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# Association of the polygenic risk score for schizophrenia with mortality and suicidal behavior - A Danish population-based study

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ABSTRACT

*Background:* It is unknown whether an increased genetic liability to schizophrenia influences the risk of dying early. The aim of the study was to determine whether the genetic predisposition to schizophrenia is associated with the risk of dying early and experience a suicide attempt.
*Method:* Case control study, Denmark. The main measure was the mortality rate ratios (MRR) for deaths and odds ratios (OR) for multiple suicide attempts, associated with one standard deviations increase of the polygenic risk-score for schizophrenia (PRS).
*Results:* We replicated the high mortality MRR = 9.01 (95% CI: 3.56–22.80), and high risk of multiple suicide attempts OR = 33.16 (95% CI: 20.97–52.43) associated with schizophrenia compared to the general population. However, there was no effect of the PRS on mortality MRR = 1.00 (95% CI 0.71–1.40) in the case-control setup or in cases only, MRR = 1.05 (95% CI 0.73–1.51). Similar, no association between the PRS and multiple suicide attempts was found in the adjusted models, but in contrast, family history of mental disorders was associated with both outcomes.
*Conclusions:* A genetic predisposition for schizophrenia, measured by PRS, has little influence on the excess mortality or the risk of suicide attempts. In contrast there is a strong significant effect of family history of mental disorders. Our findings could reflect that the common variants detected by recent PRS only explain a small proportion of risk of schizophrenia, and that future, more powerful PRS instruments may be able to predict excess mortality within this disorder.



## 1. Background

Studies have shown that persons with schizophrenia have 2 to 3 fold higher mortality rates compared to the general population (Harris and Barraclough, 1998; Osby et al., 2000; Laursen et al., 2007; Saha et al., 2007), resulting in 15–20 years shorter life expectancy (Laursen, 2011). The excess mortality stem from higher mortality rates from both natural and unnatural causes of death (Laursen et al., 2007). As early as the start of the 20th century, Odegard (1951) showed an excess mortality in patients with schizophrenia admitted to a Norwegian mental hospital in the period 1916–1941. Since then, different environmentally related explanations of this unacceptable high mortality have been suggested (Thornicroft, 2011; Laursen et al., 2012, 2014b). Firstly, persons with schizophrenia tend to have suboptimal health-related behavior including unhealthy diets, excessive smoking and alcohol use, as well as a sedentary lifestyle, which all are well-known risk factors for early mortality (Juel and Sørensen, 2006; Scheewe et al., 2012). Secondly, antipsychotic drugs may have adverse side effects, e.g. weight gain and serious medical illnesses such as diabetes and sudden cardiovascular death, which have negative effects on the life expectancy in this group of patients (Jerrell et al., 2010; Ribe et al., 2014). Thirdly, the

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risks of suicide and accidents among patients with schizophrenia are high (Nordentoft et al., 2011). Fourth and lastly, somatic and mental comorbidities, including psychoactive substance use disorders and alcohol use disorders, are common among schizophrenia patients, but diagnosed later and treated insufficiently compared to mentally healthy persons (Laursen and Nordentoft, 2011; Laursen et al., 2011, 2014a).

Genetic epidemiological studies of schizophrenia have for decades shown high heritability and family aggregation (McGue et al., 1983; Mortensen et al., 1999). Since 2009 evidence for specific genetic variants has been accumulating (Purcell et al., 2009), and a total of 108 schizophrenia-associated loci have very recently been identified by the Psychiatric Genomics Consortium, confirming that schizophrenia is a highly polygenic disorder. Despite the small effect size of each individual variant, together, the genome-wide-significant loci were estimated to explain 3.4% of the variance in liability, and the cumulative effect of common loci expressed as a polygenic risk score (PRS) was estimated to explain7% of the variance in liability (2014). Furthermore, it has previously been demonstrated that there is a dose-response relationship between the PRS and the risk of schizophrenia, showing that the higher PRS score the higher risk of schizophrenia (Agerbo et al., 2015).

Given the strong genetic influence on schizophrenia described above, it seems plausible that the well-described excess mortality in this patient group can also be in part attributed to a genetic vulnerability. We hypothesized that persons with schizophrenia not only have a genetic predisposition towards schizophrenia, but furthermore, that this genetic predisposition may also predict premature death, and thus explain a part of the excess mortality. Ideally, a test of single genes known to cause schizophrenia should be tested against early mortality or suicide attempts. However, as no single genes can accurately be used as biomarkers to diagnose or predict schizophrenia a more broad approach are necessary. We therefore aimed to study the impact of the genetic predisposition, measured by the PRS for schizophrenia for two different outcomes: mortality and suicide attempts. Firstly, our goal was to test to which extent we in our sample could replicate associations of schizophrenia on mortality rates and suicidal behavior. Secondly, we aimed to specifically measure the impact of PRS on the selected outcomes jointly in our cases and controls and separately. Finally, the results of the PRS analysis were compared to the effect of family history of severe mental disorders, which is an alternative and commonly used measure of genetic loading.

