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# Do adverse perinatal events predict mortality in schizophrenia during midlife?

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ABSTRACT

*Background:* We examined mortality in schizophrenia spectrum disorder (SSD) and non-schizophrenic psychosis (NSSD) compared to individuals without psychosis, and whether perinatal factors predict mortality.
*Methods:* Within Northern Finland Birth Cohort 1966 (n = 10 933; 203 with SSD, 178 with NSSD), mortality was followed until end of 2011 by national register. Wantedness of pregnancy, mother's antenatal depression, smoking and age, parity, paternal socio-economic status (SES) and family type at birth were examined as predictors of mortality.
*Results:* Mortality was higher in SSD (hazard ratio (HR) 3.60; 95% confidence interval (CI) 2.38–5.45) and NSSD (4.05; 2.65–6.17) compared to persons without psychoses after adjustment for gender. HR for natural death was 2.01 (0.82–4.91) in SSD and 4.63 (2.43–8.80) in NSSD after adjustment for gender. Corresponding figures for unnatural deaths were 4.71 (2.94–7.54) and 2.94 (1.56–5.55), respectively. Among non-psychotic persons, mother's depression, smoking and low SES predicted mortality after adjustment for gender and parental psychoses (and SES), whereas among psychosis those whose father was a farmer had lower risk of mortality compared to those with high SES.
*Conclusions:* Individuals with SSD had a higher risk of unnatural death and individuals with NSSD of natural and unnatural deaths. Perinatal factors seem to be more important predictors of mortality in individuals without psychoses than with psychoses. According to population-based long follow-up data, it is important to pay attention to somatic morbidity behind natural causes of death in psychoses and to prevent suicides in order to prevent excess mortality.



## 1. Introduction

Excess mortality in psychotic disorders is a major public health concern and therapeutic challenge (Crump et al., 2013b; Saha et al., 2007; Termorshuizen et al., 2013; Walker et al., 2015; Ösby et al., 2000). Individuals with psychotic disorders have over a 2- to 4-fold higher all-cause mortality risk than the general population (Crump et al., 2013b; Høye et al., 2011; Kiviniemi et al., 2010; Lumme et al., 2016; Olfson et al., 2015; Saha et al., 2007; Termorshuizen et al., 2013) and their life expectancy is 10–25 years lower (Crump et al., 2013b; Tiihonen et al., 2009). Furthermore, those differences are continuing into old age (Talaslahti et al., 2015).

The mortality rate is higher for natural and unnatural causes (Crump et al., 2013b; Kiviniemi et al., 2010; Reininghaus et al., 2015; Ösby et al., 2000). Common natural causes of death in schizophrenia are diseases of the circulatory system (Brown et al., 2000; Bushe et al., 2010; Crump et al., 2013b; Kiviniemi et al., 2010; Ösby et al., 2000), neoplasms (Brown et al., 2000; Bushe et al., 2010; Crump et al., 2013b; Ösby et al., 2000), diabetes (Crump et al., 2013b; Schoepf et al., 2014) and respiratory illnesses (Crump et al., 2013b; Kredentser et al., 2014; Termorshuizen et al., 2013; Ösby et al., 2000). About 2-fold ischemic heart disease and 1.5-fold cancer mortality risks have been shown in schizophrenia

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compared to the rest of the population (Crump et al., 2013b). Diseases of the digestive system, especially alcohol-related ones are also common causes of death (Reininghaus et al., 2015). From the unnatural causes of death, the leading cause is suicide (Brown et al., 2000; Reininghaus et al., 2015) with the risk being 12- to 20-fold compared to the general population (Reininghaus et al., 2015; Saha et al., 2007; Ösby et al., 2000). Most of the suicides are committed during the first years after the onset of psychoses (Alaräisänen et al., 2009; Ösby et al., 2000). The risk for accidental/injury deaths is also higher for schizophrenia sufferers than the general population (Crump et al., 2013a; Crump et al., 2013b; Kredentser et al., 2014).

Few studies have examined differences in mortality in schizophrenia and non-schizophrenic psychoses (Castagnini et al., 2013; Healy et al., 2012). Individuals with schizophrenia may die younger than those with other psychotic disorders (Healy et al., 2012), but natural-cause mortality did not differ between schizophrenia and acute and transient psychotic disorders (ATPD) (Castagnini et al., 2013). However, individuals with ATPD were more likely to commit suicide during the first year following the initial episode than individuals with schizophrenia (Castagnini et al., 2013).

Suggested reasons for excess mortality are unhealthy lifestyle (Connolly and Kelly, 2005; Laursen et al., 2012; Ringen et al., 2014; Suvisaari et al., 2013) and use (Joukamaa et al., 2006) or non-use of antipsychotics (Tiihonen et al., 2016; Torniainen et al., 2015). Studies have mainly focused on predictors of mortality prevalent in the later stages of life (Fazel et al., 2014; Joukamaa et al., 2006; Suvisaari et al., 2013; Tiihonen et al., 2016) reporting that self-harm, alcohol/drug use disorders (Fazel et al., 2014), older age at onset of schizophrenia, long duration of illness and inability to work are predictors of mortality (Ran et al., 2007). More information also from earlier stages of life is needed. As far as we know, paternal older age in women (Miller et al., 2010) and lower maternal education have predicted mortality in psychoses (Dickerson et al., 2016). Furthermore, birth complications in men have predicted mortality in psychoses (Fazel et al., 2014). Because deviances in environment in early life are risk factors for schizophrenia (Laurens et al., 2015; Matheson et al., 2011), it is important to study whether they also predict prognosis of psychoses.

