Predictors of type 2 diabetes in a nationally representative sample of adults with psychosis

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Antipsychotic drugs such as clozapine and olanzapine are associated with an increased risk for type 2 diabetes, but relatively little is known about the relationship between risk factors for type 2 diabetes established in the general population and type 2 diabetes in people with psychosis. We estimated the prevalence of established risk factors and their association with type 2 diabetes in a nationally representative sample of people with an ICD-10 psychosis (N=1642) who gave a fasting blood sample (N=1155). Logistic regression was used to summarize associations adjusted for age and sex. In this sample, whose mean duration of psychosis was 14.7 years, 12.1% (13.1% of women and 11.5% of men) had type 2 diabetes at age 18–64 years based on current fasting blood glucose levels or treatment with a hypoglycaemic drug. Risk was greatly increased in young adults compared with the general population and peaked in middle age. Risk factors in the general population were common in people with psychosis and strongly associated with type 2 diabetes in those people. Treatment with clozapine was associated with an increased risk and treatment with olanzapine with a decreased risk for type 2 diabetes. The development of diabetes or pre-diabetes may therefore influence the likelihood of treatment with olanzapine over time. The strongest predictors of type 2 diabetes in a multivariate model were a body mass index of at least 40 and treated hypercholesterolemia, followed by a body mass index between 35 and 39.9, a family history of diabetes and treated hypertension. There was minimal to no confounding of the association between type 2 diabetes and current clozapine or olanzapine treatment, but neither association remained significant after adjustment for other predictors. Longitudinal relationships among predictors are likely to be complex, and previous antipsychotic drug treatment may at least partly explain risks associated with severe obesity, dyslipidemia and hypertension. A focus on weight loss is warranted in people with psychosis, but prevention strategies for type 2 diabetes should be broadened to include those with emerging dyslipidemia, hypertension and a family history of diabetes.

Key words: Type 2 diabetes, psychosis, risk factors, clozapine, olanzapine, body mass index, hypercholesterolemia, hypertension

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The co-occurrence of diabetes and schizophrenia has been noted for over a century (1,2). A recent analysis of this comorbidity using prospectively collected Danish population registry data provided strong evidence that there is an increased risk for type 2 diabetes in people with schizophrenia both before (3) and especially after exposure to antipsychotic drugs (4).

Among those taking the commonly prescribed second generation antipsychotic drugs, the risk of developing type 2 diabetes during the first 6 years is greatest for clozapine and olanzapine. The former is used in many parts of the world for treatment-resistant cases of schizophrenia (5), while the latter is one of the most commonly prescribed antipsychotic drugs (6).

The increased risk for type 2 diabetes in association with antipsychotic drug treatment and interventions directed at related weight gain have deservedly received substantial attention (7–13). Much less attention has been paid to other risk factors which contribute to the context within which treatment effects are expressed.

Type 2 diabetes in the general population is a complex multifactorial disease (14). Established risk factors include increasing age, obesity, sedentary lifestyle, diet, family history,

hypertension, elevated cholesterol and gestational diabetes (15). The interpretation of the observed association between antipsychotic drug treatment and risk for type 2 diabetes has been queried in the past because established risk factors have not been controlled for and may therefore be an important source of unmeasured confounding (16,17). The above-mentioned Danish study (4), for example, could control for only age, sex, blood pressure medication and cholesterol medication.

The importance of risk factors for type 2 diabetes established in the general population has not yet been explored in a large representative cohort of adults with psychosis, and we therefore do not know which factors should be tested as potential confounders of the observed association between type 2 diabetes and antipsychotic drug treatment. The aims of this study were: a) to estimate the prevalence, in a national sample of adults with psychosis, of the risk factors for type 2 diabetes established in the general population; b) to estimate the association of those factors with type 2 diabetes in the above-mentioned sample and c) to test if they confound the observed cross-sectional association between type 2 diabetes and treatment with clozapine or olanzapine.

