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An association between YKL-40 and type 2 diabetes in psychotic disorders

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Objective: This study examines if YKL-40 is increased in individuals with psychotic disorders and if elevated YKL-40 levels at baseline is associated with subsequent development of type 2 diabetes.
Method: A total of 1383 patients with a diagnosis of schizophrenia or affective psychosis and 799 healthy controls were recruited in the period 2002–2015. Plasma YKL-40 and metabolic risk factors were measured and medication was recorded. Using national registry data, association between baseline risk factors and later development of type 2 diabetes was assessed using Cox proportional hazards models.
Results: Plasma YKL-40 was higher in patients vs. healthy controls also after adjusting for metabolic risk factors, with no difference between the schizophrenia and affective psychosis groups. Patients were diagnosed with type 2 diabetes at a significantly younger age. Multivariate Cox regression analyses showed that elevated YKL-40 (hazard ratio (HR) = 5.6, P = 0.001), elevated glucose (HR = 3.6, P = 0.001), and schizophrenia diagnosis (HR = 3.0, P = 0.014) at baseline were associated with subsequent development of type 2 diabetes.
Conclusions: Patients with psychotic disorders have at baseline increased levels of YKL-40 beyond the effect of comorbid type 2 diabetes and metabolic risk factors. Elevated YKL-40 level at baseline is associated with later development of type 2 diabetes.

Significant outcomes

- Patients with psychotic disorders have increased risk of developing type 2 diabetes and they are diagnosed at a younger age compared to healthy controls.
- YKL-40 is associated with subsequent type 2 diabetes in patients with psychotic disorders.

Limitations

- The study lack fasting glucose levels on the majority of the healthy controls and did not include information regarding HbA1c.
- YKL-40 is considered a novel marker without established normal ranges for clinical settings

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Key words: schizophrenia; bipolar disorder; YKL-40; type 2 diabetes

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Introduction

Patients with psychotic disorders have significantly higher mortality compared to the general population partly due to somatic diseases such as metabolic and cardiovascular diseases (CVD) (1). Recent findings of elevated levels of metabolic risk factors in young first-episode and drug-naïve psychotic patients indicate that some of the increased somatic comorbidity might be related to underlying metabolic disturbances and not solely due to unhealthy lifestyle and side-effects of second-generation antipsychotics (2–4).

Immune-mediated mechanisms seem to play a pathogenic role in metabolic diseases. Low-grade chronic inflammation is associated with type 2 diabetes (5), obesity (6), and atherosclerosis (7). Recent evidence also implicates immune-related mechanisms in psychotic disorders. Genomewide association studies have identified immune-related genes associated with schizophrenia (8) and epidemiological studies suggest that infections and autoimmune diseases increase the risk for schizophrenia and bipolar disorder (9–11). In addition, postmortem brain studies show increased expression of immune-related genes in psychotic disorders (12). Several clinical studies demonstrate higher levels of inflammatory markers in the circulation and cerebrospinal fluid (CSF) in both schizophrenia and bipolar disorder (13–15). Interestingly, different studies also suggest overlapping mechanisms between psychotic disorders and type 2 diabetes (16) and metabolic comorbidity may manifest at an early stage in psychotic disorders (17). Thus, we hypothesize that inflammatory mechanisms involved in the development of psychotic disorders are also underlying the comorbid metabolic related diseases such as type 2 diabetes in these patients (2, 18, 19).

YKL-40 is a glycoprotein that has repeatedly been associated with adverse outcome in patients with manifest type 2 diabetes and CVD (20–22). Some findings suggest that this protein might be a potential pathogenic factor underlying psychotic disorders (23, 24). YKL-40 is expressed in the brain and is essential in the activation of microglia cells and astrocytes in the CNS (25), and is involved in the fetal development of the blood–brain barrier (26). YKL-40 has been implicated in many diseases affecting the CNS such as Alzheimer's disease and multiple sclerosis (25, 27, 28), but is less studied in psychiatric disorders. Recently, YKL-40 levels in CSF were found to be higher in patients with bipolar disorders and associated with poorer cognitive function (29, 30). Compared to bipolar disorder, the existing evidence linking YKL-40 to schizophrenia is scarcer. However, the *chitinase-3-like 1* gene coding for YKL-40 has been shown to be up-regulated in postmortem brains and suggested as a susceptibility gene for schizophrenia (24, 31).

