   |
| 1. Certain infectious and parasitic diseases        | 60   | 26.4 | 1.35 1.04-1.75| 64    | 29.2 | 1.31 1.26-1.36| 2013  | 19.2 | <.0001 |
| 2. Neoplasms                                        | 54   | 23.8 | 1.33 1.01-1.74| 40    | 9.3  | 1.69 1.26-2.28| 2118  | 20.2 | <.0001 |
| 3. Diseases of the blood and blood forming organs and certain disorders involving the immune mechanism | 18   | 7.9  | 2.00 1.25-3.22| 19    | 9.5  | 2.29 1.45-3.64| 425   | 4.0  | <.0001 |
| 4. Endocrine, nutritional and metabolic diseases    | 51   | 22.5 | 1.81 1.36-2.39| 58    | 4.1  | 2.42 1.86-3.15| 1330  | 12.7 | <.0001 |
| 5. Diseases of the nervous system                   | 55   | 24.2 | 1.08 0.83-1.41| 70    | 6.5  | 1.61 1.27-2.05| 2345  | 22.3 | <.0001 |
| 6. Diseases of the eye and adnexa                   | 42   | 18.5 | 1.19 0.88-1.62| 34    | 6.3  | 1.04 0.74-1.46| 1739  | 16.6 | <.0001 |
| 7. Diseases of the ear and mastoid process          | 30   | 13.2 | 1.23 0.86-1.77| 30    | 6.3  | 1.40 0.97-2.01| 1149  | 10.9 | <.0001 |
| 8. Diseases of the circulatory system               | 67   | 29.5 | 1.23 0.97-1.57| 85    | 5.5  | 1.53 1.23-1.90| 2804  | 26.7 | <.0001 |
| 9. Diseases of the respiratory system               | 11   | 5.0  | 0.88-1.25   | 67    | 0.5  | 1.27 1.06-1.52| 5014  | 47.7 | <.0001 |
| 10. Diseases of the digestive system                | 14   | 6.3  | 0.96-1.34   | 7     | 0.8  | 1.31 1.10-1.55| 6233  | 59.4 | <.0001 |
| 11. Diseases of the skin and subcutaneous tissue    | 51   | 22.5 | 1.16 0.88-1.53| 65    | 7.0  | 1.72 1.34-2.09| 2014  | 19.2 | <.0001 |
| 12. Diseases of the musculoskeletal system and connective tissue | 85   | 37.4 | 0.68 0.54-0.84| 3     | 1.2  | 1.21 1.00-1.45| 5117  | 48.7 | <.0001 |
| 13. Diseases of the genitourinary system            | 74   | 32.6 | 0.90-1.43   | 35    | 4.1  | 1.59 1.29-1.96| 3193  | 30.4 | <.0001 |

AHR = adjusted hazard ratio, 95% CI = 95% confidence interval, BH p-value = Benjamini-Hochberg corrected p-value.
Table 3. Somatic comorbidity in men with schizophrenia, non-schizophrenic psychoses and non-psychotic controls.

