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ORIGINAL ARTICLE

Type 1 diabetes mellitus and the risk for schizophrenia or schizoaffective disorder: a Swedish nationwide register-based cohort study

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Abstract

OBJECTIVES: Type 1 diabetes mellitus (T1DM), resulting from an immune-associated destruction of insulin-secreting pancreatic β-cells, has been reported in a few earlier studies to be inversely associated with schizophrenia, but not with schizophrenia-like psychoses. The aim of this study was to verify this finding by carrying out a Swedish register study.

METHODS: Data from the Total Population- and Medical Birth-Registers were used to create a cohort of all individuals born in Sweden 1987–2004. The cohort individuals were linked with the Inpatient- and Outpatient-Registers and followed from birth to 2017 to identify onset of T1DM, schizophrenia and schizoaffective disorder. Cox proportional hazard regression models were used to assess the association between T1DM and risk of developing schizophrenia or schizoaffective disorder during a follow-up from age 13.

RESULTS: The study population included 1 745 977 individuals and the length of follow-up was maximally 18.0 (median 9.7) years. During the follow-up, 1 280 individuals developed schizophrenia and 649 individuals schizoaffective disorder. The risk of developing schizophrenia was significantly lower among individuals with, than among individuals without, a diagnosis of T1DM, whereas the risk of developing schizoaffective disorder did not differ among individuals with or without a T1DM diagnosis [adjusted hazard ratio (95% confidence interval); schizophrenia: 0.29 (0.09–0.91), p=0.0338, schizoaffective disorder: 1.50 (0.71–3.16), p=0.2909].

CONCLUSIONS: This study, in line with previous studies, shows that a diagnosis of T1DM is associated with a decreased risk of schizophrenia. This finding of an inverse association between T1DM and schizophrenia may bring an interesting piece, related to autoimmunity, into the schizophrenia-aetiology puzzle.

INTRODUCTION

Schizophrenia is a chronic psychotic disorder that affects approximately 0.5% of the population worldwide (Freedman, 2003; McGrath *et al.* 2008), and whose aetiology still, in the main, is unknown. Nevertheless, the literature provides strong evidence for a role of genetic factors in its aetiology (Giegling *et al.* 2017; Li *et al.* 2017; Pardiňas *et al.* 2018; Ptacek *et al.* 2011; Ripke *et al.* 2014). There are also indications that schizophrenia is a systemic disorder and not only a brain disease (Flyckt, 2001; Kirkpatrick *et al.* 2014; Moises *et al.* 2002).

Somatic comorbidity in schizophrenia is rather common, and prevalences of several somatic diseases, abnormalities and syndromes, such as a larger range of autoimmune diseases, cardiovascular disease, HIV infection and hepatitis, inguinal hernia, metabolic syndrome, neurologic abnormalities, neuromuscular dysfunction and the velocardiofacial syndrome, are higher in schizophrenia patients than in the general population (Benros *et al.* 2011; Chen *et al.* 2012; Karayiorgou *et al.* 1995; Leucht *et al.* 2007; Melkersson & Wernroth, 2017; Meltzer, 1976; Nasrallah, 2005; Saari *et al.* 2005). In contrast, some other somatic diseases, such as cancer and the autoimmune disease rheumatoid arthritis, occur less frequently in patients with schizophrenia (Chen *et al.* 2012; Eaton *et al.* 1992; Leucht *et al.* 2007; Melkersson, 2009; Pilkington, 1956; Sellgren *et al.* 2014).

Concerning comorbidity of diabetes mellitus (DM) and schizophrenia, there are many studies published reporting that type 2 diabetes mellitus (T2DM), which is characterized by relative insulin deficiency caused by pancreatic β-cell dysfunction and insulin resistance in target organs (Chatterjee *et al.* 2017), occurs more commonly in schizophrenia patients than in the general population (Mukherjee *et al.* 1996; Stubbs *et al.* 2015; Vancampfort *et al.* 2016). This is thought to result from the schizophrenia illness itself, lifestyle factors such as excessive cigarette smoking, unhealthy diet and physical inactivity, and the antipsychotic treatment (Brown *et al.* 1999; Greenhalgh *et al.* 2017; Hirsch *et al.* 2017; Melkersson & Dahl, 2004; Melkersson *et al.* 2004; Perry *et al.* 2016; Ryan *et al.* 2003; Spelman *et al.* 2007). In contrast, type 1 diabetes mellitus (T1DM), which results from an immune-associated destruction of insulin-secreting pancreatic β-cells (Atkinson *et al.* 2014), seems to be negatively associated with schizophrenia, though not with schizophrenia-like psychoses (Benros *et al.* 2011, 2014a, 2014b; Eaton *et al.* 2006, 2010; Finney, 1989; Juvonen *et al.* 2007; Mortensen & Eaton, 2008).

In Sweden, we have population- and health-registers with satisfactory validity of diagnoses and high technical quality (Dalman *et al.* 2002; Kristjansson *et al.* 1987), which are well suited for epidemiological studies. A recently published review of the last 30 years of Swedish register studies regarding causes for schizophrenia also shows that these registers have added considerably to our understanding of several risk factors for schizophrenia (Harper *et al.* 2015). Since only two studies and one preliminary report on the comorbidity of T1DM and schizophrenia hitherto have been published (Eaton *et al.* 2006; Finney, 1989; Juvonen *et al.* 2007), more studies are needed to verify the previous finding of an inverse association between these two disorders. Therefore, we carried out a Swedish population-based register study to assess the association between T1DM and schizophrenia or its related schizoaffective disorder.