The first aim of the current study was to determine whether circulating levels of YKL-40 were higher in schizophrenia and bipolar disorder than in healthy controls after controlling for comorbid metabolic risk factors and type 2 diabetes. Second, we applied registry data with a maximum follow-up time of 13 years and explored whether YKL-40 could predict future type 2 diabetes in patients with psychotic disorders.

Material and methods

Participants were included in a large ongoing study, the Thematically Organized Psychosis (TOP) Study, at the Oslo University Hospital and other hospitals in the eastern part of Norway during the period 2002–2015. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All participants were able to give written informed consent according to the Declaration of Helsinki, and were informed that participation was voluntarily and that they could withdraw from the study at any time. The sample in the present study consists of patients with a DSM-IV diagnosis within the psychotic spectrum, divided into two groups: schizophrenia (SZ) and affective psychosis (Affective). In addition, healthy controls (HC) were included. The SZ group included patients with schizophrenia, schizophreniform disorder, schizoaffective disorder, and psychosis not otherwise specified. The Affective group included patients with bipolar disorder I, bipolar disorder II, and depression with psychotic symptoms. All participants were between 18 and 65 years at the time of enrollment. Criteria of exclusion were head injury, neurological disorder, and IQ<70. Trained physicians and clinical psychologists performed the clinical assessments. Diagnosis was based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) with an inter-rater reliability of 82%, $\kappa = 0.77$ (95% CI: 0.60–0.94) for severe mental illness diagnoses. Current psychotic symptoms were rated with the Positive and Negative Syndrome Scale (PANSS), depressive symptoms with the Inventory of Depressive Symptomatology (IDS) Clinician Rating and current manic symptoms were rated using the

Young Mania Rating Scale (YMRS). Psychosocial functioning in patients was assessed with the Global Assessment of Functioning (GAF) scale, split version. We calculated duration of disease by subtracting the age at the patients first encounter with the psychiatric health care system from the age at the time of inclusion. The total number of hospital admissions was used as a measure of disease course.

Patients were examined by a physician and fasting blood samples were collected in the morning. The same techniques were used for sampling and analyses during the whole inclusion period. Blood sampling was performed in the laboratory located next door to the interview facilities and performed on the same day as physical examination.

Detailed records of the current medication and physical health were obtained through medical records and information from the patients. Smoking habits were defined as daily use of cigarettes or not, alcohol use was measured as self-reported number of international units (IE) consumed in the last two weeks prior to inclusion and drug use was measured as number of times that any illegal drug had been taken in the last two weeks prior to inclusion. Defined daily dosages (DDD) were calculated in accordance with the guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (hhtp://www.whocc.no/atcdd). We divided the patients into three groups based on their antipsychotic medication and corresponding risk profile regarding metabolic side-effects, one 'high-risk group' using olanzapine, clozapine or quetiapine, one 'low-risk group' using any other type of antipsychotic medication and one 'no antipsychotic (AP) group'.

The HC were randomly drawn from the National Registry and contacted by letter with an invitation to participate in the study. All HC were screened for psychiatric disease and drug abuse. In contrast to the patient sample, the majority of the blood samples were drawn from the HC in a non-fasting state. We did, however, retrieve between 65 and 112 fasting blood samples from HC. Although we found a difference between fasting YKL-40 levels (mean = 31.6 ng/ml) and non-fasting (mean = 39.1 ng/ml) levels, we chose to include the non-fasting samples as this in the worst case would influence our results negatively and thereby serve as a conservative correction of any significant difference between cases and controls. In addition, fasting plasma levels of glucose were similar in fasting (mean = 5.1 mmol/l) and non-fasting subjects (mean = 5.1 mmol/l). Participants (n = 42) who had been diagnosed with type 1 diabetes, type 2 diabetes or using any glucose-lowering medication before entering the TOP-study were excluded from all analyses.