Table 1 The prevalence of current type 2 diabetes by age and gender in a national sample of adults with psychosis

Age	Total (N=1155) % (95% CI)	Women (N=444) % (95% CI)	Men (N=711) % (95% CI)
18-24	5.8 (2.8-11.5)	5.3 (1.5-17.3)	6.0 (2.6-13.3)
25-34	7.1 (4.9-10.2)	9.0 (5.1-15.4)	6.1 (3.7-9.8)
35-44	11.7 (8.6-15.7)	13.3 (8.6-20.1)	10.4 (6.8-15.7)
45-54	21.3 (16.6-26.9)	19.2 (12.6-28.0)	22.8 (16.7-30.2)
55-64	17.1 (11.1-25.5)	16.0 (8.3-28.5)	18.2 (10.2-30.3)
18-64	12.1 (10.4-14.1)	13.1 (10.2-16.5)	11.5 (9.4-14.1)

METHODS

The Australian National Survey of Psychosis is a population-based cross-sectional study with a target population defined by psychosis, place of residence, age 18-64 years and contact with public mental health services or relevant non-government organizations (18). The study was conducted in 2010 at seven sites across the five mainland Australian states. The research protocol for the study was approved by relevant institutional ethics committees and all participants gave written informed consent.

Data analysed here are for participants with a diagnosis of non-organic psychosis (N=1642) who also gave a fasting blood sample (N=1155). This subset of the cohort comprised individuals with schizophrenia (51.2%, 591/1155); bipolar disorder with psychotic features (19.5%, 225/1155); schizoaffective disorder (18.2%, 210/1155); depressive psychosis (5.5%, 63/1155) and delusional disorders or other non-organic psychoses (5.7%, 66/1155).

The Diagnostic Interview for Psychosis (19) was used to diagnose psychosis following the ICD-10. Mean duration of illness was estimated by self-report. Current type 2 diabetes was diagnosed, according to the American Diabetes Association (20), on the basis of a current fasting blood glucose of at least 7.0 mmol/L or a current drug treatment for hyperglycaemia. Our diagnosis of type 2 diabetes did not include an oral glucose tolerance test, which is difficult to obtain in people with psychosis.

Central obesity was defined as a waist circumference of at least 94 cm in men or 80 cm in women. Obesity was subdivided into class I (a body mass index of at least 30 but lower than 35), class II (a body mass index of at least 35 but lower than 40) and class III (a body mass index of at least 40). Dietary adequacy was estimated by the number of servings of fruit and vegetables consumed daily in the past week (those consuming at least two serves of fruit and five serves of vegetables were coded as having an adequate intake). The level and frequency of physical activity during the previous week was assessed using the International Physical Activity Questionnaire (21), and defined as a four-category variable (1 – any level of vigorous activity, at least once for at least 10 consecutive minutes; 2 – any level of moderate activity, at least once for at least 10 consecutive minutes; 3 – any walk-

ing, at least once for at least 10 consecutive minutes; 4 – no activity, i.e., not 1 or 2 or 3). Family history of diabetes in first-degree relatives was assessed by self-report.

Current prescribed medication use during the past four weeks was recorded based on participant report, with inspection of pill bottles or medication chart review for those in hospital at the time of interview. Current antipsychotic drug treatment was coded as a four category variable (1 – clozapine but not olanzapine; 2 – olanzapine but not clozapine; 3 – clozapine and olanzapine; 4 – anything else, i.e., any other antipsychotic drug treatment or no antipsychotic drug treatment).

The 95% confidence interval for the estimated prevalence of type 2 diabetes was calculated using STATA version 12.1 (22). All other data analysis was conducted using SPSS Version 21 (23). Logistic regression was used to estimate associations with type 2 diabetes. Univariate and multivariate odds ratios were adjusted for age (because risk for type 2 diabetes increases with age in the general population, and our cohort varied in age between 18 and 64 years) and for gender (because men are at slightly greater risk than women in the general population, and in our cohort there was an unequal sex ratio). Sex differences in the prevalence of risk factors were assessed using a two-tailed Pearson chi-square test. Sex differences in the association of risk factors with type 2 diabetes were assessed by the Wald test. Bias associated with giving a fasting blood sample was assessed by comparing those who gave a sample with those who declined using a two-tailed Pearson chi-square test.

