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Endogenous and antipsychotic-related risks for diabetes mellitus in young people with schizophrenia: A Danish population-based cohort study

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Authors' contributions:

Anto P. Rajkumar (APR), Christiane Gasse (CG), Theresa Wimberley, and Ole Mors (OM) were involved in the conception and the design of this study. APR analysed the data. All authors contributed to the interpretation of our results. This study was supervised by CG and OM. APR wrote the initial manuscript. All authors were involved in the critical revisions and final approval of the manuscript.

Abstract:

Objective: Diabetes Mellitus contributes to excessive cardiovascular deaths and reduced life expectancy in schizophrenia. This population-based cohort study investigated the endogenous risk for DM in antipsychotic-naive schizophrenia, and evaluated the risks, added by starting antipsychotics in people with schizophrenia.

Method: We followed all people, born in Denmark on or after 01/01/1977 until 01/01/2013 (N=2,736,510). The Danish Psychiatric Central Research Register ascertained schizophrenia diagnoses. The Danish National Prescription Registry provided data on prescriptions of antipsychotics. Diabetes was ascertained from the Danish National Patient Register and Danish National Prescription Registry. We estimated the endogenous and antipsychotic-related risks for diabetes using Cox proportional hazards regression models, while accounting for potential confounders.

Results: 14,118 (0.52%) developed diabetes, and 8,945 (0.33%) developed schizophrenia during follow-up (49,582,279 person-years). Adjusted hazard ratio for diabetes was 3.07 (95% CI 1.71-5.41) in antipsychotic-naive schizophrenia compared with the general population. Risk for diabetes after starting antipsychotics was significantly higher (Adjusted hazard ratio =3.64; 95% CI 1.95-6.82) than the risk in antipsychotic-naive schizophrenia, after adjusting for family history of diabetes and other potential confounders. First-line treatment with either first-generation antipsychotics (Adjusted hazard ratio =3.06; 95% CI 1.32-7.05) or second generation antipsychotics (Adjusted hazard ratio=3.44; 95% CI 1.73-6.83) increased risks for diabetes without statistically significant difference ($\chi^2=0.13$; $p=0.72$). Appropriate sensitivity analyses, limited to type-2 diabetes, corroborated these results.

Conclusions: Schizophrenia confers high endogenous risk for diabetes, and the risks are further increased by both first-generation and second-generation antipsychotics. Early detection and effective treatment of diabetes should be an integral part of multidisciplinary management of schizophrenia regardless of antipsychotic drug exposure.

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Introduction:

Prevalence of Diabetes Mellitus is four to five times higher among people with schizophrenia than the general population (1). Those, who suffer from both diabetes and schizophrenia, have 3-4 fold higher overall mortality rates than general population, and at least one-third of those deaths can be attributed to diabetes (2). Diabetes contributes to excessive cardiovascular deaths and more than 20 years of reduced life expectancy in people with schizophrenia (3,4). Young people with schizophrenia, aged less than 40 years, are at high risk (5) for early-onset type-2 diabetes that is a rapidly progressing severe disease subtype with increased risks for microvascular and macrovascular complications (4,6-8).

Studies from the pre-neuroleptic era (9) have reported increased prevalence of diabetes, impaired glucose tolerance, and increased insulin resistance in people with schizophrenia (10-12). Abnormal glucose tolerance is more prevalent in antipsychotic naïve people with schizophrenia than among healthy controls, and this association is independent of the effects of Body Mass Index and of poor health habits (13-15). Moreover, increased prevalence of diabetes among the first-degree relatives of people with schizophrenia indicates a potential genetic link between schizophrenia and diabetes (16,17). *TCF7L2* and *IGF2BP2*, two of the most replicated susceptibility genes for type-2 diabetes, have been associated with schizophrenia (18-20). Furthermore, linkage studies, genetic association studies, and pathway analyses have supported shared genetic risks between these two disorders (21-23).