Metabolic parameters

Plasma levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and glucose were measured at Department of Clinical Chemistry, Oslo University Hospital, using an Integra 800 instrument from Roche Diagnostics, according to standard methods. All subjects were weighed on calibrated digital weights under equal conditions, height was measured with standard methods and body mass index (BMI) (kg/m^2) calculated.

As reference ranges are often used as guidance in clinical settings, dichotomous variables were made with cut-off values for TG $\geq$ 1.7 mmol/l, total cholesterol $\geq$ 5.2 mmol/l, glucose $\geq$ 5.6 mmol/l, HDL-C (women) $\leq$1.22 mmol/l and HDL-C (men) $\leq$ 1.00 mmol/l and BMI $\geq$ 25 kg/m^2 (32, 33).

Insulin resistance was calculated in a subsample (n = 988) using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) download computer model HOMA2 by the University of Oxford (34). Insulin resistance is problematic to characterize and cut-off values for HOMA-IR vary according to race, sex, age, and other comorbidity (35). As our sample also included different ethnicities, we have followed the recommendations for non-diabetics from the World Health Organization which is defining an elevated HOMA-IR as higher than the 75 percentile (35). In our sample, we defined the cut-off value for HOMA-IR according to the 75 percentile for the healthy controls which was set at >2.1.

Inflammatory measures

Plasma levels of YKL-40 and C-reactive protein (CRP) were measured using enzyme immunoassay (R&D systems, Minneapolis, MN, USA) with intra- and inter-assay coefficients of variation <10%. For immunoassays, blood was taken using EDTA vials and the plasma was isolated the next working day and stored at −80°C. Most of the samples have been frozen and thawed two times, while the oldest samples have been frozen and thawed three times. We have compared the levels of YKL-40 according to the time period when the blood sample was drawn corresponding to the number of thaw/freeze cycles and found no significant differences.

Elevated CRP was defined as $\geq$ 1 mg/l (36). Elevated levels of YKL-40 are defined as being above

the age-adjusted 97.5th percentile according to plasma YKL-40 levels in a normal population (37): YKL-40 > 96 ng/ml for ages ≤ 30, YKL-40 ≥ 117 ng/ml for ages 31–40, YKL-40 ≥ 143 ng/ml for ages 41–50, YKL-40 ≥ 175 ng/ml for ages 51–60 and YKL-40 ≥ 213 ng/ml for ages 61–70.

Registry data

Data on diagnoses set by primary care physicians (GPs) were retrieved from the 'Kontroll og Utbetaling av Helserefusjon' (KUHR) database. KUHR was established in 2006 and is administered by the Norwegian Health Economics Administration (HELFO). The KUHR database include information on International Classification of Primary Care diagnoses (ICPC-2), as registered by health service providers within primary health care for governmental financial reimbursement. For the current study, we included the ICPC-code T90 Non-insulin dependent diabetes. In addition, we retrieved diagnoses from the Norwegian Patient Register (NPR). The NPR includes information on all patients who have been in contact with specialist health care. The NPR provides data on diagnoses set by government hospitals from 2008 and was supplemented with diagnoses set by private specialists who receive governmental reimbursement from 2012. Diagnoses in the NPR are set according to the international Classification of Disease, version 10 (ICD-10) and for the present study, we identified patients who had received a diagnosis of type 1 diabetes (ICD-10 code E10) and type 2 diabetes (ICD-10 code E11). All patients who had a type 1 diabetes diagnosis, including four participants who had received a type 2 diabetes diagnosis by their general practitioner (KUHR) and a type 1 diabetes in the specialist health care system (NPR) were excluded from the analyses.

Statistical analysis

Statistical analyses were done using the SPSS software package for Windows, version 25 (SPSS, Chicago, IL, USA) and GRAPHPAD PRISM version 6.0 for Windows (GraphPad Software, San Diego, CA, USA).