RESULTS

Among the subsample of participants with an ICD-10 diagnosis of psychosis who gave a fasting blood sample (N=1155/1642), 61.6% (711/1155) were male and 38.4% (444/1155) were female. Their mean age was 38.4±11.0 years (range=18–64 years) and their mean duration of psychotic illness was 14.7±10.2 years (range=0-50 years).

One hundred and forty patients (12.1%) met the American Diabetes Association's criteria for type 2 diabetes based on current fasting blood glucose levels or current hypoglycaemic drug treatment (Table 1). The prevalence of type 2 diabetes was non-significantly higher in women (13.1%, 58/444) than in men (11.5%, 82/711) ($\chi^2=0.67$, $p=0.45$). The prevalence was 5.8% and 7.1%, respectively, among people aged 18–24 and 25–34 years, while it was 0.3% in people aged 25–34 years in the latest Australian general population survey (24). The prevalence increased with age, with a peak (21.3%) among people aged 45–54 years (Table 1).

In the univariate analysis, after adjustment for age and gender, the risk for type 2 diabetes was significantly increased in association with class I-III obesity, central obesity, treated hypercholesterolemia, treated hypertension, family history of diabetes and current treatment with clozapine (Table 2). The risk was significantly decreased in association with at least

Table 2 Univariate associations between risk factors for type 2 diabetes established in the general population and current type 2 diabetes in adults with psychosis

Risk factor	Assessed by	Total sample (N=1155)				Women (N=444)				Men (N=711)			
		%	OR	95% CI	p	%	OR	95% CI	p	%	OR	95% CI	p
Obesity	Overweight	30.2	1.38	0.61-3.09	0.43	24.1	3.36	0.70-16.14	0.12	34.0	0.90	0.34-2.39	0.84
	Obese, class I	23.4	2.76	1.27-5.99	0.01	22.5	3.15	0.64-15.39	0.15	24.0	2.66	1.08-6.52	0.03
	Obese, class II	13.0	7.28	3.34-15.86	0.0001	16.0	10.40	2.29-47.72	0.003	11.1	6.30	2.48-16.03	0.0001
	Obese, class III	11.7	10.15	4.64-22.18	0.0001	17.6	13.77	3.06-61.84	0.001	8.1	9.34	3.56-24.44	0.0001
	<i>Reference: normal weight</i>	20.3				18.5				21.3			
	Waist ≥ 84 (female), ≥ 90 (male)	83.8	2.86	1.35-6.04	0.006	93.7	*	*	*	77.7	2.32	1.08-4.98	0.03
	<i>Reference: normal waist circumference</i>	16.2				6.3				22.3			
Sedentary lifestyle	Any vigorous activity past week (10+ min)	21.7	0.39	0.18-0.83	0.015	17.8	0.49	0.16-1.47	0.20	24.2	0.34	0.12-0.95	0.04
	Any moderate activity past week (10+ min)	20.6	0.70	0.37-1.32	0.27	20.5	0.59	0.22-1.58	0.59	20.7	0.77	0.33-1.79	0.55
	Any walking past week (10+ min)	46.2	1.03	0.61-1.76	0.89	48.6	0.93	0.42-2.04	0.93	44.7	1.12	0.54-2.31	0.75
	<i>Reference: none of the above</i>	11.4				13.1				10.4			
Diet	2+ serves of fruit and 5+ serves of vegetables daily	6.2	1.29	0.65-2.57	0.45	9.0	1.19	0.47-3.01	0.70	4.4	1.43	0.51-3.95	0.48
	<i>Reference: less than the above</i>	93.8				91.0				95.6			
Family history	Self report in first degree relatives	37.3	2.76	1.88-4.03	0.0001	48.1	4.67	2.36-9.23	0.0001	30.5	2.04	1.26-3.30	0.004
	<i>Reference: no reported history</i>	62.7				51.9				69.5			
High blood pressure	Treated with an antihypertensive drug	11.0	3.23	2.04-5.11	0.0001	11.7	3.40	1.65-7.00	0.001	10.5	3.18	1.75-5.76	0.0001
	<i>Reference: no current antihypertensive treatment</i>	89.0				88.3				89.5			
High cholesterol	Treated with a lipid regulating drug	12.6	5.88	3.87-8.92	0.0001	13.3	7.85	4.06-15.15	0.0001	12.1	4.86	2.81-8.40	0.0001
	<i>Reference: no current lipid regulating treatment</i>	87.4				86.7				87.9			
Antipsychotic drugs	Clozapine, not olanzapine	17.7	1.56	1.00-2.43	0.048	13.3	1.71	0.83-3.52	0.14	20.4	1.51	0.86-2.65	0.14
	Olanzapine, not clozapine	18.1	0.51	0.28-0.91	0.02	15.3	0.55	0.21-1.47	0.55	20.8	0.48	0.23-0.99	0.049
	Clozapine + olanzapine	0.6	3.09	0.58-16.45	0.18	0.9	**	**	**	0.4	12.70	1.10-146.13	0.041
	<i>Reference: neither clozapine nor olanzapine</i>	63.6				71.4				58.8			
Male gender	<i>Reference: female</i>	61.6	0.97	0.67-1.42	0.90	-	-	-	-	-	-	-	-