Tab. 1. Classification codes used for each diagnosis in the study

Diagnosis	ICD-7 codes[a] in 1958-1968	ICD-8 codes[a] in 1969-1986	ICD-9 codes[a] in 1987-1996	ICD-10 codes[a] in 1997-2017
Schizophrenia	years 1958-1963: 300.0-300.5, 300.7 years 1964-1968: 300.99	295.00-295.30, 295.60, 295.99	295A-295D, 295G, 295W, 295X	F20.0-F20.3, F20.5, F20.6, F20.9
Schizoaffective disorder	years 1958-1963: 300.6 years 1964-1968: not specified, included in 300.99	295.70	295H	F25.0-F25.2, F25.8, F25.9
Diabetes mellitus; type 1	years 1958-1963: 260 years 1964-1968: 260.09, 260.20, 260.21, 260.29, 260.30, 260.40, 260.49, 260.99	250.00-250.09	250A-250H, 250X	E10
Diabetes mellitus; type 2				E11
Diabetes mellitus; other types, including unspecified type				E12-E14

[a] According to The International Classification of Diseases (ICD) 7th, 8th, 9th and 10th revisions (http://www.socialstyrelsen.se)

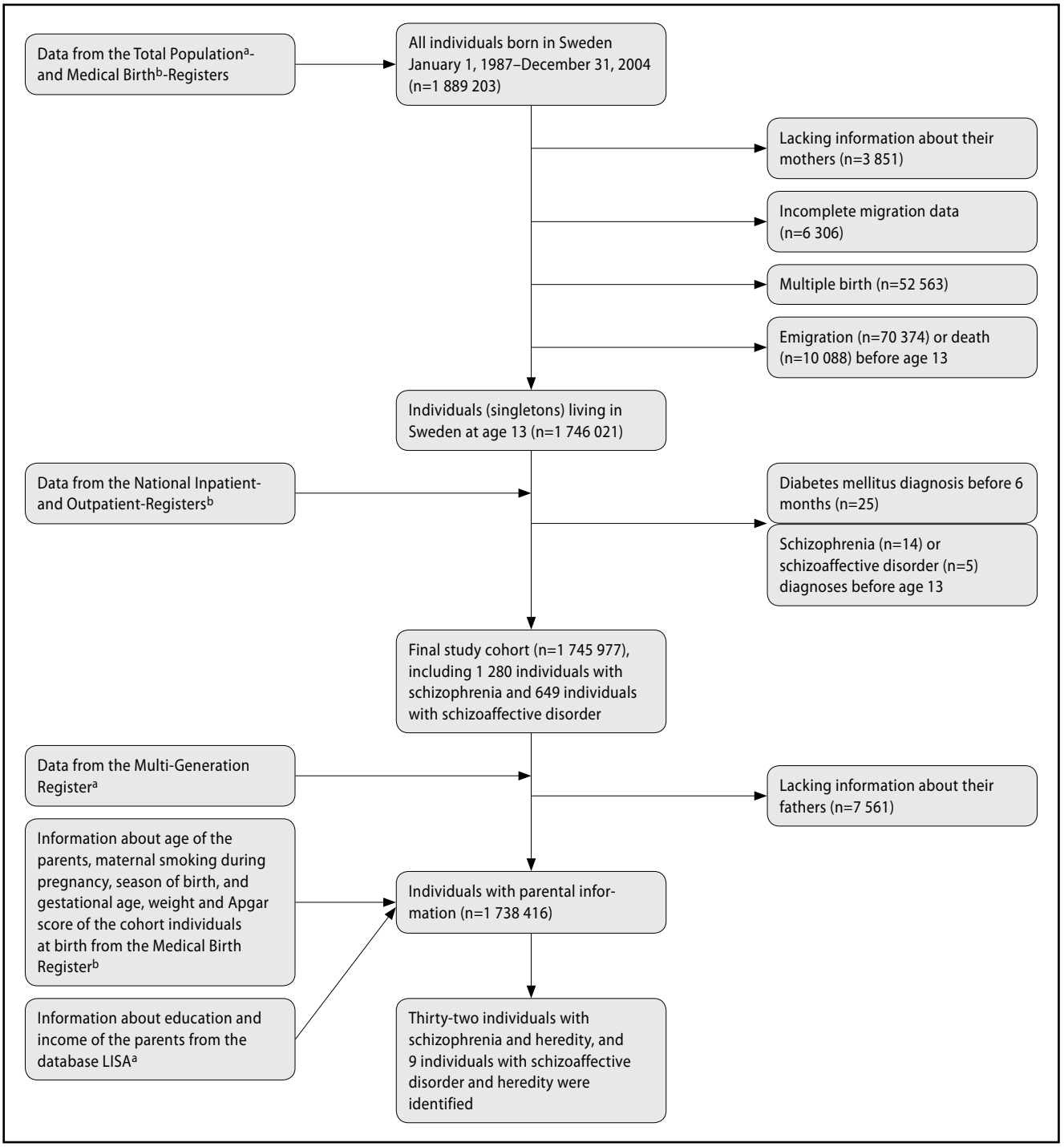

Fig. 1. Flow diagram of the study population. [a]Held by Statistics Sweden; [b]Held by the National Board of Health and Welfare in Sweden.

MATERIAL & METHODS

The study was approved by the Regional Ethical Review Board, Stockholm, Sweden. A flow diagram of the study population is shown in Figure 1. Data from the Total Population- and Medical Birth-Registers were used to create a cohort of all individuals born in Sweden from January 1, 1987 to December 31, 2004 (n=1 889 203). Individuals who were lacking information about their mothers (n=3 851), had incomplete migration data (n=6 306), were part of multiple births (n=52 563), or had emigrated (n=70 374) or died (n=10 088) before 13 years of age were excluded. The final study cohort consisted of total 1 745 977 individuals living in Sweden at age 13 (Figure 1).

The individuals of the study cohort were linked with the National Inpatient- and Outpatient-Registers and followed to identify onset of T1DM, schizophrenia and schizoaffective disorder from birth until death, emigration or December 31, 2017, whichever came