As soon as chlorpromazine was introduced in 1952, there were several reports of its association with diabetes and impaired glucose tolerance (10). After the introduction of second-generation antipsychotic drugs, their association with diabetes has been investigated more

systematically (24-28). A meta-analysis, not including data on aripiprazole, ziprasidone, and amisulpride, has concluded that second-generation antipsychotics confer more risk for diabetes in schizophrenia than first-generation antipsychotic drugs (29). However, a longitudinal study has reported that both second-generation antipsychotics and first-generation antipsychotics increase the risk for diabetes, and that second-generation antipsychotics, as a class, confer significantly less risk for incident diabetes than first-generation antipsychotics (30). Individual first-generation and second-generation antipsychotics may differ widely on their risks for diabetes (30-32). Clozapine may confer higher risk for diabetes than other second-generation antipsychotics (31,33). A recent meta-analysis has reported the incidence of type-2 diabetes in 2-24 year olds, exposed to antipsychotics, as 3.09 (95% CI, 2.35-3.82) per 1000 person-years, and it has added that the risk for early-onset type-2 diabetes was significantly higher in those, who received second-generation antipsychotics prescriptions (34). Dose-response effects (30) and several plausible biological mechanisms (21) indicate a causal association between antipsychotics and diabetes. Antagonism of central and peripheral M₃, H₁, 5HT_{2c}, other serotonergic, and of adrenergic receptors may have direct diabetogenic effects, or can increase the risk of diabetes by indirect mechanisms, such as weight-gain, and reduced insulin sensitivity (21,31,35).

There are several caveats in our current understanding of endogenous and antipsychotic-related risks of diabetes in schizophrenia. Firstly, there has not been any large population-based cohort study investigating endogenous risk for diabetes in antipsychotic naïve people with schizophrenia compared with the general population. Secondly, population-based cohort studies focusing on the risks for early-onset diabetes in young people with schizophrenia are sparse (34). Thirdly, despite a large volume of literature, impact of the first-line therapeutic decision of

choosing between first-generation and second-generation antipsychotics on the antipsychotic-related risk for diabetes in schizophrenia remains uncertain (29,30). Fourthly, previous studies investigating the antipsychotic-related risks for diabetes in schizophrenia have seldom been adjusted for the effects of family history of diabetes and for the dosage of other potentially diabetogenic psychotropic medications (36-38). Hence, this population-based cohort study included all young people (more than 2.7 million), born on 01/01/1977 or later in Denmark, investigated endogenous risk for early-onset diabetes in antipsychotic naïve schizophrenia, and evaluated the antipsychotic-related risks in people with schizophrenia, after adjusting for the effects of potential confounders.

Method:

Study population: This population-based cohort study included people from the Danish Civil Registration System (39), recording data of all Danish citizens since 1968. Each Danish citizen is assigned a unique 10-digit personal identification number at birth. This number is used in all Danish registries enabling unambiguous linkage among them. Danish Civil Registration System provides data on gender, date of birth, date of death, date of migration, and parental identity. Our cohort included all people that were born in Denmark on or after 01/01/1977. They were followed up until 01/01/2013.

People with diabetes: Information on diabetes was derived from the Danish National Patient Register (40), and the Danish National Prescription Registry (41). Danish National Patient Register, established in 1977, collects data on all hospitalisations from non-psychiatric hospitals, including dates of admission and discharge, and discharge diagnoses, coded by the treating physicians according to the International Classification of Diseases (ICD) (8th revision (ICD-8))

(42) until the end of 1993, and 10th revision (ICD-10) (43) thereafter). Since 1995, outpatient visits have also been recorded. We identified all hospital discharge diagnoses of diabetes (ICD-8: 249 (insulin-dependent diabetes (type-1)) and 250 (non-insulin-dependent diabetes (type-2)); and ICD-10: E10 (brittle, juvenile, and ketoacidosis prone diabetes), E11 (adult-onset, maturity-onset, nonketotic, and stable diabetes), E12-14 (malnutrition, other specified and unspecified diabetes), H36.0 (diabetic retinopathy), O24 (diabetes in pregnancy, childbirth and puerperium excluding O24.4 (gestational diabetes))). Both the ICD-8 and ICD-10 do not provide specific codes for late-onset type-1 diabetes in adults or drug-induced diabetes. As people with schizophrenia may develop type-2 diabetes at younger ages than the general population, as well as coding practice of diabetes in the Danish registers indicating more frequent use of unspecified diabetes codes in people with schizophrenia, we examined the complete spectrum of ICD diabetes codes. Although using Danish National Patient Register and Danish National Prescription Registry to identify people with diabetes has proven to be of high quality and almost complete (44,45), we cannot reliably distinguish type-1 and type-2 diabetes using the registers (46,47).