Odds ratio for male gender in the total sample is adjusted for age, all other odds ratios in the total sample are adjusted for age and sex; odds ratios in females and males are adjusted for age

*Odds ratio could not be estimated because 100% of women with psychosis and type 2 diabetes had an at-risk waist circumference; **odds ratio could not be estimated because no woman with type 2 diabetes was taking clozapine and olanzapine

10 minutes per week of vigorous physical activity and with current treatment with olanzapine (Table 2).

In the multivariate analysis, after adjustment for age and gender, and all other predictors, the risk for type 2 diabetes was significantly increased in association with class II-III obesity, treated hypercholesterolemia, treated hypertension and family history of diabetes (Table 3). After adjustment for

the additive effects of other predictors, the association with treated hypertension and obesity was attenuated by 40–50% and the association with family history of diabetes and treated hypercholesterolemia was attenuated by 20–30%. The estimated associations with use of clozapine and olanzapine were reduced marginally in the total sample, but a little more in men treated with olanzapine or olanzapine plus

Table 3 Multivariate associations between risk factors for type 2 diabetes established in the general population and current type 2 diabetes in adults with psychosis adjusted for age and sex

Risk factor	Assessed by	Total sample (N=1155)			Women (N=444)			Men (N=711)		
		OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Obesity	Overweight	1.12	0.43-2.90	0.80	2.51	0.48-13.10	0.27	0.75	0.22-2.53	0.64
	Obese, class I	1.75	0.65-4.66	0.26	1.62	0.29-8.86	0.57	1.80	0.50-6.47	0.36
	Obese, class II	3.74	1.39-10.10	0.009	4.96	0.97-25.34	0.054	3.40	0.91-12.72	0.069
	Obese, class III	5.49	2.06-14.62	0.001	5.23	1.06-25.78	0.042	6.55	1.74-24.65	0.005
	<i>Reference: normal weight</i>									
	Waist ≥ 84 (female), ≥ 90 (male)	0.97	0.34-2.71	0.95	*	*	*	0.82	0.25-2.75	0.76
	<i>Reference: normal waist circumference</i>									
Sedentary lifestyle	Any vigorous activity past week (10+ min)	0.51	0.21-1.23	0.13	0.38	0.08-1.67	0.20	0.67	0.22-2.04	0.48
	Any moderate activity past week (10+ min)	0.83	0.39-1.74	0.62	0.67	0.20-2.27	0.52	0.96	0.36-2.53	0.94
	Any walking past week (10+ min)	1.08	0.58-2.02	0.79	0.90	0.33-2.42	0.83	1.24	0.54-2.84	0.61
	<i>Reference: none of the above</i>									
Diet	2+ serves of fruit and 5+ serves of vegetables daily	0.93	0.40-2.15	0.86	0.65	0.19-2.14	0.48			
	<i>Reference: less than the above</i>									
Family history	Self report in first degree relatives	2.22	1.44-3.44	<0.0001	2.56	1.17-5.59	0.018	1.99	1.14-3.46	0.015
	<i>Reference: no reported history</i>									
High blood pressure	Treated with an antihypertensive drug	1.87	1.08-3.26	0.025	2.23	0.91-5.48	0.08	1.68	0.81-3.47	0.16
	<i>Reference: no current antihypertensive treatment</i>									
High cholesterol	Treated with a lipid regulating drug	4.26	2.64-6.85	<0.0001	6.10	2.79-13.31	<0.0001	3.89	2.03-7.44	<0.0001
	<i>Reference: no current lipid regulating treatment</i>									
Antipsychotic drugs	Clozapine, not olanzapine	1.52	0.91-2.54	0.10	1.50	0.63-3.56	0.33	1.64	0.84-3.17	0.14
	Olanzapine, not clozapine	0.55	0.28-1.08	0.08	0.28	0.07-1.04	0.062	0.72	0.32-1.60	0.42
	Clozapine + olanzapine	2.73	0.39-18.78	0.30	**	**	**	7.46	0.55-99.86	0.13
	<i>Reference: neither clozapine nor olanzapine</i>									
Male gender	<i>Reference: female</i>	1.66	1.05-2.64	0.03	-	-	-	-	-	-

