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ORIGINAL ARTICLE

Schizophrenia- or schizoaffective disorder diagnosis and the risk for subsequent type 1- or type 2 diabetes mellitus: a Swedish nationwide register-based cohort study

Kristina Melkersson[1]

1 Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Correspondence to: Kristina Melkersson, MD, PhD
Department of Molecular Medicine and Surgery, Karolinska Institutet, Old Karolinska University Hospital Solna, L1:00, SE-171 76 Stockholm, Sweden
e-mail: Kristina.Melkersson@ki.se

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Abstract

OBJECTIVES: The aim of this study was to examine the effect of schizophrenia or schizoaffective disorder on the risk of developing subsequent type 1 (T1)- or type 2 (T2) diabetes mellitus (DM), by carrying out a Swedish register study.

MATERIAL & 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 2018 to identify onset of schizophrenia, schizoaffective disorder and DM. Cox proportional hazard models were applied to assess the associations between schizophrenia or schizoaffective disorder and risk for T1DM or T2DM during a follow-up from age 13.

RESULTS: The study population included 1 736 281 individuals and the length of follow-up was maximally 19.0 (median 10.6) years. The risk of developing T1DM was significantly higher among individuals with, than without, schizophrenia [adjusted hazard ratio (HR) (95% confidence interval (CI)): 2.84 (1.18–6.82), p=0.0195], whereas among individuals with or without schizoaffective disorder, the risk of developing T1DM did not differ [adjusted HR (95% CI): 1.23 (0.17–8.74), p=0.8377]. The risk of developing T2DM was significantly higher both among individuals with schizophrenia and schizoaffective disorder, than among those without such diagnoses [adjusted HR (95% CI): 13.98 (8.70–22.46), p<0.0001 and 14.27 (7.36–27.70), p<0.0001, respectively].

CONCLUSIONS: This study shows that schizophrenia is associated with increased risk for subsequent T1DM. It also shows that both schizophrenia and schizoaffective disorder are associated with increased risk for subsequent T2DM.

INTRODUCTION

Somatic comorbidity in schizophrenia is relative common, and prevalences of several somatic diseases, abnormalities and syndromes, such as 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 (Cullen *et al.* 2019; Karayiorgou *et al.* 1995; Leucht *et al.* 2007; Melkersson & Wernroth, 2017; Meltzer, 1976; Nasrallah, 2005; Saari *et al.* 2005). On the other hand, some other somatic diseases, such as cancer and the autoimmune disease rheumatoid arthritis, occur less frequently in patients with schizophrenia (Eaton *et al.* 1992; Leucht *et al.* 2007; Melkersson, 2009; Mors *et al.* 1999; Sellgren *et al.* 2014).

Concerning comorbidity of diabetes mellitus (DM) in schizophrenia, type 2 diabetes mellitus (T2DM), which is characterized by relative insulin deficiency caused by pancreatic ß-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). In contrast, type 1 diabetes mellitus (T1DM), which results from an immune-associated (probably autoimmune) destruction of insulin-secreting pancreatic ß-cells (Atkinson *et al.* 2014), has been found to be inversely associated with development of schizophrenia (Eaton *et al.* 2006; Finney, 1989; Juvonen *et al.* 2007; Melkersson & Wernroth, 2019).

Up to now, the effect of a prior diagnosis of schizophrenia on the risk of developing T2DM has been examined in several studies (Mukherjee *et al.* 1996; Stubbs *et al.* 2015; Vancampfort *et al.* 2016). Also, the effect of a prior diagnosis of T1DM on the risk of developing schizophrenia has earlier been investigated in a number of studies (Eaton *et al.* 2006; Finney, 1989; Juvonen *et al.* 2007; Melkersson & Wernroth, 2019). However, although the effect of a prior diagnosis of schizophrenia spectrum disorders (i.e. schizophrenia and schizophrenia-like psychoses, including schizoaffective disorder) on the risk of developing T1DM has been studied in two previous studies (Benros *et al.* 2014; Chen *et al.* 2012), the effect of a prior diagnosis of schizophrenia alone on the risk of developing T1DM has not earlier been studied as far as I know. Therefore, as Sweden has population- and health-registers with satisfactory validity of diagnoses and high technical quality which are well-suited for epidemiological studies (Dalman *et al.* 2002; Kristjansson *et al.* 1987; Ludvigsson *et al.* 2011; Miao *et al.* 2005; Ragnarson Tennvall *et al.* 2000), I accessed the associations between a prior diagnosis of schizophrenia or its related schizoaffective disorder and subsequent development of T1DM or T2DM, by carrying out a Swedish population-based register study.