In addition to hospital contacts with diabetes, we identified antidiabetic prescriptions from the Danish National Prescription Registry, because many people with diabetes are treated only in primary care. The Danish National Prescription Registry contains data from 1995 on all prescription drugs, dispensed at all Danish pharmacies, including their Anatomical Therapeutic Chemical (ATC) classification system codes, dispensing dates, drug names, dose units, number of dose units in package, number of sold Daily Defined Doses (DDD) (48), and dispensing pharmacy codes. Antidiabetic drugs are only available by prescription in Denmark, so we identified all prescription redemptions for antidiabetic drugs (ATC-codes: A10). However,

women with polycystic ovary syndrome may be treated with metformin (ATC-code: A10BA02). Thus, to avoid inclusion of these nondiabetic people, we excluded all metformin-prescriptions, redeemed by women aged 20 or more years in this cohort. Onset of diabetes was defined as the date of first admission with diabetes since birth or as the date of the first prescription for an antidiabetic drug since 1995 or later, whatever came first.

People with schizophrenia: Danish Psychiatric Central Research Register (DPCRR) (49) was established as an electronic database in 1969, and has been recording data on all psychiatric admissions since 1969. Diagnoses in DPCRR are coded in accordance with the ICD-8 (42) until the end of 1993, and ICD-10 (43) thereafter. DPCRR includes data on all out-patient visits since 1995. We identified all hospital discharge diagnoses of schizophrenia (ICD-8: 295 (excluding 295.79) and ICD-10: F20). These diagnoses have been validated (50), and have contributed substantially to epidemiological research (49). As Danish National Prescription Registry data has been complete only since 1995, we excluded all people (n=97), who developed schizophrenia before 01/01/1996, to ensure that we had complete psychopharmacological data and at least one year prescription use history of all people with schizophrenia after they had been diagnosed. Hence, we included all incident schizophrenia cases since 01/01/1996.

Exposure to antipsychotics: We traced all oral and depot antipsychotic prescriptions (ATC-codes: N05A, excluding N05AN: lithium) since 1995 using information from the Danish National Prescription Registry (48). The Danish National Prescription Registry is a powerful pharmacoepidemiological tool that provides complete high quality data of all filled prescriptions of antipsychotics, prescribed by various psychiatric departments, general practitioners, or other specialists, after 1995. It does not record the drugs that are dispensed within hospitals. All Danish pharmacies are obliged to register all dispensed prescriptions, and they have a high

economic incentive for completeness of prescription registration, because of the universal reimbursement system of prescription drugs in Denmark. Antipsychotics were subdivided into first-generation antipsychotics, second-generation antipsychotics (ATC-codes: N05AD03, N05AE03-4, N05AH04, N05AL01, N05AL05, N05AX08, and N05AX13), olanzapine, aripiprazole, and clozapine (See eAppendix-1 in the supplemental data).

Covariates of interest: We chose our covariates a priori on the basis of their availability, previous research associating them with diabetes or schizophrenia, and their influence on the prescribing pattern of antipsychotics. From the Danish National Prescription Registry, we identified other potentially diabetogenic psychotropic medications, such as tricyclic (ATC-codes: N06AA) and tetracyclic (ATC-codes: N06AA21, N06AX03, N06AX11) antidepressants (36), and valproate (ATC- code: N03AG01) (37,38). Data on gender, urbanicity, and calendar period were derived from Danish Civil Registration System and Danish National Patient Register (40). Using the parental identity from Danish Civil Registration System, we identified siblings and half-siblings, and linked them to Danish National Patient Register and Danish National Prescription Registry to establish family history of diabetes.

Statistical analyses: We calculated age-specific and gender-specific incidence rates of diabetes and their 95% confidence intervals (95% CI). In order to investigate the endogenous risk for diabetes, we used Cox proportional hazards regression models to compute adjusted hazard ratio for diabetes in antipsychotic naïve people with schizophrenia, compared with antipsychotic naïve people without schizophrenia. Follow-up began on the date of birth and ended on the date of diabetes diagnosis, first prescription of antipsychotics, emigration, death, or on 01/01/2013. The first registered diagnosis of schizophrenia during follow-up was included as a time-dependent

variable. Gender, family history of diabetes, urbanicity, and exposure to valproate and tricyclic or tetracyclic antidepressants were included as covariates.