In the total sample male gender was significantly associated with risk for type 2 diabetes after adjustment for all other risk factors (OR=1.66, 95% CI: 1.04-2.64, p=0.03), as was age (OR=1.028, 95% CI: 1.006-1.051, p=0.013)

*Odds ratio could not estimated because 100% of women with psychosis and type 2 diabetes had an at-risk waist circumference waist circumference; **odds ratio could not be estimated because no woman with type 2 diabetes was taking clozapine and olanzapine

clozapine. Current treatment with clozapine and olanzapine was not significantly associated with type 2 diabetes in the multivariate model, neither was central obesity nor physical activity. The strongest predictors of current type 2 diabetes in the multivariate model were a body mass index of at least 40 (adjusted OR=5.5) and treated hypercholesterolemia (adjusted OR=4.3). This was true for the total sample as well as for men and women considered separately.

Severe obesity, low levels of physical activity and a positive family history of diabetes were all more common in women than men (Table 4). Current treatment with clozapine or olanzapine was more common in men than women (Table 4). The prevalence of treated hypercholesterolemia and treated hypertension did not vary by gender. Male gender was not significantly associated with risk for type 2 diabetes (Table 2) until after adjustment for all other predictors

Table 4 Sex differences in the prevalence of risk factors for type 2 diabetes established in the general population and their association with current type 2 diabetes in adults with psychosis

Risk factor	Assessed by	Test for sex difference in prevalence of risk factor	Test for sex difference in association with type 2 diabetes (adjusted for age)
		Pearson chi-square	Wald test
General obesity	Obese class I, II, III, over, normal and underweight	42.06 (df=5), $p<0.0001$, $F>M$	3.88 (df=5), $p=0.56$
Central obesity	Waist circumference at-risk vs. not at-risk	63.91 (df=1), $p<0.0001$, $F>M$	0.00 (df=1), $p=0.99$
Sedentary lifestyle	Any vigorous act, moderate act, walking, none of these	8.19 (df=3), $p=0.042$, $F>M$	1.09 (df=3), $p=0.77$
Diet	2+ fruit and 5+ vegetable servings daily	10.08 (df=1), $p=0.002$, $M>F$	1.20 (df=1), $p=0.78$
Family history	Self report in first degree relatives, yes or no	33.03 (df=1), $p<0.0001$, $F>M$	4.01 (df=1), $p=0.045$, $F>M$
Hypertension	Currently treated with an antihypertensive drug or not	0.92 (df=1), $p=0.34$	0.09 (df=1), $p=0.76$
High cholesterol	Currently treated with a lipid regulating drug or not	0.58 (df=1), $p=0.46$	0.60 (df=1), $p=0.43$
Antipsychotic drugs	Currently treated with clozapine or not	23.06 (df=1), $p<0.0001$, $M>F$	0.01 (df=1), $p=0.89$
	Currently treated with olanzapine or not	7.89 (df=1), $p=0.005$, $M>F$	0.04 (df=1), $p=0.83$

(Table 3). The association between type 2 diabetes and a family history of diabetes was significantly stronger in women than men (Table 2), but this difference was attenuated after adjustment for other predictors (Table 3).