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=70 425) or died (n=10 094) before 13 years of age were excluded, leading to a study cohort consisting of 1 745 964 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 schizophrenia, schizoaffective disorder and DM from birth until death, emigration or December 31, 2018, whichever came 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) (https://www.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. Individuals with childhood-onset schizophrenia (n=14) or schizoaffective disorder (n=5), defined as being diagnosed with schizophrenia or schizoaffective disorder before age 13 (Lachman, 2014), and individuals being diagnosed with DM before age 13 (n=9 664) were excluded, reducing the study cohort to finally 1 736 281 individuals (Figure 1). Furthermore, information about age of the parents, maternal body mass index (BMI) and smoking during pregnancy, season of birth, and gestational age, weight and Apgar score 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). Moreover, heredity for schizophrenia, schizoaffective disorder, T1DM and T2DM 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). As the ICD 7th, 8th and 9th revisions did not allow separation of T1DM from T2DM or other types of DM (Table 1), age <30 years at first contact for DM was here used as criterion for being considered to present T1DM (Miao *et al.* 2005).

To assess the associations between schizophrenia or schizoaffective disorder as time-updated exposures and risk of T1DM or T2DM, Cox proportional hazard (PH) models were applied, using age as timescale. Follow-up

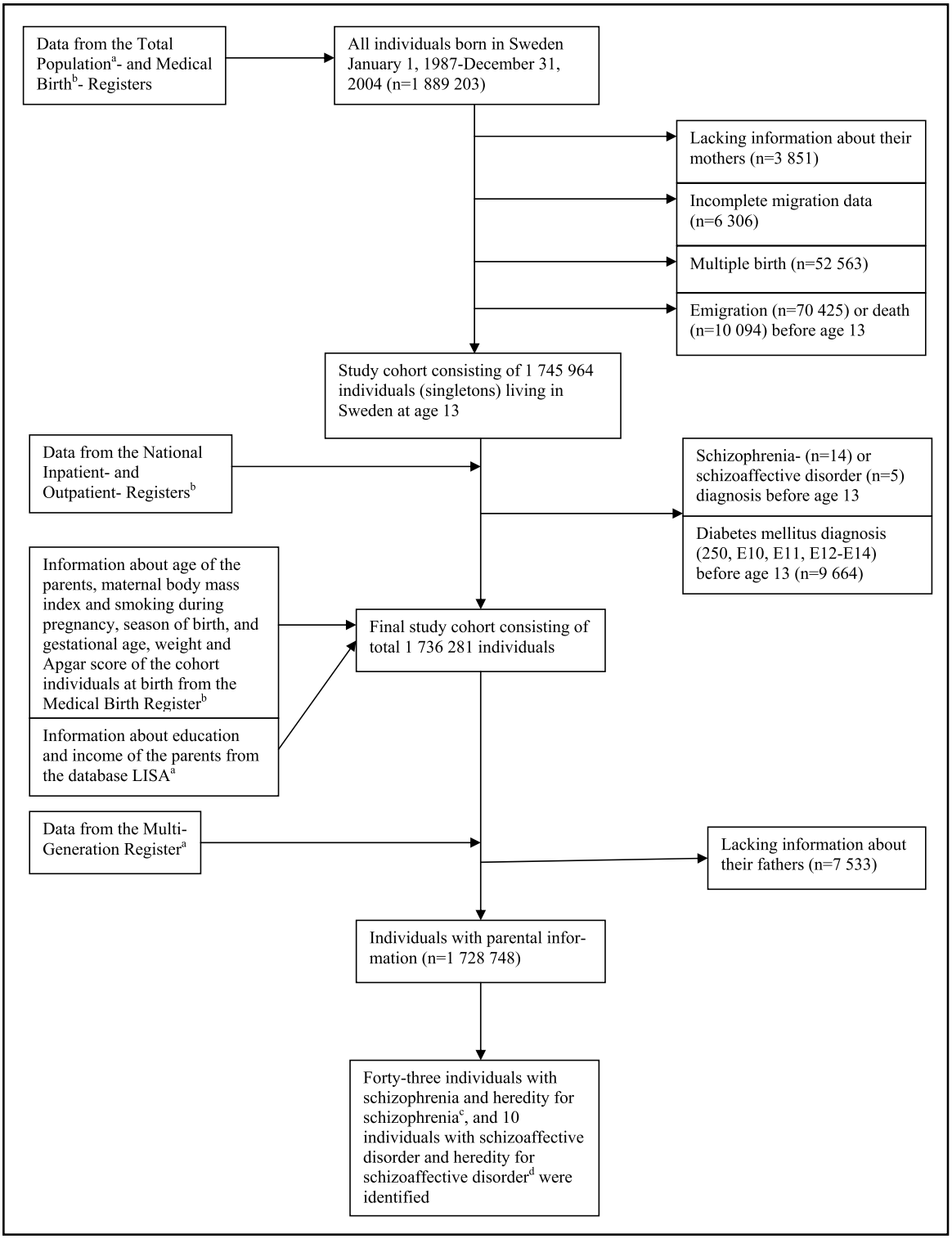

Fig. 1. Flow diagram of the study population. [a] Held by Statistics Sweden; [b]Held by the National Board of Health and Welfare in Sweden; [c]I.e. having a mother and/or father with schizophrenia; [d]I.e. having a mother and/or father with schizoaffective disorder

started at age 13, and individuals were censored at emigration, death or end of follow-up (December 31, 2018). A robust sandwich covariance matrix estimate was used to account for the lack of independence of individuals within the same family. Further, the associations between schizophrenia or schizoaffective disorder as time-updated exposures and risk of T1DM or T2DM 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

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 1997-2018