Tab. 2. Characteristics of the study population

Characteristic	Outcome: SCH		Outcome: SA	
	No T1DM before end of follow-up	T1DM before end of follow-up	No T1DM before end of follow-up	T1DM before end of follow-up
All (n)	1 730 620	15 357	1 730 617	15 360
Sex[a]				
men	888 478 (51.3)	8 520 (55.5)	888 474 (51.3)	8 524 (55.5)
women	842 142 (48.7)	6 837 (44.5)	842 143 (48.7)	6 836 (44.5)
Highest level of education achieved by either parent[a]				
> 9 years	1 602 985 (92.7)	14 455 (94.1)	1 602 984 (92.7)	14 456 (94.1)
9 years	99 087 (5.7)	771 (5.0)	99 085 (5.7)	773 (5.0)
< 9 years	15 782 (0.9)	82 (0.5)	15 782 (0.9)	82 (0.5)
missing	12 766 (0.7)	49 (0.3)	12 766 (0.7)	49 (0.3)
Household income categorized into fifths at time of birth of the cohort individual[a]				
1 (lowest)	333 853 (19.3)	2 757 (18.0)	333 852 (19.3)	2 758 (18.0)
2	350 513 (20.3)	3 247 (21.1)	350 512 (20.3)	3 248 (21.1)
3	351 229 (20.3)	3 255 (21.2)	351 229 (20.3)	3 255 (21.2)
4	350 524 (20.3)	3 161 (20.6)	350 523 (20.3)	3 162 (20.6)
5 (highest)	339 399 (19.6)	2 922 (19.0)	339 399 (19.6)	2 922 (19.0)
missing	5 102 (0.3)	15 (0.1)	5 102 (0.3)	15 (0.1)
Parent born outside Sweden[a]				
father	217 205 (12.6)	1 104 (7.2)	217 204 (12.6)	1 105 (7.2)
mother	200 756 (11.6)	950 (6.2)	200 755 (11.6)	951 (6.2)
missing	7 658 (0.4)	40 (0.3)	7 658 (0.4)	40 (0.3)
Mother living with the father at time of birth of the cohort individual[a]				
yes	1 509 195 (87.2)	13 511 (88.0)	1 509 193 (87.2)	13 513 (88.0)
no	82 996 (4.8)	644 (4.2)	82 995 (4.8)	645 (4.2)
missing	138 429 (8.0)	1 202 (7.8)	138 429 (8.0)	1 202 (7.8)
Mother's age at time of birth of the cohort individual (year)[b]	29.3 (5.1)	29.4 (5.0)	29.3 (5.1)	29.4 (5.0)
Father's age at time of birth of the cohort individual (year)[b]	32.2 (6.1)	32.1 (6.0)	32.2 (6.1)	32.1 (6.0)
missing[a]	7 522 (0.4)	39 (0.3)	7 522 (0.4)	39 (0.3)
Smoking during early pregnancy[a]				
non-smoker	1 311 153 (75.8)	11 998 (78.1)	1 311 153 (75.8)	11 998 (78.1)
1 - 9 cigarettes/ day	189 542 (11.0)	1 504 (9.8)	189 542 (11.0)	1 504 (9.8)
> 9 cigarettes/ day	105 653 (6.1)	831 (5.4)	105 651 (6.1)	833 (5.4)
missing	124 272 (7.2)	1 024 (6.7)	124 271 (7.2)	1 025 (6.7)
Season of birth[a]				
Spring	477 487 (27.6)	4 300 (28.0)	477 486 (27.6)	4 301 (28.0)
Summer	448 859 (25.9)	3 946 (25.7)	448 857 (25.9)	3 948 (25.7)
Autumn	396 476 (22.9)	3 538 (23.0)	396 476 (22.9)	3 538 (23.0)
Winter	407 798 (23.6)	3 573 (23.3)	407 798 (23.6)	3 573 (23.3)
Gestational age[a]				
< 38 weeks	166 577 (9.6)	1 814 (11.8)	166 575 (9.6)	1 816 (11.8)
38 - 40 weeks	1 104 626 (63.8)	9 836 (64.0)	1 104 625 (63.8)	9 837 (64.0)
> 40 weeks	430 396 (24.9)	3 446 (22.4)	430 396 (24.9)	3 446 (22.4)
missing	29 021 (1.7)	261 (1.7)	29 021 (1.7)	261 (1.7)
Birth weight (g)[b]	3 552.7 (556.1)	3 571.5 (556.3)	3 552.7 (556.1)	3 571.2 (556.7)
< 3000 g[a]	222 947 (12.9)	1 934 (12.6)	222 944 (12.9)	1 937 (12.6)
3000 - 3999 g[a]	1 141 439 (66.0)	9 967 (64.9)	1 141 439 (66.0)	9 967 (64.9)
≥ 4000 g[a]	335 142 (19.4)	3 177 (20.7)	335 142 (19.4)	3 177 (20.7)
missing[a]	31 092 (1.8)	279 (1.8)	31 092 (1.8)	279 (1.8)
Birth weight in relation to gestational age[a]				
small for age	40 773 (2.4)	323 (2.1)	40 772 (2.4)	324 (2.1)
normal	1 595 846 (92.2)	14 062 (91.6)	1 595 844 (92.2)	14 064 (91.6)
large for age	60 789 (3.5)	676 (4.4)	60 789 (3.5)	676 (4.4)
missing	33 212 (1.9)	296 (1.9)	33 212 (1.9)	296 (1.9)
Apgar score at 1 min[a]				
0 - 6	70 934 (4.1)	670 (4.4)	70 934 (4.1)	670 (4.4)
7 - 10	1 620 451 (93.6)	14 323 (93.3)	1 620 448 (93.6)	14 326 (93.3)
missing	39 235 (2.3)	364 (2.4)	39 235 (2.3)	364 (2.4)

Abbreviations: g = gram, min = minute, SA = schizoaffective disorder, SCH = schizophrenia, T1DM = type 1 diabetes mellitus
[a] Data are given as number (%), [b]Data are given as mean (standard deviation)

Tab. 3. Incidence rates of schizophrenia or schizoaffective disorder associated with a diagnosis of type 1 diabetes mellitus before onset of respective psychotic disorder

Somatic disease	All			Men			Women		
	Cases (n)	FU time[a]	IR (95% CI)[b]	Cases (n)	FU time[a]	IR (95% CI)[b]	Cases (n)	FU time[a]	IR (95% CI)[b]
Schizophrenia									
Type 1 diabetes mellitus	3	1.21	2.48 (0.51-7.26)	3	0.66	4.53 (0.93-13.24)	0	0.55	0.00 (na-6.77)
No type 1 diabetes mellitus	1 277	161.85	7.89 (7.46-8.33)	875	83.17	10.52 (9.83-11.24)	402	78.68	5.11 (4.62-5.63)
Schizoaffective disorder									
Type 1 diabetes mellitus	7	1.21	5.80 (2.33-11.94)	4	0.66	6.04 (1.64-15.46)	3	0.55	5.51 (1.14-16.09)
No type 1 diabetes mellitus	642	161.88	3.97 (3.66-4.28)	294	83.20	3.53 (3.14-3.96)	348	78.69	4.42 (3.97-4.91)

Abbreviations: CI = confidence interval, FU = follow-up, IR = incidence rate, n = number, na = not applicable
[a] Expressed as 100 000 person-years at risk
[b] Number of new cases per 100 000 person-years at risk

first (Figure 1). The Inpatient Register covers satisfactorily the general and mental hospital care in Sweden since 1987, and the Outpatient Register the general and mental outpatient care in Sweden since 2001. All diagnoses in the registers are defined according to The International Classification of Diseases (ICD) (http://socialstyrelsen.se), and the classification codes used for each diagnosis in this study are shown in Table 1. Individuals were categorized from the date of their first contact to a hospital or polyclinic with such a diagnosis. In addition, heredity for T1DM, schizophrenia and schizoaffective disorder was established by linking data on the biological parents of the cohort individuals, derived from the Multi-Generation Register, with the Inpatient- and Outpatient-Registers (Figure 1). Moreover, information about age of the parents, maternal smoking during pregnancy, season of birth, and gestational age, weight and Apgar score of the cohort individuals at birth was derived from the Medical Birth Register, while information about education and income of the parents was derived from the longitudinal integrated database for health insurance and labour market studies, called in Swedish LISA (Figure 1).