Demographic and clinical variables at baseline were presented as mean (SD) or %, with ANOVA, Mann–Whitney *U*-test or chi-squared tests as *post hoc* tests in order to investigate group differences. Skewed data were log-transformed when necessary. We performed Spearman or Pearson correlation analyses to investigate the relationship between YKL-40 and age, DDD of psychopharmacological medication (antipsychotics, lithium, antidepressants, and antiepileptics), symptoms (total score of PANSS, YMRS, IDS, and GAF), as well as total cholesterol, HDL-C, TG, glucose, BMI, and CRP. For comparing YKL-40 levels between groups, we used ANCOVA adjusting for BMI, total cholesterol, HDL-C, TG, age, CRP, sex, and smoking. YKL-40 levels were compared across the three medication groups according to known risk for metabolic side-effects (high risk vs. low risk vs. no AP) using ANCOVA and adjusting for age, BMI and diagnosis. Data normality was assessed evaluating the residuals. All analyses were two-tailed with a predefined level of significance of <0.05.

The occurrence of type 2 diabetes diagnoses in the three groups (i.e., SZ, Affective and HC) over time was compared using Kaplan–Meier curves and log-rank tests. Time to event was defined as years since the time of inclusion in the TOP-study to first registered type 2 diabetes diagnosis, recorded either by the participant's general practitioner (KUHR) or in the specialist health care system (NPR). Individuals without a recorded type 2 diabetes diagnosis were censored. End of follow-up was either the event of type 2 diabetes or when the registry data was drawn in September 2015. Univariate Cox proportional hazards models were applied in order to determine crude hazard ratios for potential predictive markers at baseline and type 2 diabetes as outcome. Based on these results, a multivariate Cox regression model was fitted in order to assess the relationship between clinical characteristics at baseline and type 2 diabetes (38).

Results

Clinical characteristics

Patients in the SZ group were younger than patients in the Affective and HC groups. The SZ group had higher PANSS score, lower GAF-S, and GAF-F and used more antipsychotic medications than the Affective group (Table 1). Except for glucose, there were significantly more metabolic risk factors present in the patient groups compared to controls (Table 1).

Levels of YKL-40 and metabolic risk factors at baseline

There was a highly significant ($P < 0.001$) increase in plasma levels of YKL-40 in patients (mean 47.1, SD±35.5 ng/ml) compared to HC (mean 37.9,

SD ± 23.9 ng/ml), with no significant differences between the diagnostic groups (SZ = 47.1 ng/ml, Affective = 47.1 ng/ml) (Table 2). Except for the age group 41–50 years where the difference was trend significant, levels of YKL-40 was significantly higher in the psychosis group across all age groups, including the 20 years or younger group (Fig. 1).

In the whole sample (diagnostic groups and HC), YKL-40 levels correlated with BMI ($r = 0.13$, $P < 0.001$), CRP ($r = 0.20$, $P < 0.001$), total cholesterol ($r = 0.17$, $P < 0.001$), HDL-C ($r = -0.06$, $P = 0.04$), TG ($r = 0.18$, $P < 0.001$), and age ($r = 0.15$, $P < 0.001$). After adjusting for these metabolic risk factors, the difference in YKL-40 levels between patients and HC remained significant ($F = 18.23$, df = 8, $P < 0.001$). Mean YKL-40 levels were highest among the patients using AP known to cause metabolic side-effects (mean 48.9, SD ± 39.3), followed by the patients using no AP (mean 45.4, SD ± 35.9) and the patients using AP with little metabolic side-effects (mean 44.1, SD ± 28.1), but the difference was not significant ($P = 0.2$).

In a subsample ($n = 988$), YKL-40 correlated with HOMA-IR ($r = 0.11$, $P < 0.02$). In additional analyses where adjustment for HOMA-IR was added to the model, YKL-40 levels still remained higher in both patient groups compared to HC ($F = 4.30$, df = 9, $P = 0.01$).

We found no significant bivariate correlation between YKL-40 and symptoms scores (PANSS, IDS, or YMRS), duration of disease, number of hospital admissions, current treatment of psychotropic medication (antipsychotic, antidepressants, or mood stabilizers), or alcohol or drug use in the previous two weeks before blood sampling.