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 (https://www.socialstyrelsen.se)

effect on schizophrenia or schizoaffective disorder and T1DM or T2DM (Bertelsen & Gottesman, 1995; Bingley *et al.* 2000; Craddock *et al.* 2005; Crump *et al.* 2020; Guo *et al.* 2017; Harper *et al.* 2015; Hidayat *et al.* 2019; Hultman *et al.* 1999; Häfner, 2003; Jaddoe *et al.* 2014; Kautzky-Willer *et al.* 2016; Khandaker *et al.* 2012; Khashan *et al.* 2015; Marshall *et al.* 2004; Tuomilehto, 2013; Waernbaum *et al.* 2019; Wu *et al.* 2014; Zammit *et al.* 2009; Zhao *et al.* 2018). Hence, adjustments were made for sex, gestational age, birth weight in relation to gestational age, maternal smoking during pregnancy (only data from early pregnancy was available), parity, heredity for schizophrenia or schizoaffective disorder, and heredity for T1DM or T2DM. Furthermore, to adjust for unmeasured and measured environmental and genetic confounding factors shared by siblings, a stratified Cox PH model conditional on sibling cluster was estimated (D'Onofrio *et al.* 2013). Only clusters with at least one T1DM- or T2DM-event individual and at least one event-free individual at the age of event in the T1DM- or T2DM-individual, contribute to the estimations in the sibling analyses; informative sample size is thus reported for sibling analyses. Finally, subgroup analyses by heredity for schizophrenia or schizoaffective disorder were also conducted. 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).

RESULTS

The study population included 1 736 281 individuals (51.4% males, 48.6% females) and the length of follow-up was maximally 19.0 (median 10.6) years from their 13th birthday. Characteristics of the study population are given in Table 2 (characteristics of the T1DM- and T2DM study cohorts separated were similar; data not shown). During the follow-up, 6 404 individuals developed T1DM and 2020 individuals T2DM (Table 3). The median (min-max) age at diagnosis of T1DM was 16.9 (13.0–31.6) years in all individuals [25.0 (21.0–27.5) years in the individuals with schizophrenia and 19.8 (19.8–19.8) years in the individual with schizoaffective disorder], and that at diagnosis of T2DM was 20.7 (13.0–31.8) years in all individuals [23.9 (17.6–30.0) years in the individuals with schizophrenia and 23.7 (22.0–27.5) years in the individuals with schizoaffective disorder].