We assessed antipsychotic-related risk for diabetes by including only people with schizophrenia, who were antipsychotic naive at the time of their diagnosis. We employed Cox proportional hazards regression models estimating adjusted hazard ratio by comparing the rates of diabetes in people with schizophrenia with and without antipsychotics. Follow-up began on the date of first diagnosis of schizophrenia, and ended on the date of diabetes diagnosis, emigration, death, or on 01/01/2013. Age was chosen as the time scale. Our Cox regression model included gender, family history of diabetes, and urbanicity as time-independent covariates, and calendar period, DDD of antipsychotics, DDD of valproate, and DDD of tricyclic or tetracyclic antidepressants as time-varying covariates. Moreover, we estimated Adjusted hazard ratio and their 95% CI comparing the risks for diabetes before and after starting selected antipsychotics in people with schizophrenia. Furthermore, we performed sensitivity analyses following the people until their first type-2 diabetes contact (ICD-8: 250, ICD-10: E11, O24.1, and/or oral antidiabetic drug (ATC-codes: A10B) ignoring any previous contacts due to type-1 diabetes or insulin prescriptions. We tested the proportional hazards assumption by repeating the Cox regression models including the primary independent variable as one of the time-varying covariates, and we did not find any violations. All analyses were performed using the statistical software STATA 13.1 (StataCorp, Texas, USA).

Results:

Population Characteristics: We followed 2,736,510 young people for a total of 49,582,279 person-years. Median duration of follow-up was 18.80 (IQR=16.99) years. Maximum period of

follow-up was 35.96 years, thus the oldest in our cohort was less than 36 years old. A total of 8,945 (0.33%) people developed schizophrenia during follow-up. Mean duration of follow-up after the diagnosis of schizophrenia was 5.07 (SD=4.24) years, and mean duration of follow-up after the first antipsychotic drug prescription was 6.40 (SD=4.34) years. Table 1 presents the sociodemographic, and clinical characteristics of our cohort. People with schizophrenia were significantly more likely to have family history of diabetes than other people ($\chi^2 > 1300$; $p < 0.001$).

Incidence of diabetes: A total of 14,118 (0.52%) people developed diabetes in this cohort (See eFigure 1 in the supplemental data). Age-specific incidence rates of diabetes in people with and without schizophrenia are presented in Table 2 (See eFigure 2 in the supplemental data). Gender-specific incidence rates of diabetes for men and women without schizophrenia were 0.26 (95% CI 0.26-0.27), and 0.30 (95% CI 0.29-0.31) per 1000 person-years, respectively. Gender-specific incidence rates of diabetes for men and women with schizophrenia were 4.02 (95% CI 3.35-4.83), and 4.69 (95% CI 3.81-5.77) per 1000 person-years, respectively.

Endogenous risk for diabetes: Among the people, who have not been exposed to any antipsychotics, 12,976 (0.5%) without schizophrenia, and 11 (0.9%) with schizophrenia developed incident diabetes during our follow-up. Table 3 presents the incidence rates and the Adjusted hazard ratio for diabetes in antipsychotic naïve people with schizophrenia. Family history of diabetes significantly increased the risk of diabetes (Adjusted hazard ratio=3.96; 95% CI 3.82-4.11). People with schizophrenia had higher incidence rates of diabetes, and they had approximately three-fold higher rates (Adjusted hazard ratio=3.07; 95% CI 1.71-5.41) of diabetes, compared with people without schizophrenia, after adjusting for the effects of potential confounders including family history of diabetes.

Antipsychotic-related risks: A total of 4,322 (48.3%) people with schizophrenia were antipsychotic naïve at the time of their diagnosis, and the remaining 4,623 (51.7%) had received an antipsychotic drug, before schizophrenia was diagnosed. A total of 83 (1.9%) people with schizophrenia, who were antipsychotic naïve at diagnosis, developed diabetes during follow-up. Gender-specific incidence rates of diabetes for antipsychotics treated men and women with schizophrenia, were 4.22 (95% CI 3.17-5.62), and 3.33 (95% CI 2.23-4.96) per 1000 person-years, respectively. Table 4 presents the incidence rates and the Adjusted hazard ratio for diabetes in people with schizophrenia comparing their risks before and after starting selected antipsychotics. Rates for diabetes significantly increased by more than three-fold (Adjusted hazard ratio=3.64; 95% CI 1.95-6.82) in people with schizophrenia after starting any antipsychotic, compared with their rates before receiving antipsychotics, while accounting for the effects of potential confounders including family history of diabetes.