Table 1. Clinical characteristics

	SZ (n = 907)		Affective (n = 475)		HC (n = 799)		
	Mean or %	SD	Mean or %	SD	Mean or %	SD	*P* value
Age (years)	30.6	9.7	33.8	12.1	33.1	9.5	<0.001
Sex (male)	59.4		40.8		52.7		<0.001
Medication							
Antipsychotics DDD	1.5	2.0	0.9	0.8	–	–	<0.001
Lithium DDD	0.9	0.6	1.2	0.5	–	–	n.s.
Antidepressants DDD	1.6	0.9	1.5	0.9	–	–	n.s.
Antiepileptics DDD	0.7	0.5	0.8	0.5	–	–	n.s.
Symptoms and course							
PANSS total score	62.5	16.6	47.2	12.0	–	–	<0.001
YMRS total score	5.3	5.1	3.5	4.7	–	–	
IDS total score	18.0	12.6	17.9	12.5	–	–	<0.001
GAF-symptom score	42.8	11.6	55.5	12.1	–	–	<0.001
GAF-function score	44.3	11.7	53.3	12.7	–	–	<0.001
Duration of disease (years)	4.2	6.4	5.2	8.2			n.s.
Hospital admissions (n)	2.8	5.3	2.0	2.9			<0.001

Affective, affective psychosis; DDD, defined daily dosage; GAF, Global Assessment of Function; HC, healthy controls; IDS, Inventory of Depressive Symptoms; n.s., non-significant; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; SZ, schizophrenia psychosis; YMRS, Young Mania Rating Scale.

Table entries are mean (SD) or %.

DDD is calculated in accordance with the guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (http://www.whocc.no/atcdd). Significant differences in demographic and clinical variables between the three groups were investigated using either ANOVA, Mann–Whitney *U* test or Pearson's chi-squared test.

Table 2. Metabolic risk factors

	SZ		Affective		HC		
	Mean or% (SD)	*N*	Mean or% (SD)	*N*	Mean or% (SD)	*N*	*P* value
Tobacco daily use (yes)	55.3	872	53.6	468	20.9	358	<0.001
TC mmol/l	5.1 (1.1)	775	5.1 (1.1)	434	5.0 (1.0)	762	0.03
HDL-C mmol/l	1.3 (0.4)	775	1.5 (0.5)	434	1.6 (0.5)	762	<0.001
TG mmol/l	1.5 (1.1)	773	1.3 (1.0)	433	1.3 (0.8)	762	0.001
Glucose mmol/l	5.1 (0.7)	777	5.0 (0.6)	432	5.1 (0.8)	753	n.s.
BMI kg/m^2	26.3 (5.0)	821	25.6 (4.6)	438	24.5 (3.5)	542	<0.001
CRP mg/l	2.9 (5.1)	757	3.7 (10.9)	423	2.1 (3.7)	759	<0.001
YKL-40 ng/ml	47.1 (36.4)	610	47.1 (33.8)	302	37.9 (23.9)	611	<0.001
Insulin pmol/l	94.0 (53.9)	582	83.3 (42.1)	341	70.2 (30.5)	65	0.006
HOMA-IR	1.7 (1.0)	582	1.5 (0.8)	341	1.3 (0.6)	65	0.005

Affective, affective psychosis; BMI, body mass index; CRP, C-reactive protein; HC, healthy controls; HDL-C, high density level cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; *N*, number of individuals; n.s., non-significant; SD, standard deviation; SZ, schizophrenia psychosis; TC, total cholesterol; TG, triglycerides.

Table entries are mean (SD) or %. Significant differences in demographic and clinical variables between the three groups were investigated using either ANOVA or Pearson's chi-squared test.

Type 2 diabetes

Among a total of 2182 participants, 63 had been diagnosed with type 2 diabetes after baseline inclusion in the study. There was a significant difference in type 2 diabetes cases between the groups; HC $n = 6$, SZ $n = 45$ and Affective $n = 12$, X^2 (2, $n = 2182$) =27.1, $P < 0.001$. There was a significant difference (log-rank *P*-value <0.001) between the diagnostic groups in time from baseline to receiving a type 2 diabetes diagnosis as illustrated by a Kaplan–Meier plot (Fig. 2). Mean ages at the time of type 2 diabetes diagnoses were 51.0 ± 8.7 years for the HC group, 48.9 ± 12.6 for the Affective group and 41.6 ± 11.4 for the SZ group.