The incidence rates (IRs) of T1DM or T2DM associated with a prior diagnosis of schizophrenia or schizoaffective disorder are given in Table 3, and the cumulative incidence estimates are shown in Figures 2A-B and 3A-B. The risk of developing T1DM was significantly higher among individuals with, than without, a diagnosis of schizophrenia [unadjusted hazard ratio (HR) (95% confidence interval (CI)): 3.28 (1.48–7.29), p=0.0036; adjusted HR (95% CI): 2.84 (1.18–6.82), p=0.0195], whereas among individuals with or without a diagnosis of schizoaffective disorder, the risk of developing T1DM did not differ [unadjusted HR (95% CI): 1.07 (0.15–7.57), p=0.9481; adjusted HR (95% CI): 1.23 (0.17–8.74), p=0.8377]. The risk of developing T2DM was significantly higher both among individuals with a diagnosis of schizophrenia and schizoaffective disorder, than among those without such diagnoses [unadjusted HR (95% CI): 13.10 (8.19–20.95), p<0.0001; adjusted HR (95% CI): 13.98 (8.70–22.46), p<0.0001 and unadjusted HR (95% CI): 12.95 (6.69–25.07), p<0.0001; adjusted HR (95% CI): 14.27 (7.36–27.70), p<0.0001, respectively].

Tab. 2. Characteristics of the study population

Characteristic	Outcome: DM (E10, E11)		Outcome: DM (E10, E11)	
	No SCH before end of follow-up	SCH before end of follow-up	No SA before end of follow-up	SA before end of follow-up
All (n)	1 734 816	1 465	1 735 547	734
Sex[a]				
men	890 995 (51.4)	999 (68.2)	891 650 (51.4)	344 (46.9)
women	843 821 (48.6)	466 (31.8)	843 897 (48.6)	390 (53.1)
Highest level of education achieved by either parent[a]				
>9 years	1 606 996 (92.7)	1 281 (87.5)	1 607 624 (92.7)	653 (89.0)
9 years	99 267 (5.7)	136 (9.3)	99 342 (5.7)	61 (8.3)
<9 years	15 796 (0.9)	24 (1.6)	15 810 (0.9)	10 (1.4)
missing	12 757 (0.7)	24 (1.6)	12 771 (0.7)	10 (1.4)
Household income categorized into fifths at time of birth of the cohort individual[a]				
1 (lowest)	334 553 (19.3)	349 (23.8)	334 728 (19.3)	174 (23.7)
2	351 414 (20.3)	326 (22.3)	351 584 (20.3)	156 (21.3)
3	352 178 (20.3)	272 (18.6)	352 313 (20.3)	137 (18.7)
4	351 404 (20.3)	254 (17.3)	351 518 (20.3)	140 (19.1)
5 (highest)	340 169 (19.6)	253 (17.3)	340 300 (19.6)	122 (16.6)
missing	5 098 (0.3)	11 (0.8)	5 104 (0.3)	5 (0.7)
Parent born outside Sweden[a]				
father	217 308 (12.5)	241 (16.5)	217 438 (12.5)	111 (15.1)
mother	200 818 (11.6)	220 (15.0)	200 955 (11.6)	83 (11.3)
missing	7 657 (0.4)	12 (0.8)	7 665 (0.4)	4 (0.5)
Mother living with the father at time of birth of the cohort individual[a]				
yes	1 512 955 (87.2)	1 204 (82.2)	1 513 545 (87.2)	614 (83.7)
no	83 106 (4.8)	142 (9.7)	83 184 (4.8)	64 (8.7)
missing	138 755 (8.0)	119 (8.1)	138 818 (8.0)	56 (7.6)
Mother's age at time of birth of the cohort individual (year)[b]	29.3 (5.1)	29.2 (5.8)	29.3 (5.1)	28.7 (5.5)
Father's age at time of birth of the cohort individual (year)[b]	32.2 (6.1)	32.6 (6.9)	32.2 (6.1)	31.9 (6.5)
missing[a]	7 521 (0.4)	12 (0.8)	7 529 (0.4)	4 (0.5)
Maternal BMI at the first visit to the antenatal clinic (kg/m^2)[b]	23.7 (4.0)	22.8 (3.7)	23.7 (4.0)	23.3 (4.4)
mother having data[a]	1 198 725 (69.1)	801 (54.7)	1 199 124 (69.1)	402 (54.8)
missing[a]	536 091 (30.9)	664 (45.3)	536 423 (30.9)	332 (45.2)
Maternal smoking during early pregnancy[a]				
non-smoker	1 314 424 (75.8)	992 (67.7)	1 314 946 (75.8)	470 (64.0)
1-9 cigarettes/day	189 965 (11.0)	208 (14.2)	190 040 (10.9)	133 (18.1)
>9 cigarettes/day	105 912 (6.1)	149 (10.2)	105 981 (6.1)	80 (10.9)
missing	124 515 (7.2)	116 (7.9)	124 580 (7.2)	51 (6.9)
Season of birth[a]				
Spring	478 692 (27.6)	381 (26.0)	478 891 (27.6)	182 (24.8)
Summer	449 879 (25.9)	389 (26.6)	450 077 (25.9)	191 (26.0)
Autumn	397 458 (22.9)	330 (22.5)	397 622 (22.9)	166 (22.6)
Winter	408 787 (23.6)	365 (24.9)	408 957 (23.6)	195 (26.6)
Gestational age[a]				
<38 weeks	167 094 (9.6)	164 (11.2)	167 165 (9.6)	93 (12.7)
38-40 weeks	1 107 249 (63.8)	945 (64.5)	1 107 729 (63.8)	465 (63.4)
>40 weeks	431 377 (24.9)	338 (23.1)	431 553 (24.9)	162 (22.1)
missing	29 096 (1.7)	18 (1.2)	29 100 (1.7)	14 (1.9)
Birth weight (g)[b]	3 552.8 (556.1)	3 509.9 (602.7)	3 552.7 (556.1)	3 501.1 (606.4)
<3000 g[a]	223 462 (12.9)	244 (16.7)	223 590 (12.9)	116 (15.8)
3000-3999 g[a]	1 144 134 (66.0)	928 (63.3)	1 144 581 (65.9)	481 (65.5)
≥4000 g[a]	336 049 (19.4)	275 (18.8)	336 201 (19.4)	123 (16.8)
missing[a]	31 171 (1.8)	18 (1.2)	31 175 (1.8)	14 (1.9)
Birth weight in relation to gestational age[a]				
small for age	40 857 (2.4)	56 (3.8)	40 892 (2.4)	21 (2.9)
normal	1 599 700 (92.2)	1 341 (91.5)	1 600 374 (92.2)	667 (90.9)
large for age	60 961 (3.5)	47 (3.2)	60 978 (3.5)	30 (4.1)
missing	33 298 (1.9)	21 (1.4)	33 303 (1.9)	16 (2.2)
Apgar score at 1 min[a]				
0-6	71 121 (4.1)	70 (4.8)	71 156 (4.1)	35 (4.8)
7-10	1 624 355 (93.6)	1 364 (93.1)	1 625 036 (93.6)	683 (93.1)
missing	39 340 (2.3)	31 (2.1)	39 355 (2.3)	16 (2.2)