To assess the associations between T1DM as a time-updated exposure and risk of schizophrenia or schizoaffective disorder, we applied Cox proportional hazard (PH) models, using age as timescale. Follow-up started at age 13, and individuals with childhood-onset schizophrenia or schizoaffective disorder, defined as being diagnosed with schizophrenia or schizoaffective disorder before age 13 (Lachman, 2014), were excluded (n=19). Individuals were censored at emigration, death or end of follow-up (December 31, 2017). We used a robust sandwich covariance matrix estimate to account for the lack of independence of individuals within the same family. The assumption of PHs was visually checked by plotting the Schoenfeld residuals against rank time and fitting a smooth curve with 95% confidence bands. The residuals showed that the PH assumption was violated for sex. We therefore stratified by sex, after no more violations were observed. Further, the associations between T1DM as a time-updated exposure and risk of schizophrenia or schizoaffective disorder were visualized using Simon-Makuch plots (Simon & Makuch, 1984).

Potential confounders were selected for adjustment based on directed acyclic graphs (Greenland *et al.* 1999) taking into account prior knowledge regarding their effect on T1DM and schizophrenia or schizoaffective disorder (Bertelsen & Gottesman, 1995; Bingley *et al.* 2000; Craddock *et al.* 2005; Harper *et al.* 2015; Hidayat *et al.* 2019; Hultman *et al.* 1999; Häfner, 2003; Khashan *et al.* 2015; Malaspina *et al.* 2001; Marshall *et al.* 2004; Tuomilehto, 2013; Waernbaum *et al.* 2019; Zammit *et al.* 2009). Hence, we adjusted for sex, gestational age, birth weight in relation to gestational age, maternal smoking during pregnancy (only data from early pregnancy was available), paternal age, parity, heredity for T1DM, and heredity for schizophrenia or schizoaffective disorder. Furthermore, to adjust for unmeasured and measured environmental and genetic confounding factors shared by siblings, we estimated a stratified Cox PH model conditional on sibling cluster (D'Onofrio *et al.* 2013). Only clusters with at least one schizophrenia- or schizoaffective disorder-event individual and at least one event-free individual at the age of event in the schizophrenia or schizoaffective disorder individual, contribute to the estimations in the sibling analyses; informative sample size is thus reported for sibling analyses. Finally, we also conducted subgroup analyses by heredity for schizophrenia or schizoaffective disorder.

A p-value of less than 0.05 was considered statistically significant. All calculations were made with the statistical program SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

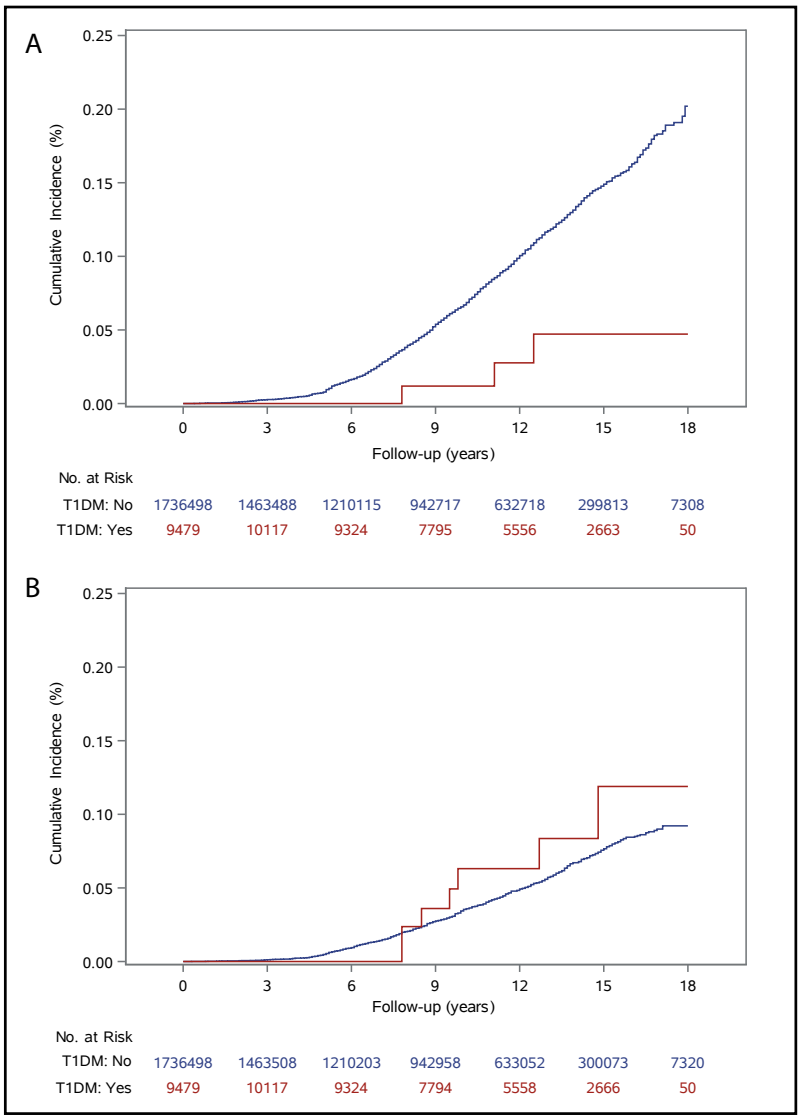

Fig. 2. Simon-Makuch estimates of cumulative incidence of schizophrenia (A) or schizoaffective disorder (B) in percentage (%) in relation to follow-up time in years among all individuals with (red line) or without (blue line) a diagnosis of type 1 diabetes mellitus (T1DM) before onset of respective psychotic disorder. Follow-up of the individuals started at 13 years of age and the number of individuals at risk with or without T1DM (in red or blue) at different follow-up points of time are given below the figures.