## 2. Method

### 2.1. Study population, cases and controls

We conducted a case control study. People with schizophrenia were defined among all singleton births in Denmark since 1981 with a DNA sample available from the Danish Neonatal Screening Bio-bank (Norgaard-Pedersen and Hougaard, 2007) and an ICD-10 F20 code for schizophrenia between January 1, 1994, and December 31, 2008, $N = 1780$. We selected a control as a randomly selected person from the CPR register (Pedersen et al., 2006), born in Denmark, with the same gender and the same birthday, not previously having a contact to a psychiatric hospital with a F20 schizophrenia diagnosis (Mors et al., 2011), $N = 1768$.

### 2.2. Approval

The study did not require informed consent from participants according to Danish legislation (Act of Processing Personal Data), and the study did not involve any contact with study participants. The study was approved by the Danish Data Protection Agency, the Danish Research Ethics Committee, and the Steering Committee for the Danish Neonatal Screening Biobank.

### 2.3. Calculation of the PRS for schizophrenia

DNA was extracted from the dried blood samples stored in the Danish neonatal bio-bank (Norgaard-Pedersen and Hougaard, 2007), whole-genome amplified (in triplicate using the Qiagen REPLI-g mini kit and the 3 separate reactions were pooled), and genotyped with Illumina Human 610-Quad BeadChip array (Borglum et al., 2014) and Illumina's HumanCoreExome beadchip (Illumina, San Diego, CA, USA) (Meier et al., 2015). The PRS for schizophrenia with $p$-value threshold 0.05 and normalized to the sample was calculated using the SNP information from the Psychiatric Genomics Consortium, (discovery sample of 34,600 cases and 45,968 control individuals, excluding the Danish data). We also calculated the PRS using threshold 1.00. More detailed description of the cases has been published previously (Nature, 2014; Agerbo et al., 2015; Borglum et al., 2014). We used the score as a continuous variable in the analysis, but we also tabulated the 10% percentiles in the first descriptive table.

### 2.4. Definition of outcome variables: mortality and suicide attempts

The outcome measures, suicide attempts and mortality, were defined from the Danish National Registers. The suicide attempts measure was constructed from the National patients register (Lynge et al., 2011) and the Psychiatric Central Register (Mors et al., 2011): We chose all contacts, where the reason for the contact was suicide attempts. Furthermore, all ICD10 F diagnosis with comorbid diagnosis code T36-T50, T52-T60, S51, S55, S59, S61, S65, S69 or any hospital contact with diagnosis code T39, T42, T43, T58, X60-X84. For further description of the definition of suicide attempts, see Christiansen (Christiansen et al., 2015). We have truncated the number of suicide attempts to 0, 1 or 2+ attempts. Mortality was defined as the date of death stated in the death certificates in the Cause of Death Register (Helweg-Larsen, 2011).

### 2.5. Definition of covariates

All analysis had a basic adjustment for age, gender and calendar year. Analyses including the PRS were also adjusted for ancestry using the first 10 principal components estimated from genome-wide SNP genotypes (Price et al., 2006). Furthermore, we examined the impact of any mental disorders in the family. We used an overall yes/no contact (in or out patient) to a psychiatric hospital for any mental disorder in the mother or the father of the proband. Somatic comorbidity was defined using the Charlson Comorbidity Index (Charlson et al., 1987). The Index includes 19 chronic diseases to which a weight from one to six to each disorder is assigned according to the severity of the disease. The score of the Index is the sum of all weights. In the present study we have truncated the index to include the scores 0, 1, 2+.

### 2.6. Statistical analysis

Mortality rates were analyzed in a Cox regression model with time since first schizophrenia diagnosis in cases and time since matching in controls as the underlying time scale. Number of suicide attempts was analyzed in a multinomial logistic regression model with outcome consisting of 0, 1, or 2+ suicide attempts. The polygenic score was analyzed as a continuous variable with one standard deviation increase as the measurement unit. In Table 1 the score is also shown in deciles with the lowest decile as the reference.

For each outcome the effect of polygenic score risk was evaluated in the case-control setting and in cases and controls only. Because of limited power due to the fact that only 5 controls died during follow-up, the association between the polygenic score and mortality was not evaluated in controls.

The two outcomes, mortality and suicide attempts, were analyzed in two models:

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