Abbreviations: BMI=body mass index, DM=diabetes mellitus, g=gram, kg=kilogram, m=metre, min=minute, SA=schizoaffective disorder, SCH=schizophrenia

[a]Data are given as number (%), [b]Data are given as mean (standard deviation)

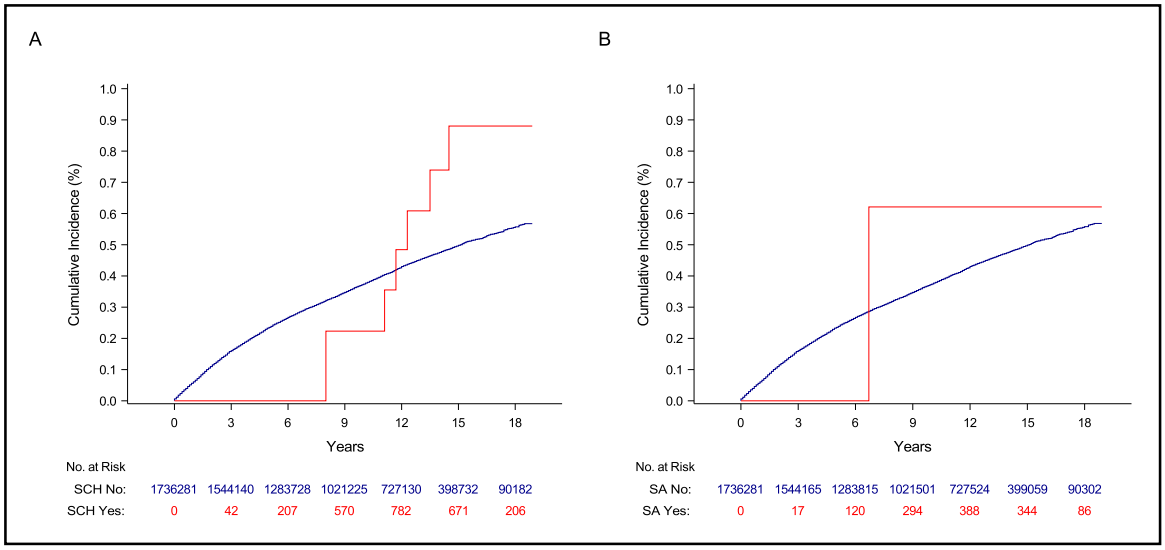

Fig. 2A-B. Simon-Makuch estimates of cumulative incidence of type 1 diabetes mellitus (A, B) in percentage (%) in relation to follow-up time in years among all individuals with (red line) or without (blue line) a prior diagnosis of schizophrenia (SCH) or schizoaffective disorder (SA). Follow-up of the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