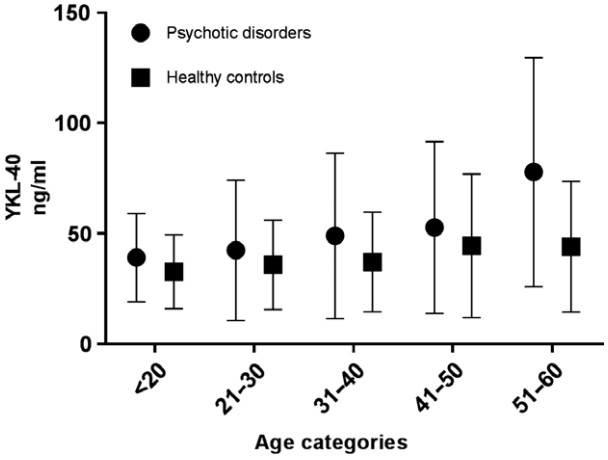

Fig. 1. Mean levels of YKL-40 according to age. Mean plasma levels of YKL-40 ng/ml with error bars according to age categories. Except for the age group 41–50 years where the difference was trend significant ($P = 0.068$), YKL-40 was higher in patients with psychotic disorders across all age groups with *P*-values ranging from 0.028–9.0 $\times 10^{-6}$.

Association with subsequent type 2 diabetes

Univariate Cox proportional analyses showed that elevated glucose, elevated YKL-40, BMI≥25, elevated TG, SZ, elevated total cholesterol, elevated CRP, age, and low HDL-cholesterol were significantly associated with long-term development of type 2 diabetes (Table 3). We found no significant associations between sex, antipsychotic medication or smoking, and type 2 diabetes. In adjusted multivariate Cox regression analysis including variables with a univariate association, elevated YKL-40 levels (HR=5.6), elevated glucose levels (HR=3.6) and having a SZ diagnosis (HR=3.0) at baseline remained significantly associated with obtaining a type 2 diabetes diagnosis at a later stage (Table 3). Univariate Cox proportional analysis in a subsample ($n = 988$) showed that HOMA-IR was associated with subsequent type 2 diabetes (HR = 4.9, $P < 0.001$). In adjusted multivariate Cox regression analysis with all variables included, the association between HOMA-IR and subsequent type 2 diabetes was not significant.

Discussion

In the current study, we find increased levels of circulating YKL-40 in a large sample of patients with psychotic disorders after controlling for type 2 diabetes and other metabolic risk factors such as lipids, glucose levels, insulin resistance, overweight, and CRP levels. We also show that YKL-40 is associated with enhanced risk of future type 2 diabetes in patients with psychotic disorder.

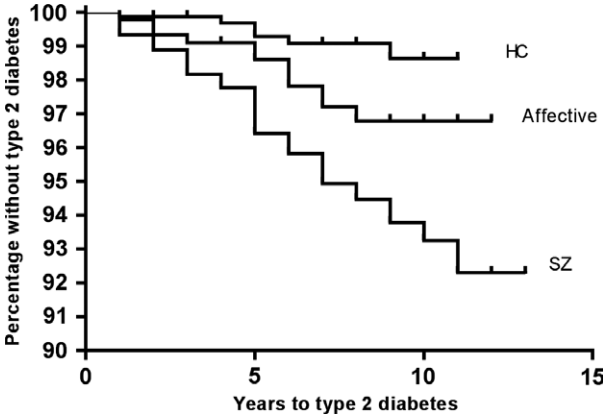

Fig. 2. Kaplan–Meier plot displaying type 2 diabetes survival curves according to psychosis diagnoses and healthy controls. Affective, affective psychosis; HC, healthy controls; SZ, schizophrenia psychosis.