RESULTS

The study population included 1 745 977 individuals (52% males, 48% females) and the length of follow-up was maximally 18.0 (median 9.7) years from their 13th birthday. Characteristics of the study cohort are given in Table 2. During the follow-up, 1 280 individuals developed schizophrenia and 649 individuals schizoaffective disorder (Figure 1). The median age at diagnosis of schizophrenia was 22.2 years, and that at diagnosis of schizoaffective disorder was 22.1 years.

The incidence rates (IRs) of schizophrenia or schizoaffective disorder associated with a diagnosis of T1DM before onset of respective psychotic disorder are given in Table 3, and the cumulative incidence estimates are shown in Figures 2A and 2B. The risk of developing schizophrenia was significantly lower among individuals with, than among those without, a diagnosis of T1DM before onset of schizophrenia [unadjusted hazard ratio (HR) (95% confidence interval (CI)): 0.29 (0.09–0.89), p=0.0301; adjusted HR (95% CI): 0.29 (0.09–0.91), p=0.0338]. In contrast, the risk of developing schizoaffective disorder did not differ among individuals with or without a diagnosis of T1DM before onset of schizoaffective disorder [unadjusted HR (95% CI): 1.33 (0.63–2.80), p=0.4517); adjusted HR (95% CI): 1.50 (0.71–3.16), p=0.2909].

In the sibling analyses, similar associations, although not significant, were observed [schizophrenia (n=1621); adjusted HR (95% CI): 0.37 (0.07–2.04), p=0.2560,

Tab. 4. Risk of schizophrenia or schizoaffective disorder associated with a diagnosis of type 1 diabetes mellitus before onset of respective psychotic disorder in individuals with or without heredity for schizophrenia or schizoaffective disorder

Variable		Cases (n)	FU time[a]	IR (95% CI)[b]	Adjusted HR (95% CI), *p*-value
			Schizophrenia		
Heredity for schizophrenia	Type 1 diabetes mellitus	0	0.003	0.00 (na-1093.19)	na
	No type 1 diabetes mellitus	32	0.41	78.78 (53.89-111.21)	
No heredity for schizophrenia	Type 1 diabetes mellitus	3	1.20	2.50 (0.52-7.30)	0.31 (0.10-0.96), *p*=0.0420
	No type 1 diabetes mellitus	1235	160.76	7.68 (7.26-8.12)	reference 1.00
			Schizoaffective disorder		
Heredity for schizoaffective disorder	Type 1 diabetes mellitus	0	0.002	0.00 (na-2358.72)	na
	No type 1 diabetes mellitus	9	0.22	40.71 (18.62-77.28)	
No heredity for schizoaffective disorder	Type 1 diabetes mellitus	7	1.20	5.82 (2.34-11.99)	1.51 (0.72-3.19), *p*=0.2756
	No type 1 diabetes mellitus	629	160.97	3.91 (3.61-4.23)	reference 1.00

Abbreviations: CI = confidence interval, FU = follow-up, HR = hazard ratio, IR = incidence rate, n = number, na = not applicable
[a] Expressed as 100 000 person-years at risk
[b] Number of new cases per 100 000 person-years at risk

schizoaffective disorder (n=801); adjusted HR (95% CI): 2.77 (0.47–16.30), p=0.2606], and in the analyses by heredity for schizophrenia or schizoaffective disorder, similar associations were noted independent of heredity, even if two of the subgroups studied were too small to be included in calculations (Table 4).

DISCUSSION

In this nationwide population-based register study, we found that a diagnosis of T1DM is associated with a decreased risk of developing schizophrenia, but not of developing its related schizoaffective disorder. The results remained when controlling for known confounders, and in the additional sibling-cohort analysis, matching for shared genetic and environmental risks, similar associations were also observed.

Our finding of an inverse association between T1DM and schizophrenia is fully in line with previous results of two studies and one preliminary report, also showing such an inverse association (Eaton *et al.* 2006; Finney, 1989; Juvonen *et al.* 2007). However, when patients with schizophrenia spectrum disorder (i.e. not only with schizophrenia, but also with schizophrenia-like psychoses) have been studied earlier, no inverse association between T1DM and the psychotic spectrum disorder has been revealed (Benros *et al.* 2011, 2014a; Eaton *et al.* 2010), indicating that this inverse association is specific for schizophrenia, as found in our study.

The question arises of what is the reason for this inverse association between T1DM and schizophrenia. Both neurodevelopmental and autoimmune mechanisms have been implicated in the pathogenesis of schizophrenia (Goldsmith & Rogers, 2008; Harrison, 1999), and for long time it also has been hypothesized that schizophrenia is fundamentally a diabetic brain state, i.e. a cerebral form of diabetes (Holden & Mooney, 1994). Clinical and post mortem studies have shown signs of impaired metabolism and insulin receptor deficits in the brain, as well as decreased insulin sensitivity peripherally and increased prevalence of T2DM in patients with schizophrenia (Brambilla *et al.* 1976; Holden & Mooney, 1994; Ryan *et al.* 2003; Zhao *et al.* 2006). Insulin resistance and increased heredity for, and prevalence of, T2DM have also been reported in unaffected siblings and parents of schizophrenia patients (Fernandez-Egea *et al.* 2008a, 2008b; Huang *et al.* 2019; Miller *et al.* 2016; Mukherjee *et al.* 1989; Spelman *et al.* 2007). In addition, increased prevalence of T1DM has been reported in unaffected first-degree relatives of schizophrenia patients (Eaton *et al.* 2006; Gilvarry *et al.* 1996; Mortensen & Eaton, 2008; Wright *et al.* 1996). In this study, in the subgroup analysis by heredity for schizophrenia, our result of an inverse association between T1DM and schizophrenia independent of heredity points to that T1DM exerts protection against schizophrenia independently of its familial or non-familial form. However, it is not clear whether it is the T1DM disease itself, or the insulin therapy that is continuously used for the treatment of T1DM, or a combination of both, which protects against the development of schizophrenia as a possible diabetic brain state (Holden & Money, 1994). Interestingly, before the introduction of neuroleptics in the early 1950s, insulin coma- (or subcoma-) therapy was used in the treatment of schizophrenia, and in spite of undesirable fatal hypoglycaemia in a few patients, often with good antipsychotic effect (Cohen, 1949; Sakel, 1994).