| Somatic disease | Schizophrenia (n=131) | Non-schizophrenic psychoses (n=106) | Non-psychotic controls (n=5352) |
|-----------------|----------------------|------------------------------------|---------------------------------|
|                 | 95 % | BH p-value | 95 % | BH p-value | 95 % | BH p-value |
|                 | n   | AHR | CI    |        | n   | AHR | CI    |        | n   | AHR | CI    |
| 1. Certain infectious and parasitic diseases |     |     |       |        |     |     |       |        |     |     |       |       |
| 15.3 | 29 | 0.98 | 1.35 | 0.14 | 31 | 2 | 1.38 | 1.97 | .13 | 1179 | 22.0 |
| 15.3 | 1.35 | 0.86 | 1.87 | .07 | 31 | 2 | 1.38 | 1.97 | .13 | 1179 | 22.0 |
| 2. Neoplasms |     |     |       |        |     |     |       |        |     |     |       |       |
| 1.3 | 20 | 0.15 | 1.34 | 0.32 | 11 | 4 | 0.90 | 1.64 | .74 | 658 | 12.3 |
| 1.3 | 1.34 | 0.86 | 0.92 | .02 | 11 | 4 | 0.90 | 1.64 | .74 | 658 | 12.3 |
| 3. Diseases of the blood and blood forming organs and certain disorders involving the immune mechanism |     |     |       |        |     |     |       |        |     |     |       |       |
| 1.5 | 10 | 0.76 | 2.88 | 5.48 | .01 | 8 | 7.5 | 2.89 | 5.90 | .01 | 145 | 2.7 |
| 1.5 | 2.88 | 0.52 | 5.48 | 0.01 | 8 | 7.5 | 2.89 | 5.90 | .01 | 145 | 2.7 |
| 4. Endocrine, nutritional and metabolic diseases |     |     |       |        |     |     |       |        |     |     |       |       |
| 1.2 | 21 | 0.87 | 1.35 | 0.32 | 21 | 8 | 1.88 | 2.91 | .01 | 604 | 11.3 |
| 1.2 | 1.35 | 0.46 | 1.35 | 0.32 | 21 | 8 | 1.88 | 2.91 | .01 | 604 | 11.3 |
| 5. Diseases of the nervous system |     |     |       |        |     |     |       |        |     |     |       |       |
| 1.2 | 28 | 0.69 | 1.97 | 2.89 | .01 | 21 | 8 | 1.88 | 2.91 | .01 | 604 | 11.3 |
| 1.2 | 1.97 | 0.32 | 2.89 | 0.01 | 21 | 8 | 1.88 | 2.91 | .01 | 604 | 11.3 |
| 6. Diseases of the eye and adnexa |     |     |       |        |     |     |       |        |     |     |       |       |
| 1.2 | 30 | 0.80 | 1.19 | 1.71 | .45 | 32 | 2 | 1.64 | 2.33 | .01 | 1054 | 19.7 |
| 1.2 | 1.19 | 0.34 | 1.71 | 0.45 | 32 | 2 | 1.64 | 2.33 | .01 | 1054 | 19.7 |
| 7. Diseases of the ear and mastoid process |     |     |       |        |     |     |       |        |     |     |       |       |
| 1.0 | 19 | 0.66 | 1.10 | 1.85 | .77 | 13 | 3 | 1.22 | 2.12 | .62 | 572 | 10.7 |
| 1.0 | 1.10 | 0.32 | 1.85 | 0.77 | 13 | 3 | 1.22 | 2.12 | .62 | 572 | 10.7 |
| 8. Diseases of the circulatory system |     |     |       |        |     |     |       |        |     |     |       |       |
| 1.4 | 25 | 0.99 | 1.28 | 1.92 | .14 | 44 | 5 | 1.89 | 2.56 | .0004 | 1352 | 25.3 |
| 1.4 | 1.28 | 0.39 | 1.92 | 0.14 | 44 | 5 | 1.89 | 2.56 | .0004 | 1352 | 25.3 |
| 9. Diseases of the respiratory system |     |     |       |        |     |     |       |        |     |     |       |       |
| 1.2 | 60 | 0.80 | 1.41 | 1.92 | .54 | 44 | 5 | 1.89 | 2.56 | .0004 | 1352 | 25.3 |
| 1.2 | 1.41 | 0.32 | 1.92 | 0.54 | 44 | 5 | 1.89 | 2.56 | .0004 | 1352 | 25.3 |
| 10. Diseases of the digestive system |     |     |       |        |     |     |       |        |     |     |       |       |
| 1.0 | 51 | 0.94 | 1.01 | 1.28 | .94 | 63 | 4 | 1.05 | 1.35 | .74 | 2938 | 54.9 |
| 1.0 | 1.01 | 0.32 | 1.28 | 0.94 | 63 | 4 | 1.05 | 1.35 | .74 | 2938 | 54.9 |
| 11. Diseases of the skin and subcutaneous tissue |     |     |       |        |     |     |       |        |     |     |       |       |
| 1.3 | 64 | 0.76 | 1.17 | 1.47 | .29 | 67 | 3 | 1.37 | 1.75 | .02 | 3141 | 58.7 |
| 1.3 | 1.17 | 0.32 | 1.47 | 0.29 | 67 | 3 | 1.37 | 1.75 | .02 | 3141 | 58.7 |
| 12. Diseases of the musculoskeletal system and connective tissue |     |     |       |        |     |     |       |        |     |     |       |       |
| 0.9 | 36 | 0.52 | 0.69 | 0.92 | .04 | 56 | 8 | 1.23 | 1.60 | .18 | 2520 | 47.1 |
| 0.9 | 0.69 | 0.32 | 0.92 | 0.04 | 56 | 8 | 1.23 | 1.60 | .18 | 2520 | 47.1 |
| 13. Diseases of the genitourinary system |     |     |       |        |     |     |       |        |     |     |       |       |
| 1.2 | 25 | 0.52 | 1.28 | 1.87 | 2.73 | .01 | 23 | 7 | 1.90 | 2.88 | .01 | 669 | 12.5 |
| 1.2 | 1.28 | 0.32 | 1.87 | 0.27 | 23 | 7 | 1.90 | 2.88 | .01 | 669 | 12.5 |