In the sibling analyses, similar associations, although only in part statistically significant, were observed for a prior diagnosis of schizophrenia and T1DM (n=3981 sibling pairs) [unadjusted HR (95% CI): 3.64 (0.37–35.72), p=0.2678; adjusted HR (95% CI): 3.93 (0.40–38.93), p=0.2416] or T2DM (n=990 sibling pairs) [unadjusted HR (95% CI): 10.50 (1.30–84.84), p=0.0274; adjusted HR (95% CI): 12.47 (1.50–103.58), p=0.0195], while for a prior diagnosis of schizoaffective disorder and T1DM or T2DM, the groups of sibling pairs were too small to be calculated. In the analyses by heredity for schizophrenia or schizoaffective disorder, similar associations were also noted (Table 4).

DISCUSSION

In this nationwide population-based register study, it was found that a prior diagnosis of schizophrenia, but not of schizoaffective disorder, is associated with increased risk of developing T1DM. It was also found that both a prior diagnosis of schizophrenia and of schizoaffective disorder are associated with increased risk of developing T2DM. The results for both T1DM and T2DM remained when controlling for known confounders, and in the additional sibling-analyses, matching for shared genetic and environmental risks, similar associations were also found.

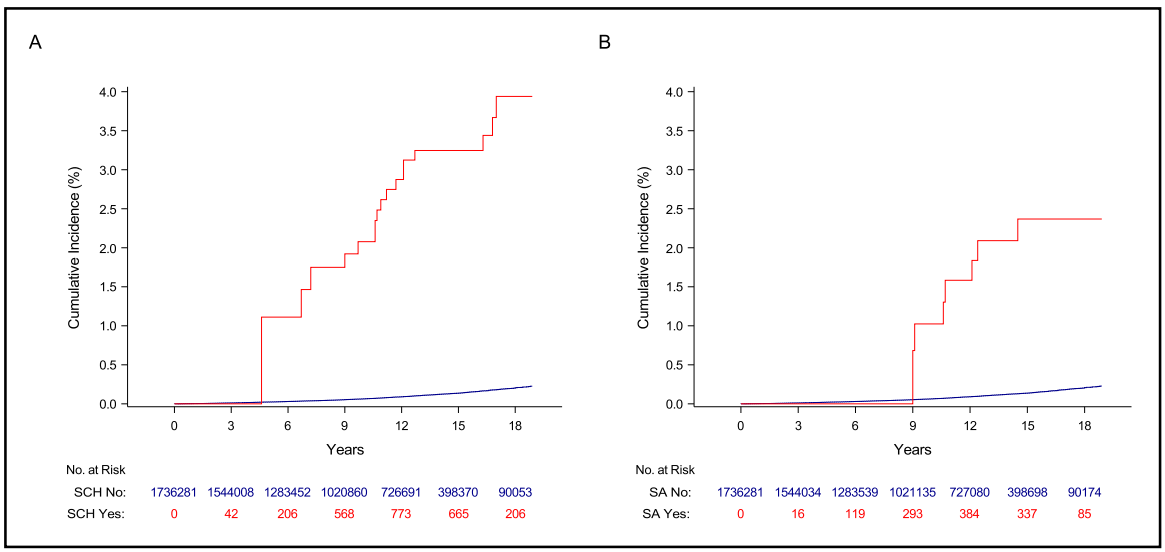

Fig. 3A-B. Simon-Makuch estimates of cumulative incidence of type 2 diabetes mellitus (A, B) in percentage (%) in relation to follow-up time in years among all individuals with (red line) or without (blue line) a prior diagnosis of schizophrenia (SCH) or schizoaffective disorder (SA). Follow-up of the individuals started at 13 years of age and the number of individuals at risk with (in red) or without (in blue) SCH or SA at different follow-up points of time are given below the figures.