Childhood-onset schizophrenia (defined as an onset of schizophrenia before age 13) is a rare early-onset

variant of the more common adult-onset schizophrenia (Asarnow & Forsyth, 2013; Kolvin, 1971; Lachman, 2014; Nicolson & Rapoport, 1999). Although the current diagnostic classification systems DSM-5 (American Psychiatric Association, 2013) and ICD-10 (http://www.socialstyrelsen.se) use the same criteria to diagnose schizophrenia in children as in adults (Lachman, 2014), childhood-onset schizophrenia is associated with a greater familial aggregation of schizophrenia spectrum disorders and a higher rate of rare genetic variants than the adult-onset schizophrenia (Asarnow & Forsyth, 2013). In this study, we therefore focused on individuals with adult-onset schizophrenia or schizoaffective disorder and excluded the 19 individuals with onset of either of the two disorders before 13 years of age from the final study cohort. A separate investigation of these 19 individuals also showed that one of the 14 individuals with onset of schizophrenia before age 13 developed T1DM, but at age 14.3 years, i.e. first after getting the diagnosis of schizophrenia. We also excluded the 25 individuals who had a diagnosis of DM occurring before 6 months of age from the final study cohort. This form of DM, termed neonatal DM, is a DM form other than T1DM or T2DM that is predominantly monogenically caused (Greely *et al.* 2011; Lemelman *et al.* 2018). A separate follow-up of these 25 individuals showed however that none of them developed schizophrenia or schizoaffective disorder, neither before or after 13 years of age. To further limit the presence of potential confounders in the study (Nokoff & Rewers, 2013; Waernbaum *et al.* 2019), we also chose to exclude all individuals who were part of multiple births from our final study cohort.

The major strength of this study includes its prospective and population-based design, ensuring that all events of schizophrenia or schizoaffective disorder were recorded prospectively and independently of the exposure (i.e. T1DM) and therefore not subject to selection or recall bias. A further strength includes the narrow diagnostic selection of only schizophrenia and its related schizoaffective disorder, and not of all nonaffective psychoses, allowing investigation of specific associations between T1DM and schizophrenia or schizoaffective disorder. The limitations, on the other hand, consist of lack of analyses of associations between T1DM and schizophrenia or schizoaffective disorder with onset between 32–40 years of age or late-onset, i.e. after the age of 40 (Harris & Jeste, 1988; Howard *et al.* 2000), which could not be carried out in this study that only allowed a follow-up of the cohort individuals up to maximally age 31. The limitations also include the unavailability of data on the variable maternal weight during pregnancy, which may be a risk factor for both T1DM and schizophrenia or schizoaffective disorder (Hidayat *et al.* 2019; Khandaker *et al.* 2012; MacKay *et al.* 2017). However, it is unlikely that this variable can explain the associations found, as the sibling cohort-analysis, although it had a low power because only siblings disconcordant for the outcome contributed, seemed to show a similar result to the cohort-analysis itself in this study.

In conclusion, this study shows that having T1DM is associated with a decreased risk specifically of developing schizophrenia, but not of developing its related schizoaffective disorder. Whether it is the T1DM per se, or the insulin therapy that is used continuously for the treatment of T1DM, or a combination of both, which can explain this inverse association remains however still elusive.

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REFERENCES

1 American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders, 5th edn. Arlington, VA, USA: American Psychiatric Publishing.
2 Asarnow RF, Forsyth JK (2013). Genetics of childhood-onset schizophrenia [review]. Child Adolesc Psychiatric Clin N Am. **22**: 675–687.
3 Atkinson MA, Eisenbarth GS, Michels AW (2014). Type 1 diabetes [review]. Lancet. **383**: 69–82.
4 Benros ME, Eaton WW, Mortensen PB (2014a). The epidemiologic evidence linking autoimmune diseases and psychosis [review]. Biol Psychiatry. **75**: 300–306.
5 Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB (2011). Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. Am J Psychiatry. **168**: 1303–1310.
6 Benros ME, Pedersen MG, Rasmussen H, Eaton WW, Nordentoft M, Mortensen PB (2014b). A nationwide study on the risk of autoimmune diseases in individuals with a personal or a family history of schizophrenia and related psychosis. Am J Psychiatry. **171**: 218–226.
7 Bertelsen A, Gottesman II (1995). Schizoaffective psychoses: genetical clues to classification [review]. Am J Med Genet. **60**: 7–11.
8 Bingley PJ, Douek IF, Rogers CA, Gale EAM on behalf of the BOX (Bart´s-Oxford) Study Group (2000). Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. BMJ. **321**: 420–424.
9 Brambilla F, Guastalla A, Guerrini A, Riggi F, Rovere C, Zanoboni A, et al. (1976). Glucose-insulin metabolism in chronic schizophrenia. Dis Nerv Syst. **37**: 98–103.
10 Brown S, Birtwistle J, Roe L, Thompson C (1999). The unhealthy lifestyle of people with schizophrenia. Psychol Med. **29**: 697–701.
11 Chatterjee S, Khunti K, Davies MJ (2017). Type 2 diabetes [review]. Lancet. **389**: 2239–2251.
12 Chen S-J, Chao Y-L, Chen C-Y, Chang C-M, Wu EC-H, Wu C-S, et al. (2012). Prevalence of autoimmune diseases in in-patients with schizophrenia: nationwide population-based study. Br J Psychiatry. **200**: 374–380.
13 Cohen N (1949). Treatment of mental illness at home by small doses of insulin. A follow-up report and appraisal of results in twenty-six cases. New Eng J Med. **240**: 669–676.
14 Craddock N, O´Donovan MC, Owen MJ (2005). The genetics of schizophrenia and bipolar disorder: dissecting psychosis [review]. J Med Genet. **42**: 193–204.