The present findings of increased circulating YKL-40 in patients with schizophrenia have not been shown before. Our result in affective disorders is in line with a recent report with a smaller sample (29), which further supports the validity of our findings. Of importance for underlying pathophysiology is that YKL-40 is higher also in young patients (≤20 years). Taken together with our results showing that patients develop type 2 diabetes at a younger age than the healthy control group, this may indicate that the risk of type 2 diabetes in psychotic disorders follows a leftwards shifted trajectory compared to the normal population. Our findings after controlling for confounders suggest that YKL-40 represents common

Table 3. Crude and adjusted hazard ratios for metabolic risk factors and subsequent type 2 diabetes

	Crude			Adjusted		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
YKL-40	7.1	3.2–16.1	<0.001	5.6	2.1–14.9	0.001
Glucose	4.9	2.9–8.3	<0.001	3.6	1.6–7.7	0.001
SZ	3.7	2.2–6.2	<0.001	3.0	1.2–7.1	0.014
Age, years	1.1	1.0–1.1	<0.001	1.0	1.0–1.1	0.019
BMI	5.2	2.5–10.6	<0.001	2.0	0.7–5.5	n.s
TG	3.7	2.2–6.2	<0.001	1.9	0.8–4.5	n.s
CRP	3.0	1.4–6.3	0.004	1.3	0.5–3.7	n.s
TC	2.0	1.1–3.3	0.015	0.7	0.3–1.5	n.s
HDL-C	2.8	1.7–4.7	<0.001	1.9	0.8–4.3	n.s

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; HDL-C, high density level cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HR, hazard ratio; SZ, schizophrenia; TC, total cholesterol; TG, triglycerides.
Elevated levels of YKL-40, glucose, BMI, TG, CRP are defined as: YKL-40 > 96 ng/ml for ages ≤ 30, YKL-40 ≥ 117 ng/ml for ages 31–40, YKL-40 ≥ 143 ng/ml for ages 41–50, YKL-40 ≥ 175 ng/ml for ages 51–60 and YKL-40 ≥ 213 ng/ml for ages 61–70, TG ≥ 1.7 mmol/l, total cholesterol ≥ 5.2 mmol/l, glucose ≥ 5.6 mmol/l, BMI ≥ 25 kg/m^2 and CRP ≥ 1 mg/l. Low level of HDL-C is defined as: HDL-C (women) ≤1.2 mmol/l and HDL-C (men) ≤ 1.0 mmol/l. SZ diagnosis vs. Affective and HC.
Number of individuals included in the analyses: YKL-40:1522, Glucose:1962, Diagnosis:2182, Age:2181, BMI:1801, TG:1968, CRP:1939, Total cholesterol:1971, HDL-C:1971.

underlying pathophysiology in type 2 diabetes and psychotic disorders, beyond the comorbidity seen between these disorders. Further support for the involvement of YKL-40 in core disease mechanisms in psychotic disorders is our finding of no effect of either antipsychotics or any other psychotropic medication.

Evidence indicates that YKL-40 is produced and secreted by macrophages and neutrophils (39), and is among others regulated by interleukin-6 (40), which is one of the inflammatory markers found consistently increased in both psychotic disorders (41) and metabolic disorders (42). Increased levels of YKL-40 have been found in other diseases affecting the CNS such as multiple sclerosis (43) and Alzheimer's disease (44), and it has been implicated in blood–brain barrier defects and abundant glial activity (26). With an emerging number of epidemiological, clinical and genetic (1, 16) studies indicating overlap between psychotic disorders and metabolic diseases, it is likely that there are overlapping molecular pathways underlying these two conditions. Drawing upon advances within inflammatory and immunologic research might thus provide new insight into disease mechanisms of psychotic disorders. It is intriguing that YKL-40, which is a predictive marker for type 2 diabetes prognosis, atherosclerotic burden and CVD mortality (21, 45, 46), also shows a pattern of overexpression in prefrontal cortex (31) and hippocampus (47) in schizophrenia.