Tab. 3. Incidence rates of type 1- or type 2 diabetes mellitus associated with a prior diagnosis of schizophrenia or schizoaffective disorder

Psychotic disorder	Type 1 diabetes mellitus			Type 2 diabetes mellitus		
	Cases (n)	FU time[a]	IR (95% CI)[b]	Cases (n)	FU time[a]	IR (95% CI)[b]
Schizophrenia	6	0.07	82.12 (30.14-178.74)	18	0.07	247.89 (146.92-391.77)
No schizophrenia	6 398	178.59	35.83 (34.95-36.71)	2 002	178.94	11.19 (10.70-11.69)
Schizoaffective disorder	1	0.04	26.88 (0.68-149.76)	9	0.04	244.22 (111.68-463.61)
No schizoaffective disorder	6 403	178.63	35.85 (34.97-36.74)	2 011	178.98	11.24 (10.75-11.74)

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

To the best of my knowledge, no earlier study has been published regarding the risk for T1DM in patients with prior schizophrenia. However, this result of a higher risk for T1DM in patients with, than without, schizophrenia is supported by the only two earlier studies published (Benros *et al.* 2014; Chen *et al.* 2012), showing increased risk for T1DM, but in patients with schizophrenia spectrum disorders (i.e. in patients not only with schizophrenia, but also with schizophrenia-like psychoses, schizoaffective disorder included among others). In addition, a number of previous studies have reported increased prevalence of T1DM in unaffected parents or siblings of patients specifically with schizophrenia (Eaton *et al.* 2006; Mortensen & Eaton, 2008; Wright *et al.* 1996), supporting the notion for increased risk for T1DM even in unaffected first-degree relatives to schizophrenia patients, i.e. in those who have a predisposition to schizophrenia, but have not developed the disease. Moreover, increased risk of several other autoimmune diseases, such as autoimmune hepatitis, hypersensitivity vasculitis and primary adrenocortical insufficiency, have been reported in patients with prior schizophrenia spectrum disorders (Benros *et al.* 2014; Chen *et al.* 2012). In contrast, a prior diagnosis of T1DM has been shown in earlier studies to be inversely associated with development

Tab. 4. Risk of type 1- or type 2 diabetes mellitus associated with a prior diagnosis of schizophrenia or schizoaffective disorder in individuals with or without heredity for schizophrenia or schizoaffective disorder

Variable		Cases (n)	FU time[a]	IR (95% CI)[b]	Unadjusted HR (95% CI), p-value
			Type 1 diabetes mellitus		
Heredity for schizophrenia[c]	Schizophrenia	1	0.002	535.52 (13.56-2983.72)	20.35 (2.70-153.68), *p*=0.0035
	No schizophrenia	18	0.45	40.25 (23.86-63.61)	reference 1.00
No heredity for schizophrenia	Schizophrenia	5	0.07	70.73 (22.97-165.07)	2.82 (1.17-6.77), *p*=0.0207
	No schizophrenia	6367	177.39	35.89 (35.02-36.79)	reference 1.00
Heredity for schizoaffective disorder[d]	Schizoaffective disorder	0	0.00	0.00 (na-7964.75)	na
	No schizoaffective disorder	11	0.25	44.94 (22.43-80.41)	
No heredity for schizoaffective disorder	Schizoaffective disorder	1	0.04	27.39 (0.69-152.58)	1.09 (0.15-7.68), *p*=0.9341
	No schizoaffective disorder	6379	177.62	35.91 (35.04-36.81)	reference 1.00
			Type 2 diabetes mellitus		
Heredity for schizophrenia[c]	Schizophrenia	1	0.002	518.79 (13.14-2890.51)	15.00 (2.07-108.55), *p*=0.0073
	No schizophrenia	7	0.45	15.62 (6.28-32.19)	reference 1.00
No heredity for schizophrenia	Schizophrenia	17	0.07	242.25 (141.12-387.87)	12.85 (7.93-20.83), *p*<0.0001
	No schizophrenia	1985	177.74	11.17 (10.68-11.67)	reference 1.00
Heredity for schizoaffective disorder[d]	Schizoaffective disorder	0	0.00	0.00 (na-7964.75)	na
	No schizoaffective disorder	7	0.25	28.54 (11.48-58.81)	
No heredity for schizoaffective disorder	Schizoaffective disorder	9	0.04	248.87 (113.80-472.44)	13.25 (6.85-25.66), *p*<0.0001
	No schizoaffective disorder	1994	177.97	11.20 (10.72-11.71)	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, [c]I.e. having a mother and/or father with schizophrenia, [d]I.e. having a mother and/or father with schizoaffective disorder