15 Dalman C, Broms J, Cullberg J, Allebeck P (2002).Young cases of schizophrenia identified in a national inpatient register. Are the diagnoses valid? Soc Psychiatry Psychiatr Epidemiol. **37**: 527–531.
16 D'Onofrio BM, Lahey BB, Turkheimer E, Lichtenstein P (2013). Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. Am J Public Health. **103**(suppl 1): S46–S55.
17 Eaton WW, Byrne M, Ewald H, Mors O, Chen C-Y, Agerbo E, et al. (2006). Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. Am J Psychiatry. **163**: 521–528.
18 Eaton WW, Hayward C, Ram R (1992). Schizophrenia and rheumatoid arthritis: a review. Schizophr Res. **6**: 181–192.
19 Eaton WW, Pedersen MG, Nielsen PR, Mortensen PB (2010). Autoimmune diseases, bipolar disorder, and non-affective psychosis. Bipolar Disord. **12**: 638–646.
20 Fernandez-Egea E, Bernardo M, Parellada E, Justicia A, Garcia-Rizo C, Esmatjes E, et al. (2008a). Glucose abnormalities in the siblings of people with schizophrenia. Schizophr Res. **103**: 110–113.
21 Fernandez-Egea E, Miller B, Bernardo M, Donner T, Kirkpatrick B (2008b). Parental history of type 2 diabetes in patients with non-affective psychosis. Schizophr Res. **98**: 302–306.
22 Finney GOH (1989). Juvenile onset diabetes and schizophrenia? [letter] The Lancet. **18**: 1214–1215.
23 Flyckt L (2001). Schizophrenia as a systemic disorder – studies of peripheral and central biological functions [dissertation]. Stockholm, Sweden: Karolinska Institutet.
24 Freedman R (2003). Schizophrenia [review]. N Engl J Med. **349**: 1738–1749.
25 Giegling I, Hosak L, Mössner R, Serretti A, Bellivier F, Claes S, et al. (2017). Genetics of schizophrenia: a consensus paper of the WFSBP Task Force on Genetics [review]. World J Biol Psychiatry. **18**: 492–505.
26 Gilvarry CM, Sham PC, Jones PB, Cannon M, Wright P, Lewis SW, et al. (1996). Family history of autoimmune diseases in psychosis. Schizophr Res. **19**: 33–40.
27 Goldsmith C-AW, Rogers DP (2008). The case for autoimmunity in the etiology of schizophrenia [review]. Pharmacotherapy. **28**: 730–741.
28 Greely SAW, Naylor RN, Philipson LH, Bell GI (2011). Neonatal diabetes: an expanding list of genes allows for improved diagnosis and treatment [review]. Curr Diab Rep. **11**: 519–532.
29 Greenhalgh AM, Gonzalez-Blanco L, Garcia-Rizo C, Fernandez-Egea E, Miller B, Arroyo MB, et al. (2017). Meta-analysis of glucose tolerance, insulin, and insulin resistance in antipsychotic-naïve patients with nonaffective psychosis. Schizophr Res. **179**: 57–63.
30 Greenland S, Pearl J, Robins JM (1999). Causal diagrams for epidemiologic research. Epidemiology. **10**: 37–48.
31 Harper S, Towers-Evans H, MacCabe J (2015). The aetiology of schizophrenia: what have the Swedish Medical Registers taught us? [review] Soc Psychiatry Psychiatr Epidemiol. **50**: 1471–1479.
32 Harris MJ, Jeste DV (1988). Late-onset schizophrenia: an overview [review]. Schizophr Bull. **14**: 39–55.
33 Harrison PJ (1999). The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain. **122**: 593–624.
34 Hidayat K, Zou S-Y, Shi B-M (2019). The influence of maternal body mass index, maternal diabetes mellitus, and maternal smoking during pregnancy on the risk of childhood-onset type 1 diabetes mellitus in the offspring: systematic review and meta-analysis of observational studies. Obes Rev. **20**: 1106–1120.
35 Hirsch L, Yang J, Bresee L, Jette N (2017). Second-generation antipsychotics and metabolic side effects: a systematic review of population-based studies. Drug Saf. **40**: 771–781.
36 Holden RJ, Mooney PA (1994). Schizophrenia is a diabetic brain state: an elucidation of impaired neurometabolism. Med Hypotheses. **43**: 420–435.
37 Howard R, Rabins PV, Seeman MV, Jeste DV, and the International late-onset schizophrenia group (2000). Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus [review]. Am J Psychiatry. **157**: 172–178.
38 Huang M-H, Chen M-H, Huang K-L, Hsu J-W, Bai Y-M, Cheng C-M, et al. (2019). Increased risk of type 2 diabetes among siblings of patients with schizophrenia. CNS Spectr. **24**: 453–459.
39 Hultman CM, Sparén P, Takei N, Murray RM, Cnattingius S (1999). Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study. BMJ. **318**: 421–426.
40 Häfner H (2003). Gender differences in schizophrenia [review]. Psychoneuroendocrinology. **28**: 17–54.
41 Juvonen H, Reunanen A, Haukka J, Muhonen M, Suvisaari J, Arajärvi R, et al. (2007). Incidence of schizophrenia in a nationwide cohort of patients with type 1 diabetes mellitus. Arch Gen Psychiatry. **64**: 894–899.
42 Karayiorgou M, Morris MA, Morrow B, Shprintzen RJ, Goldberg R, Borrow J, et al. (1995). Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. Proc Natl Acad Sci USA. **92**: 7612–7616.
43 Khandaker GM, Dibben CRM, Jones PB (2012). Does maternal body mass index during pregnancy influence risk of schizophrenia in the adult offspring [review]. Obes Rev. **13**: 518–527.
44 Khashan AS, Kenny LC, Lundholm C, Kearney PM, Gong T, McNamee R, et al. (2015). Gestational age and birth weight and the risk of childhood type 1 diabetes: a population-based cohort and sibling design study. Diabetes Care. **38**: 2308–2315.
45 Kirkpatrick B, Miller B, Garcia-Rizo C, Fernandez-Egea E (2014). Schizophrenia: a systemic disorder [review]. Clin Schizophr Relat Psychoses. **8**: 73–79.
46 Kolvin I (1971). Studies in the childhood psychoses. I. Diagnostic criteria and classification. Br J Psychiatry. **118**: 381–384.
47 Kristjansson E, Allebeck P, Wistedt B (1987). Validity of the diagnosis schizophrenia in a psychiatric inpatient register: a retrospective application of DSM-III criteria on ICD-8 diagnoses in Stockholm county. Nord J Psychiatry. **41**: 229–234.
48 Lachman A (2014). New developments in diagnosis and treatment update: schizophrenia/first episode psychosis in children and adolescents [review]. J Child Adolesc Mental Health. **26**: 109–124.
49 Lemelman MB, Letourneau L, Greely SAW (2018). Neonatal diabetes mellitus: an update on diagnosis and management [review]. Clin Perinatol. **45**: 41–59.
50 Leucht S, Burkard T, Henderson J, Maj M, Sartorius N (2007). Physical illness and schizophrenia: a review of the literature. Acta Psychiatr Scand. **116**: 317–333.
51 Li Z, Chen J, Yu H, He L, Xu Y, Zhang D, et al. (2017). Genome-wide association analysis identifies 30 new susceptibility loci for schizophrenia. Nat Genet. **49**: 1576–1583.
52 Mackay E, Dalman C, Karlsson H, Gardner RM (2017). Association of gestational weight gain and maternal body mass index in early pregnancy with risk for nonaffective psychosis in offspring. JAMA Psychiatry. **74**: 339–349.
53 Malaspina D, Harlap S, Fennig S, Heiman D, Nahon D, Feldman D, et al. (2001). Advancing paternal age and the risk of schizophrenia. Arch Gen Psychiatry. **58**: 361–367.
54 Marshall AL, Chetwynd A, Morris JA, Placzek M, Smith C, Olabi A, et al. (2004). Type 1 diabetes mellitus in childhood: a matched case control study in Lancashire and Cumbria, UK. Diabet Med. **21**: 1035–1040.
55 McGrath J, Saha S, Chant D, Welham J (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. **30**: 67–76.
56 Melkersson K (2009). Familial and sporadic schizophrenia: a comparison of somatic diseases and abuse in patients and their relatives. Acta Neuropsychiatr. **21**: 4–10.
57 Melkersson K, Dahl M-L (2004). Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. Drugs. **64**: 701–723.
58 Melkersson K, Dahl M-L, Hulting A-L (2004). Guidelines for prevention and treatment of adverse effects of antipsychotic drugs on glucose-insulin homeostasis and lipid metabolism. Psychopharmacol. **175**: 1–6.