First-line treatment with first-generation or second-generation antipsychotics: Compared to the people with schizophrenia, who remained antipsychotic naïve until the end of follow-up, those with schizophrenia, who received either first-generation (Adjusted hazard ratio=3.06; 95% CI 1.32-7.05) or second-generation antipsychotics monotherapy (except clozapine) (Adjusted hazard ratio=3.44; 95% CI 1.73-6.83) as their first-line treatment, had significantly higher antipsychotic-related rates for diabetes after adjusting for the effects of potential confounders including family history of diabetes. The first-line therapeutic decision of choosing between first-generation and second-generation antipsychotics did not make statistically significant difference ($\chi^2=0.13$; $p=0.72$) on the rates for diabetes in people with schizophrenia. We repeated these analyses after excluding olanzapine from the class of second-generation antipsychotics and confirmed earlier findings.

Risks associated with selected antipsychotics: Starting either olanzapine (Adjusted hazard ratio=1.88; 95% CI 1.36-2.59) or aripiprazole (Adjusted hazard ratio=2.35; 95% CI 1.70-3.26) significantly increased the rates of diabetes by almost two-fold in people with schizophrenia, after adjusting for the effects of potential confounders. We repeated these analyses including the duration of antipsychotic treatment before starting either olanzapine (Adjusted hazard ratio=1.91; 95% CI 1.37-2.65) or aripiprazole (Adjusted hazard ratio=1.69; 95% CI 1.19-2.39) in the models, and confirmed earlier findings. Among 861 (9.6%) people with schizophrenia, who received clozapine after their diagnosis, 39 (0.4%) developed incident diabetes after starting clozapine. Treatment with clozapine significantly increased the rate of diabetes by nearly four-fold (Adjusted hazard ratio=3.98; 95% CI 2.77-5.73) in people with schizophrenia, compared with people with schizophrenia not receiving clozapine, after accounting for the potential confounders including the family history of diabetes (See eAppendix 2 in the supplemental data).

Sensitivity analyses: We conducted sensitivity analyses, limited to potential type-2 diabetes diagnoses in this cohort (n=5,488; 0.20%), and confirmed earlier findings of higher rates of diabetes in antipsychotic naive schizophrenia compared with the general population (Adjusted hazard ratio=4.71; 95% CI 2.60-8.51), and increased rate of diabetes after starting any antipsychotic drug in people with schizophrenia (Adjusted hazard ratio=3.79; 95% CI 1.97-7.26) without statistically significant differences between first-generation and second-generation antipsychotics ($\chi^2=0.04$; p=0.85) (See eAppendix-2,3,5 in the supplemental data). We performed more sensitivity analyses after excluding 19 people, who developed diabetes more than 12 months after the last prescription of any antipsychotic, to distinguish direct antipsychotic effects from the potential effects of antipsychotic-related weight-gain. Results of this sensitivity analysis also corroborated our earlier findings. Antipsychotic-related risk for diabetes after starting any

antipsychotic was significantly higher (Adjusted hazard ratio=3.28; 95% CI 1.74-6.17) than the risk in people with schizophrenia, not treated with antipsychotics, and the first-line therapeutic decision of treatment with either first-generation or second-generation antipsychotics monotherapy did not make statistically significant difference ($\chi^2=0.78$; $p=0.38$). Moreover, we performed sensitivity analyses by including women, aged 20 or more years, receiving treatment only with metformin ($n=8,551$). We confirmed our findings of endogenous risk of diabetes in antipsychotic naïve schizophrenia (Adjusted hazard ratio=2.10; 95% CI 1.30-3.38), and increased rate of diabetes after starting any antipsychotic drug in people with schizophrenia (Adjusted hazard ratio=3.56; 95% CI 2.09-6.06) without statistically significant difference ($\chi^2=2.03$; $p=0.15$) between the first-line therapeutic decision of treatment with either first-generation antipsychotics (Adjusted hazard ratio=4.27; 95% CI 2.21-8.27) or second-generation antipsychotics (Adjusted hazard ratio=2.98; 95% CI 1.67-5.32) monotherapy.

Discussion:

This nation-wide population-based cohort study has revealed an increased endogenous risk for diabetes in antipsychotic naïve people with schizophrenia compared with people without schizophrenia. It has confirmed the antipsychotic-related risks for diabetes in people with schizophrenia after adjusting for potential confounders including family history of diabetes. Moreover, it has added evidence that first-line treatments with either first-generation or second-generation antipsychotics do not significantly differ on their antipsychotic-related risks for diabetes. Furthermore, it has documented that the antipsychotic-related rates of diabetes in people with schizophrenia, who had received other antipsychotics, further increased four-fold after starting clozapine. Strengths of this study include the hitherto largest sample size, the hitherto longest follow-up, studying antipsychotic naïve people with schizophrenia, focus on

early-onset diabetes in young people, and statistical adjustments for the effects of family history of diabetes and other potentially diabetogenic medications.