of schizophrenia, but not of schizoaffective disorder (Eaton *et al.* 2006; Finney, 1989; Juvonen *et al.* 2007; Melkersson & Wernroth, 2019). Consequently, this current result that a prior diagnosis of schizophrenia is associated with increased risk for T1DM, together with these earlier findings that a prior diagnosis of T1DM is associated with decreased risk for schizophrenia (Eaton *et al.* 2006; Finney, 1989; Juvonen *et al.* 2007; Melkersson & Wernroth, 2019), indicate that schizophrenia per se is associated with increased risk for T1DM, but that the insulin therapy that is continuously used for the treatment of T1DM, or the combination of the insulin therapy and T1DM, reduces the risk for schizophrenia development.

The other current results in this study, that both a prior diagnosis of schizophrenia and of schizoaffective disorder are associated with increased risk for T2DM and that no difference in risk for T2DM was found between the two psychotic disorders, are supported by a recently published meta-analysis, showing no significant difference in relative risk of T2DM in studies directly comparing schizophrenia alone versus schizophrenia spectrum disorders (including schizoaffective disorder, schizophreniform disorder and related psychoses) (Vancampfort *et al.* 2016). The onset of T2DM was also at similar younger ages in the schizophrenia- and schizoaffective disorder individuals in this study (i.e. at median 23.9 and 23.7 years of age, respectively). The reason for these current results is probably to a greater extent explained by common risk factors for T2DM in schizophrenia- and schizoaffective disorder patients, such as overweight and obesity, physical inactivity, excessive cigarette smoking, and treatment with antipsychotic drugs (Brown *et al.* 1999; Hirsch *et al.* 2017; Melkersson & Dahl, 2004; Melkersson *et al.* 2004), than by the psychotic disorders per se. However, it cannot be ruled out that particularly schizophrenia itself may contribute to the increased T2DM risk (Braceland *et al.* 1945; Greenhalgh *et al.* 2017; Melkersson & Dahl, 2004; Melkersson *et al.* 2004; Perry *et al.* 2016; Ryan *et al.* 2003; Spelman *et al.* 2007).

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 (https://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, I 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. To further limit the presence of potential confounders in the study, I also chose to exclude all individuals who were part of multiple births from the final study cohort (Hultman *et al.* 1999; Nokoff & Rewers, 2013; Vaag & Poulsen, 2007; Waernbaum *et al.* 2019).

The major strength of this study includes its prospective and population-based design, ensuring that all events of T1DM or T2DM were recorded prospectively and independently of the exposures (i.e. schizophrenia or schizoaffective disorder) and therefore not subject to selection or recall bias. A further strength includes the narrow diagnostic selection of exclusively schizophrenia and its related schizoaffective disorder, and not of all nonaffective psychoses, allowing investigation of specific associations between schizophrenia or schizoaffective disorder and T1DM or T2DM. The limitations of the study, on the other hand, consist of lack of analyses regarding schizophrenia or schizoaffective disorder with onset between 32–40 years of age or with 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. In addition, T2DM occurs in most cases in older ages (Chatterjee *et al.* 2017), but in this study only analyses of T2DM with onset in younger ages up to maximally age 31 could be carried out. The limitations also include that no adjustment was made for the variable maternal BMI during pregnancy, which may be a risk factor for both schizophrenia or schizoaffective disorder and T1DM or T2DM (Hidayat *et al.* 2019; Khandaker *et al.* 2012; Mackay *et al.* 2017; Pandey *et al.* 2015). The reason for not adjusting for maternal BMI during pregnancy was that the Medical Birth Register was incomplete on this variable for the study cohort individuals' birth years 1987–2004, with missing data in about 30% of all mothers and with no available data at all for the years 1990 and 1991. However, it is unlikely that this variable can explain the associations found in the study, as the sibling cohort-analysis, although it had a low statistical power because only siblings disconcordant for the outcome contributed, showed a similar result to the cohort-analysis itself.

In conclusion, it was found in this study that schizophrenia, but not schizoaffective disorder, is associated with increased risk for subsequent T1DM. It was also found that both schizophrenia and schizoaffective disorder are associated with increased risk for subsequent T2DM.

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