The aim of this study was to examine mortality and causes of death in schizophrenia spectrum disorder (SSD) and non-schizophrenic psychoses (NSSD) compared to individuals without psychosis and whether perinatal circumstances predict mortality in all psychoses. We hypothesized that unwanted pregnancy, mother's antenatal depression and smoking, mother's young or old age, low or high parity, low paternal socio-economic status (SES) and single-parent family at birth would increase the risk of mortality.

## 2. Methods

This study is based on the Northern Finland Birth Cohort 1966 (NFBC1966) concerning 12,058 live-born children in 1966 in the provinces of Oulu and Lapland (Rantakallio, 1969). Individuals, who were alive and living in Finland at the age of 16 years (n = 11,017) were included in this study. Overall, 84 of them denied use of their data, thus leading to the sample of 10,933 individuals. Study design was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District, and Ministry of Social and Health Affairs gave permission to gather the data.

### 2.1. Psychoses

Psychoses are based on the registers of Statistics Finland (Care Register for Health Care (CRHC), formerly the Finnish Hospital Discharge Register, followed until the end of 2011, the Register of Specialty Outpatient Health Care from 1998 until 2011 and Primary Care Outpatient Register from 2011) and Register of the Finnish Centre for Pensions (FCP) until 2011 and the Registers of the Social Insurance Institution (reimbursed medicine until 2005, pension until 2000 and sick days until the end of 1999).

Individuals were classified as having SSD (ICD-8 (1968–1986): 295, ICD-9 (1987–1995): 295, 2954, 2957, 297 and ICD-10 (1996–2013): F20, F22, F25), other NSSD (psychotic bipolar disorder (ICD-8: 2961–2969, ICD-9: 2962E, 2963E, 2964E, 2967, ICD-10: F30.2, F31.2, F31.5)) psychotic depression (ICD-8: 2960, 2980, ICD-9: 2961E, ICD-10: F32.3, F33.3) brief/reactive psychosis (ICD-8: 2981–2983, 2988, 2989, ICD-9: 2988, ICD-10: F23) and other psychosis (ICD-8: 299, ICD-9: 2989, ICD-10: F28, F29)) and without psychosis. Overall, 203 individuals had SSD (narrow ICD-8 & 9: 2950–2953, 2955, 2956, 2958, 2959, 295, ICD-10: F20 n = 149, spectrum ICD-8 & 9: 2954, 2957, 297, ICD-10: F22, F24, F25 n = 54) and 178 NSSD (psychotic bipolar disease n = 22, psychotic depression n = 62, brief or reactive psychosis n = 29 and undefined other psychosis n = 65). For further analyses, SSD and NSSD were combined as having psychosis.

### 2.2. Causes of mortality

Information on time and causes of death until 31st December 2011 were obtained from the Cause of Death Register from the Statistics Finland. The register contains data from death certificates (Lahti and Penttilä, 2001). Causes of death were classified according to ICD-8, 9 or 10, depending on the time of the death (Table 2). From the external causes of morbidity and mortality, suicide or intentional self-harm was classified in its own class. Classes from infections to congenital malformations, deformations and chromosomal abnormalities were classified as natural and classes concerning external causes of morbidity/mortality and suicide to unnatural causes of death (Table 2). Classes concerning symptoms, signs and abnormal clinical findings and no basic statistical cause of death were defined as unknown causes of death.

### 2.3. Predictors of mortality

We selected as predictors of mortality the same variables from perinatal circumstances, which have been studied earlier as predictors of suicides in the NFBC1966 (Alaräisänen et al., 2012). Data on perinatal circumstances were gathered by interviews conducted by nurses with the help of questionnaires during mothers' visits to antenatal clinics at gestation weeks of 24–28 and from the Population Register Centre (PRC).

*Wantedness of pregnancy* was asked with the question, whether mothers had wanted the pregnancy, would have preferred it later or had not wanted. Responses were dichotomized to wanted/mistimed or unwanted (Myhrman et al., 1996).

*Mother's antenatal depressed mood* was asked with the question, whether they felt that their mood was normal, depressed or very depressed during pregnancy. Responses were classified to normal and depressed (Alaräisänen et al., 2012).

*Mother's smoking during pregnancy* was classified as no, if she did not smoke or had stopped before the pregnancy and yes, if she had smoked at least one cigarette daily (Mäki et al., 2010).

*Mother's age at birth* was received from the PRC and was classified as under 20 years, 20–35 years and over 35 years (Keskinen et al., 2013).

*Parity at birth* was classified as 1, 2–5 and over 5 (Alaräisänen et al., 2012).

*Family type at birth* was based on the marital status of the mother during pregnancy (married, divorced, widowed and never married) and was classified as two-parent families (full) or single-parent families (Alaräisänen et al., 2012).

*SES at birth* was based on the father's occupation and were classified as high (classes I and II), low (classes III and IV) and farmers (class V) (Alaräisänen et al., 2012).

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