An important limitation of our study is that we could not reliably distinguish between type-1 and type-2 diabetes. Misclassification between type-1 and type-2 diabetes is likely, and a complete classification is not possible on the basis of the information available in Danish national registers (47,51). We can only distinguish between type-1 and type-2 diabetes on the basis of ICD codes and insulin-only therapy potentially indicating type-1 diabetes. Moreover, people with schizophrenia are often diagnosed with ICD-10 codes for unspecified diabetes. However, sensitivity analyses, limited to potential type-2 diabetes, corroborated our findings. A substantial proportion of incident diabetes in young people with schizophrenia is expected to be early-onset type-2 diabetes (52). Early-onset type-2 diabetes can be a distinct severe rapidly progressing disease phenotype (4,7,8). This may limit generalisability of our findings to older people with schizophrenia, but may emphasise their clinical importance. Besides, the possibility of increased surveillance of people with schizophrenia by the health services, and consequent surveillance bias may explain the increased incidence of diabetes in antipsychotic-naive schizophrenia. However, prior evidence suggests that the proportion of undiagnosed diabetes may be higher among people with schizophrenia than the general population (53,54). Moreover, studying a relatively homogenous and predominantly Caucasian population from a single country may limit generalisability of our findings, but this should strengthen their internal validity (55). Other limitations of this study include lack of data on other potential confounders, such as obesity, dyslipidaemia, smoking, other substance abuse, diet, and sedentary life style, lack of data on drugs dispensed within hospitals in Danish National Prescription Registry, and grouping diverse antipsychotics together during our analyses. Controlling for all potential

confounders is not possible in register-based research (56), and such residual confounding could have influenced our results.

High prevalence of endogenous diabetes in antipsychotic naïve people with schizophrenia has been reported in a different Danish cohort (31,33), and our findings have confirmed higher incidence of endogenous diabetes in young people with schizophrenia. In our study, young people with schizophrenia were significantly more likely to have family history of diabetes. This finding indicates familial aggregation and genetic overlap of these two disorders. A recent population-based cross-sectional study from Australia has reported that people with psychosis are at increased risk of diabetes if they have family history of diabetes or if they do not have family history of diabetes but are taking antipsychotics (57). Our results, adjusted for the family history of diabetes, have clarified this misconception, and have established that people with schizophrenia are at increased risk for diabetes regardless of their family history of diabetes, and of antipsychotic drug exposure.

Previous studies have reported that second-generation antipsychotics as a class conferred more risks for diabetes than first-generation antipsychotics (29). However, evidence to the contrary also exists (30). Our findings have added important evidence to this debate. Similarly, aripiprazole has been reported either lowering (31) or increasing (58) the risk for diabetes in schizophrenia. Our findings did not support the protective effect of aripiprazole, but documented its risk for diabetes. There is a possibility that aripiprazole and first-generation antipsychotics might have been prescribed more often for diabetes-prone people with schizophrenia, and such channelling bias might have influenced pertinent findings. Similarly, olanzapine might have been prescribed more often for people, perceived to be less prone for diabetes, by their treating clinicians, and this could have underestimated the associated risks. Considering the diabetogenic

potential of olanzapine, a three-phased algorithm for antipsychotic treatment limiting use of olanzapine only as a second-line antipsychotic agent has been proposed (33). First-line treatment with second-generation antipsychotics including olanzapine did not differ significantly from first-generation antipsychotics on their risks for diabetes in this cohort. Olanzapine has not been a second-line antipsychotic in many countries including Denmark at the time of this cohort, and it is currently recommended as a first-line antipsychotic for schizophrenia by many national (59) and international (60) guidelines. Our findings have not added evidence to change the prevailing guidelines regarding prescription of olanzapine in schizophrenia. However, they confirmed the substantial increase in the risks for diabetes by starting clozapine in people with schizophrenia.