59 Melkersson K, Wernroth M-L (2017). Early-onset inguinal hernia as risk factor for schizophrenia or related psychosis: a nationwide register-based cohort study. Neuroendocrinol Lett. **38**(5): 333–342.
60 Meltzer HY (1976). Neuromuscular dysfunction in schizophrenia [review]. Schizophr Bull. **2**: 106–135.
61 Miller BJ, Goldsmith DR, Paletta N, Wong J, Kandhal P, Black C, et al. (2016). Parental type 2 diabetes in patients with non-affective psychosis. Schizophr Res. **175**: 223–225.
62 Moises HW, Zoega T, Gottesman II (2002). The glial growth factors deficiency and synaptic destabilization hypothesis of schizophrenia. BMC Psychiatry. **2**: 8.
63 Mortensen PB, Eaton WW (2008). Diabetes mellitus and schizophrenia [letter]. Arch Gen Psychiatry. **65**: 237–238.
64 Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio P (1996). Diabetes mellitus in schizophrenic patients. Compr Psychiatry. **37**: 68–73.
65 Mukherjee S, Schnur DB, Reddy R (1989). Family history of type 2 diabetes in schizophrenic patients [letter]. The Lancet **1**: 495.
66 Nasrallah HA (2005). Neurologic comorbidities in schizophrenia [review]. J Clin Psychiatry. **66**(suppl 6): 34–46.
67 Nicolson R, Rapoport JL (1999). Childhood-onset schizophrenia: rare but worth studying [review]. Biol Psychiatry. **46**: 1418–1428.
68 Nokoff N, Rewers M (2013). Pathogenesis of type 1 diabetes: lessons from natural history studies of high-risk individuals [review]. Ann NY Acad Sci. **1281**: 1–15.
69 Pardiñas AF, Holmans P, Pocklington AJ, Escott-Price V, Ripke S, Carrera N, et al. (2018). Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat Genet. **50**: 381–389.
70 Perry BI, McIntosh G, Weich S, Singh S, Rees K (2016). The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis. Lancet Psychiatry. **3**: 1049–1058.
71 Pilkington TL (1956). The coincidence of rheumatoid arthritis and schizophrenia. J Nerv Ment Dis. **124**: 604–606.
72 Ptacek R, Kuzelova H, Stefano GB (2011). Genetics in psychiatry – up-to-date review 2011. Neuroendocrinol Lett. **32**(4): 389–399.
73 Ripke S, Neale BM, Corvin A, Walters JTR, Farh K-H, Holmans PA, et al. (2014). Biological insights from 108 schizophrenia-associated genetic loci. Nature. **511**: 421–427.
74 Ryan MCM, Collins P, Thakore JH (2003). Impaired fasting glucose tolerance in first-episode, drug-naïve patients with schizophrenia. Am J Psychiatry. **160**: 284–289.
75 Saari KM, Lindeman SM, Viilo KM, Isohanni MK, Järvelin M-R, Laurèn LH, et al. (2005). A 4-fold risk of metabolic syndrome in patients with schizophrenia: the northern Finland 1966 birth cohort study. J Clin Psychiatry. **66**: 559–563.
76 Sakel M (1994). The methodical use of hypoglycaemia in the treatment of psychosis. Am J Psychiatry. **151**(6 suppl): 241–247.
77 Sellgren C, Frisell T, Lichtenstein P, Landèn M, Askling J (2014). The association between schizophrenia and rheumatoid arthritis: a nationwide population-based Swedish study on intraindividual and familial risks. Schizophr Bull. **40**: 1552–1559.
78 Simon R, Makuch RW (1984). A non-parametric graphical representation of the relationship between survival and the occurrence of an event: application to responder versus non-responder bias. Stat Med. **3**: 35–44.
79 Spelman LM, Walsh PI, Sharifi N, Collinst P, Thakore JH (2007). Impaired glucose tolerance in first-episode drug-naïve patients with schizophrenia. Diabet Med. **24**: 481–485.
80 Stubbs B, Vancampfort D, De Hert M, Mitchell AJ (2015). The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: a systematic review and comparative meta-analysis. Acta Psychiatr Scand. **132**: 144–157.
81 Tuomilehto J (2013). The emerging global epidemic of type 1 diabetes [review]. Curr Diab Rep. **13**: 795–804.
82 Vancampfort D, Correll CU, Galling B, Probst M, De Hert M, Ward PB, et al. (2016). Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry. **15**: 166–174.
83 Waernbaum I, Dahlquist G, Lind T (2019). Perinatal risk factors for type 1 diabetes revisited: a population-based register study. Diabetologia. **62**: 1173–1184.
84 Wright P, Sham PC, Gilvarry CM, Jones PB, Cannon M, Sharma T, et al. (1996). Autoimmune diseases in the pedigrees of schizophrenic and control subjects. Schizophr Res. **20**: 261–267.
85 Zammit S, Thomas K, Thompson A, Horwood J, Menezes P, Gunnell D, et al. (2009). Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. Br J Psychiatry. **195**: 294–300.
86 Zhao Z, Ksiezak-Reding H, Riggio S, Haroutunian V, Pasinetti GM (2006). Insulin receptor deficits in schizophrenia and in cellular and animal models of insulin receptor dysfunction. Schizophr Res. **84**: 1–14.