The prevalence of the risk factors for type 2 diabetes did not differ between those who gave a fasting blood sample and those who did not.

DISCUSSION

Young adults with psychosis in the current survey had a greatly elevated prevalence of type 2 diabetes relative to the general population (24). Current guidelines and recommendations for general practitioners note that people at high risk for undiagnosed type 2 diabetes should be screened, including those taking antipsychotic drugs (25), but do not emphasize that screening in those with psychosis should begin at the earliest possible age. The recently promulgated Healthy Active Lives statement, an international consensus statement on improving the physical health of young people with psychosis, advocates assessment of diabetes risk within one month of antipsychotic drug treatment (26). Assessment prior to antipsychotic drug treatment is desirable to capture baseline risk status, but difficult to obtain when clients are first seeking treatment for acute psychosis.

The peak prevalence of type 2 diabetes in people with psychosis was observed at 45-54 years of age. The adverse consequences for cardiovascular morbidity and mortality may therefore be most evident after that peak, consistent with previous reports of elevated mortality associated with coronary heart disease relatively early in life (27).

Increasing age, obesity, sedentary lifestyle, family history of diabetes, treated hypertension and treated hypercholes-

terolemia were all associated with current type 2 diabetes in our sample of people with psychosis. A body mass index of at least 40 and treated hypercholesterolemia were the strongest predictors of current type 2 diabetes after adjustment for all other predictors. Age, male gender (after adjustment for the other risk factors), treated hypertension and family history of diabetes were also associated with an elevated risk in a multivariate model. The 6-fold increased risk of type 2 diabetes in association with treated hypercholesterolemia, 4-fold after adjustment for other predictors, was much higher than the 1.09-fold elevated risk associated with any statin use in the general population in a recent meta-analysis (28).

Obesity has been emphasized as a potent risk factor for diabetes. Reducing body weight is also a major focus of efforts to improve the physical health of those with serious mental illness (29). A body mass index of at least 40 is associated with a 7-fold increased risk of diabetes in the general population (30), while it was associated with a 9-fold increased risk in men with psychosis, and a 14-fold increased risk in women with psychosis.

Individuals with psychosis are known to lead extremely sedentary lives (31), but even a very low level of self-rated recent vigorous activity was associated with a significantly lower risk of current type 2 diabetes before adjustment for other predictors. This is encouraging for those struggling to develop interventions that reconcile national guidelines with self-rated "best" activity levels in those with psychosis. More work needs to be done to identify the minimum level of regular vigorous exercise required to significantly and persistently lower risk for type 2 diabetes in people with psychosis, given other risk factors.

The risk of type 2 diabetes is typically elevated 2- to 4-fold in association with a positive family history, depending on

the strength of that history (32), and this is exactly what we observed in people with psychosis.

Men are at slightly greater risk for type 2 diabetes in the general community (24), but a significant effect of male gender on risk for type 2 diabetes in people with psychosis was not observed until after adjustment for sex differences in the prevalence of other predictors. This underscores the very high prevalence of risk factors among women with psychosis.

Clozapine and olanzapine have been associated with an increased risk for type 2 diabetes (4,33), but the development of type 2 diabetes may also influence which antipsychotic drugs are prescribed over time (34,35). In our cross-sectional observational survey, current treatment with clozapine was associated with an elevated risk, while current treatment with olanzapine was associated with a lower risk, relative to the rest of the sample. Physicians may have taken some of their patients with diabetes or pre-diabetes off olanzapine because they know it is associated with diabetes; that risk has been well publicized. Clozapine is used in Australia only for those who are deemed treatment resistant, and physicians may be unlikely to take their diabetic patients off clozapine, because this is not recommended (36). Current clozapine and olanzapine treatment was not significantly associated with current type 2 diabetes after adjustment for other predictors.