Shared genetic factors, negative symptoms, substance abuse, and unhealthy lifestyle in schizophrenia may contribute to its endogenous risk for diabetes. Future studies should focus on underlying biological mechanisms connecting these two disorders, and on potential preventive interventions. Further studies investigating antipsychotic-related risks of individual antipsychotics and of their polypharmacy (30,61) for diabetes in people with schizophrenia are warranted. Antipsychotic-related risk for diabetes is often discussed as one of the many factors during the therapeutic decision making process of choosing an antipsychotic agent in psychiatric clinics. Combined endogenous and antipsychotic-related risks for diabetes in schizophrenia mandate more attention. Psychiatric services should either develop specific protocols or closely collaborate with primary care facilities to screen for diabetes among people with schizophrenia in community. Promoting healthy life style, early detection by regular, at least yearly, screening and effective treatment of diabetes should be an integral part of multidisciplinary management of schizophrenia.

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Table 1: Sociodemographic and clinical profile of people with (n=8,945) and without (n=2,727,565) schizophrenia

Characteristic	Without schizophrenia		With schizophrenia	
	n	%	n	%
Gender				
Men	1,384,625	50.8	5,342	59.7
Women	1,342,940	49.2	3,603	40.3
Urbanicity				
Copenhagen ^a	553,452	20.3	2,176	24.3
Other cities ^b	254,497	9.3	944	10.6
Towns ^c	678,502	24.9	2,506	28.0
Rural areas	1,241,114	45.5	3,319	37.1
Family history of Diabetes	202,500	7.4	1,537	17.2
Incident Diabetes Mellitus	13,915	0.5	203	2.3
Exposure to antipsychotics				
First-generation antipsychotics	34,691	1.3	5,050	56.5
Second-generation antipsychotics ^d	26,887	1.0	6,291	70.3
Olanzapine	7,475	0.3	3,613	40.4
Aripiprazole	5,479	0.2	3,511	39.3
Clozapine	65	0.002	912	10.2
Being antipsychotic naïve ^e	2,673,114	98.0	1,154	12.9

Exposure to antidepressants ^f	51,803	1.9	2,296	25.7
Exposure to valproate	12,757	0.5	524	5.9

^a Living in the capital city, Copenhagen, and its suburbs; ^b Living in other cities with more than 100,000 population; ^c Living in towns with population between 10,000 and 100,000; ^d Second Generation Antipsychotic drugs excluding olanzapine, aripiprazole, and clozapine; ^e People, who have not received any antipsychotic medications until the end of their follow-up; ^f Exposure to tricyclic or tetracyclic antidepressants.

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Table 2: Age-specific incidence rates of diabetes mellitus in people with (n=8,945) and without (n=2,727,565) schizophrenia

Age group (years)	People without schizophrenia				People with schizophrenia				mid-p ^b
	Person-years (millions)	Incident diabetes (n)	Incidence rates ^a	95% CI	Person-years	Incident diabetes (n)	Incidence rates ^a	95% CI	
0-9	23.66	3,449	0.15	0.14-0.15	29.12	0	0.00	-	0.99
10-14	9.16	2,654	0.29	0.28-0.30	269.44	0	0.00	-	0.93
15-19	7.34	2,462	0.33	0.32-0.35	4,824.17	13	2.69	1.56-4.64	<0.001
20-24	5.15	1,776	0.35	0.33-0.36	16,263.53	59	3.63	2.81-4.68	<0.001
25-29	2.98	2,100	0.70	0.67-0.75	16,941.88	75	4.43	3.53-5.55	<0.001
30-36	1.24	1,474	1.18	1.12-1.25	8,987.59	56	6.23	4.80-8.10	<0.001
0-36	49.53	13,915	0.28	0.28-0.29	47,315.73	203	4.29	3.74-4.92	<0.001

^a Incidence rates of diabetes mellitus per 1000 person-years; ^b Two-side exact significance comparing the incidence rates

Table 3: Endogenous risk for diabetes Mellitus in antipsychotic naive people with schizophrenia

	Incidence rates ^a	95% CI ^a	Adjusted hazard ratio	95% CI	Number Needed to Harm ^b	95% CI ^b	p-value
Follow-up censored at first antipsychotic prescription ^c							
People without schizophrenia (N=2,736,510) ^d	0.27	0.27-0.28	1.00	Reference			-
People with schizophrenia (n=4,322)	1.84	1.05-5.15	2.92 ^e	1.66-5.15 ^e	1931 ^e	894-5614 ^e	<0.001
People with schizophrenia (n=4,322)	1.84	1.05-5.15	3.07 ^f	1.71-5.41 ^f	1791 ^f	841-5219 ^f	<0.001
No use of antipsychotics during the entire follow-up ^g							
People without schizophrenia (n=2,673,114)	0.27	0.27-0.28	1.00	Reference			-
People with schizophrenia (n=1,154)	2.18	1.09-4.36	3.18 ^e	1.59-6.36 ^e	1700 ^e	692-6280 ^e	0.001
People with schizophrenia (n=1,154)	2.18	1.09-4.36	2.98 ^f	1.49-5.95 ^f	1872 ^f	749-7562 ^f	0.002