AHR = adjusted hazard ratio, 95 % CI = 95 % confidence interval, BH p-value = Benjamini-Hochberg corrected p-value.
Table 4. Somatic comorbidity in women with schizophrenia, non-schizophrenic psychoses and non-psychotic controls.

| Somatic disease | Schizophrenia (n=96) | Non-schizophrenic psychoses (n=99) | Non-psychotic controls (n=5149) |
|----------------|----------------------|------------------------------------|--------------------------------|
|                | n % AH 95 % CI BH p-value | n % AH 95 % CI BH p-value | n % AH 95 % CI BH p-value |
| 1. Certain infectious and parasitic diseases | 22 22 1.3 0.88- .58 | 3 3 2 1.49- .0002 | 834 16.2 |
| 2. Neoplasms | 34 35 1.3 0.94- .49 | 2 29 1.0 0.73- .77 | 146 28.4 |
| 3. Diseases of the blood and blood forming organs and certain disorders involving the immune mechanism | 8 8 1.4 0.71- .66 | 1 11 1.9 1.09- .05 | 280 5.4 |
| 4. Endocrine, nutritional and metabolic diseases | 23 24 1.6 1.08- .13 | 3 37 2.8 2.07- <.0001 | 726 14.1 |
| 5. Diseases of the nervous system | 25 26 0.9 0.65- .88 | 3 38 1.5 1.15- .01 | 129 25.1 |
| 6. Diseases of the eye and adnexa | 20 20 1.1 0.73- .68 | 2 21 1.1 0.74- .62 | 949 18.4 |
| 7. Diseases of the ear and mastoid process | 15 15 1.3 0.82- .58 | 1 17 1.5 0.96- .11 | 577 11.2 |
| 8. Diseases of the circulatory system | 29 30 1.0 0.74- .75 | 4 41 1.2 0.93- .17 | 145 28.2 |
| 9. Diseases of the respiratory system | 44 45 1.1 0.82- .68 | 5 57 1.6 1.29- .0005 | 207 40.3 |
| 10. Diseases of the digestive system | 63 65 1.0 0.85- .68 | 7 70 1.2 0.98- .11 | 309 60.1 |
| 11. Diseases of the skin and subcutaneous tissue | 24 25 1.2 0.81- .66 | 3 31 1.5 1.08- .04 | 103 20.1 |
| 12. Diseases of the musculoskeletal system and connective tissue | 38 39 0.6 0.47- .11 | 5 57 1.1 0.91- .26 | 259 50.4 |
| 13. Diseases of the genitourinary system | 46 47 0.9 0.69- .68 | 6 66 1.5 1.18- .004 | 252 49.0 |

AHR = adjusted hazard ratio, 95 % CI = 95 % confidence interval, BH p-value = Benjamini-Hochberg corrected p-value.
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