Antipsychotic drug treatment has been shown to be associated with weight gain and adverse changes in blood lipids in experimental studies (37). These changes begin shortly after first exposure to those drugs (38) and accrue over time (39). Some of the risk associated with current body weight and current treated hypercholesterolemia will therefore be attributable to past antipsychotic drug treatment, which we could not model, and some may be due to other causes (e.g., lifestyle, genetics). Only prospective longitudinal studies, from the point of first exposure to antipsychotic drugs, could disentangle these effects over time. We can, however, identify a list of variables that should be examined in such models, and which may also confound some published estimates of the association between antipsychotic drugs and risk for type 2 diabetes: male gender, age, severity of obesity, treated hypercholesterolemia, treated hypertension, family history of diabetes, physical inactivity and psychosis. Static adjusted odds ratios may not do justice to the complexity of the longitudinal inter-relationships among these factors. Further work is required to disentangle the architecture of risk for type 2 diabetes in people with psychosis, and to identify the most fruitful targets for intervention.

Our diagnosis of type 2 diabetes did not include cases defined on the basis of glucose tolerance testing and therefore underestimates the true prevalence of type 2 diabetes. These missing cases are important to identify in future surveys, because they are at greatest risk of early death in the general population (40). Furthermore, our survey did not record birth weight, gestational diabetes or maternal gestational diabetes, and we therefore could not estimate the effect of the intrauterine environment or diabetes in pregnancy on risk. Risk for type 2 diabetes that is associated

with low birth weight is exacerbated in those in the general population who experience excess and rapid weight gain in early adulthood, and that weight gain is associated with an earlier onset of type 2 diabetes (14). People with psychosis often experience excess and rapid weight gain in early adulthood in association with the onset of psychosis and antipsychotic drug treatment. The relationship between birth weight, excess and rapid weight gain in early adulthood and consequent risk for early onset type 2 diabetes in people with treated psychosis is unknown but warrants examination.

Current antipsychotic drug treatment does not capture the cumulative effect of all antipsychotic drug use or the associated cumulative dosage effects over a lifetime. Polypharmacy is common and occurs across many different drug classes. Background medication may therefore confound effects that appear to be due to currently prescribed antipsychotic drugs. Identifying an appropriate reference group for antipsychotic drug comparisons is difficult. Some previous studies have used haloperidol (41), but only a handful of our survey participants were being treated with that drug. We therefore elected to compare those taking clozapine or olanzapine with those taking neither, but using a different reference group may generate different findings.

In conclusion, risk factors for type 2 diabetes established in the general population are also common in people with psychosis and strongly associated with current type 2 diabetes in those people. The current study provides large sample evidence that these factors may confound estimated risk associated with antipsychotic drug treatments over time, as others have cautioned (16,17,42). However, we observed very little cross-sectional confounding in a sample diagnosed with psychosis for a mean of 15 years. Patterns of association over the course of psychotic illness for predictors of type 2 diabetes, including antipsychotic drug effects, are likely to be complex. The cross-sectional model reported here should therefore be interpreted cautiously.

A strong focus on weight reduction to reduce adverse physical health outcomes of psychosis is warranted, but effective prevention strategies for type 2 diabetes should be broadened to include targeting those with emerging dyslipidemia, hypertension (43) and positive family histories of diabetes (31,44). Lowering blood pressure is the single most effective intervention to reduce cardiovascular morbidity and mortality in those with type 2 diabetes in the general population (45). An equivalent evidence base to guide us for those with psychosis is not yet available.

Persistent lifestyle changes will likely be required to modify adverse health outcomes associated with type 2 diabetes. Small scale interventions of short duration will not suffice. This is a substantial challenge to current practice in clinical psychiatry. Drug prescriptions may be life-long, but lifestyle interventions are typically non-intensive and short lived. The smallest effects of lifestyle interventions are greeted with enthusiasm (29), but belie the enormity of the changes

actually required to extend and improve the physical health of those with psychosis.

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