^a Incidence rates of diabetes mellitus per 1000 person-years; ^b Number needed to harm in person years; ^c Data were censored at the earliest date among the following, date of diagnosis of diabetes, date of starting any antipsychotic medication, date of death, date of emigration from Denmark, and the end of follow-up on 1st January, 2013; ^d Assuming that the people with schizophrenia were at risk for diabetes after the diagnosis of schizophrenia, analyses were carried out with reference groups including data of people without schizophrenia, and of antipsychotic naive people with schizophrenia before the diagnosis of schizophrenia; ^e adjusted for the effects of gender, family history of diabetes, and urbanicity; ^f Adjusted for the effects of gender, family history of diabetes, urbanicity, exposure to valproate, and exposure to tricyclic or tetracyclic antidepressants; ^g Endogenous risk for diabetes in people with schizophrenia, who remained antipsychotic naive until the end of follow-up, was evaluated with reference to people without schizophrenia, who have not been exposed to any antipsychotics. Mean duration of follow-up after the diagnosis of schizophrenia was 3.18 (SD=3.53) years in people with schizophrenia, who remained antipsychotic naive until the end of follow-up.

Table 4: Antipsychotic-related incidence rates, adjusted hazard ratios and number needed to harm for Diabetes Mellitus in people with schizophrenia

	Incidence rates^a	95% CI^a	Adjusted hazard ratio^b	95% CI^b	Number Needed to Harm^c	95% CI^c	p-value
Risks with starting any antipsychotics							
Before starting any antipsychotic medication (n=4,322) ^d	1.69	0.94-3.05	1.00	Reference	-	-	-
After starting any antipsychotic medication (n=3,168)	3.93	3.12-4.95	3.64	1.95-6.82	226	103-625	<0.001
After first-line treatment with a first-generation antipsychotic (n=450)	3.92	2.23-6.91	3.06	1.32-7.05	289	99-1853	0.009
After first-line treatment with a second-generation antipsychotic (n=1,708) ^e	3.50	2.42-5.07	3.82	1.81-8.09	211	85-733	<0.001
After first-line treatment with a second-	3.36	2.48-4.57	3.44	1.73-6.83	244	103-813	<0.001

generation antipsychotic (n=2,311) ^f							
Risks with starting olanzapine							
Before starting olanzapine (n=7,652) ^g	3.82	3.16-4.63	1.00	Reference	-	-	-
After starting olanzapine (n=2,115)	5.13	4.01-6.55	1.88	1.36-2.59	300	166-731	<0.001
Risks with starting aripiprazole							
Before starting aripiprazole (n=8,358) ^h	3.70	3.11-4.41	1.00	Reference	-	-	-
After starting aripiprazole (n=2,719)	5.32	4.13-6.87	2.35	1.70-3.26	202	121-389	<0.001
Risks with starting clozapine							
Before starting clozapine (n=8,890) ⁱ	3.78	3.24-4.41	1.00	Reference	-	-	-
After starting clozapine (n=862)	8.81	6.44-12.06	3.98	2.77-5.73	90	57-151	<0.001

^a Incidence rates of diabetes mellitus per 1000 person-years; ^b Adjusted hazard ratios that were estimated by cox proportional hazard regression models. These models included gender, family history of diabetes, and urbanicity as time-independent covariates, and calendar period, Defined Daily Doses (DDD) of antipsychotics, DDD of valproate, and DDD of tricyclic or tetracyclic antidepressants as time-dependent covariates; ^c Number needed to harm in person years; ^d People with schizophrenia, who were antipsychotic naïve at the time of diagnosis of schizophrenia; ^e Starting monotherapy with all second-generation antipsychotics except Olanzapine and Clozapine; ^f Starting monotherapy with all second-generation antipsychotics except Clozapine; ^g People with schizophrenia, who had received olanzapine before their diagnosis of schizophrenia, were excluded from this analysis; ^h People with schizophrenia, who had received aripiprazole before their diagnosis of schizophrenia, were excluded from this analysis; ⁱ People with schizophrenia, who had received clozapine before their diagnosis of schizophrenia, were excluded from this analysis.