Schizophrenia or bipolar disorders typically develop at a young age. This often implies many years of mental health burdens, in addition to considerable increased risk of comorbid somatic disease. In contrast to other bio-markers such as CRP, YKL-40 is found to be highly expressed at the early stages of atherosclerosis and type 2 diabetes (44). The present findings of an association between circulating YKL-40 levels and future type 2 diabetes, suggest that YKL-40 could be clinically useful when assessing somatic health issues in patients with severe mental illness. Measuring circulating YKL-40 could be of particular value in schizophrenia as they develop type 2 diabetes at a younger age and YKL-40 can improve the identification of those at risk before hyperlipidemia, hyperglycemia and overweight appear. This will enable the clinician to implement proper prevention and intervention regimens at an early stage. Since medications such as statins may lower the levels of YKL-40 (21, 43), it is possible that immunomodulating and lipid-lowering drugs could be used in early phases to prevent development of type 2 diabetes and thus lower mortality rates in severe mental illness. Further, due to the independent increase of YKL-40 in psychotic disorders, these medications may have beneficial effects on psychiatric symptoms as well as metabolic comorbidity.

There are some limitations to the current study. There might be other confounders not accounted for in this cross-sectional study and the design makes it difficult to know the direction of effect. The patients were more affected with cardiometabolic risk factors at baseline than healthy controls. Although we did control for these potential confounders in the analyses, we cannot completely rule out that some of the increased YKL-40 levels are affected by baseline status.

We have used cut-off values for YKL-40 based on age-adjusted 97.5th percentiles in a normal population as suggested by the literature (37). However, YKL-40 is considered a novel marker without a standardized assay or established normal ranges (45). In addition, YKL-40 could be a more general marker and not specific for type 2 diabetes as others have found YKL-40 to be associated with other diseases such as atherosclerosis and autoimmune disorders that are not accounted for in this study. Some of the blood samples drawn in the early phases of the project have been thawed and re-frozen. Yet, all groups were included at all time periods of the project and YKL-40 is a robust protein. We also lack fasting plasma levels on glucose on the majority of the HC's and we have not measured HbA1c. Insulin resistance was associated with YKL-40 levels and subsequent type 2 diabetes in univariate analyses in a smaller subsample, but not in multivariate analyses possibly due to lack of power. In light of recent results indicating IR as a moderator in the association between another inflammatory marker (IL-6) and psychosis, future research should investigate the role of YKL-40 in this is relationship (19). In addition, these findings should be replicated in an independent first episode psychosis sample, as both exercise and poor diet might affect YKL-40 levels (48, 49) and the potential effect of medication should be explored in future randomized controlled trials. Finally, the KUHR registry was established in 2006 and the NPR in 2008. There might be subjects diagnosed with type 2 diabetes between baseline inclusion and 2006/2008 that we have missed. However, this would most probably increase the differences, as there is a higher chance of missed diagnosis of type 2 diabetes. Also the type 2 diabetes diagnoses are based on the ICD or the ICPC system, whereas the diagnoses of psychotic disorders are based on DSM. However, this did not affect the diagnosis or outcome measures in the current study. Further, we cannot be absolutely certain that the GPs or

the specialists have provided the correct diagnoses for the registries.

The dramatically reduced life expectancy for patients with psychotic disorders associated with metabolic comorbidity is an important public health issue where we need to understand the underlying mechanisms and clinicians need effective tools for identifying those at risk. There are several challenges, such as low compliance and little worry about the future health. Still, there are health care interventions that can be implemented if a high-risk individual is identified before disease onset (50). Given that future research confirms that YKL-40 is a useful marker present at early stages, preventive measures including medication could be considered. More importantly, health care providers could target the patients at risk and offer more guidance and follow-up with lifestyle related measures such as exercise and diet advice before the patient becomes overweight and develop glucose intolerance.

The current findings of a robust increase of YKL-40 in patients with psychotic disorders, that remained significant after controlling for metabolic risk factors and CRP, suggest that YKL40 is a marker of core immune-mediated pathophysiology of severe mental disorders. Furthermore, we have shown that elevated YKL-40 level is associated with subsequent type 2 diabetes development in a clinically representative and relatively young psychotic disorder group. Measuring YKL-40 might represent a useful addition to more traditional metabolic risk factors for clinicians monitoring somatic health in these patients.

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Declaration of interest

The authors report no conflict of interest and have no disclosures.

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