A meta-analysis of cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia versus general population controls

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A meta-analysis was conducted to explore the risk for cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia and age- and gender- or cohort-matched general population controls. Our literature search generated 203 relevant studies, of which 136 were included. The final dataset comprised 185,606 unique patients with schizophrenia, and 28 studies provided data for age- and gender-matched or cohort-matched general population controls (n=3,898,739). We found that multi-episode patients with schizophrenia were at increased risk for abdominal obesity (OR=4.43; CI=2.52-7.82; p<0.001), hypertension (OR=1.36; CI=1.21-1.53; p<0.001), low high-density lipoprotein cholesterol (OR=2.35; CI=1.78-3.10; p<0.001), hypertriglyceridemia (OR=2.73; CI=1.95-3.83; p<0.001), metabolic syndrome (OR=2.35; CI=1.68-3.29; p<0.001), and diabetes (OR=1.99; CI=1.55-2.54; p<0.001), compared to controls. Multi-episode patients with schizophrenia were also at increased risk, compared to first-episode (p<0.001) and drug-naïve (p<0.001) patients, for the above abnormalities, with the exception of hypertension and diabetes. Our data provide further evidence supporting WPA recommendations on screening, follow-up, health education and lifestyle changes in people with schizophrenia.

Key words: Schizophrenia, cardio-metabolic abnormalities, metabolic syndrome, obesity, hypertension, hyperlipidemia, diabetes, screening, health education, lifestyle changes

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A number of studies have demonstrated that patients with schizophrenia have an excess mortality, measured by a standardized mortality ratio that is two or three times that seen in the general population (1-11). This translates into 13-20 years of shortened life expectancy, a gap that has widened in recent decades (11-13).

It is well known that some of this excess mortality is due to suicide, but the majority is related to natural causes, such as cancer, respiratory diseases and cardiovascular disease (CVD) (13-15). Premature mortality from CVD is commonly attributed to low socio-economic status (e.g., poverty, poor education) (8), behavioural factors (e.g., alcohol and substance abuse, physical inactivity, unhealthy eating patterns) (16-23), and management factors (e.g., side effects of antipsychotic and concomitant medication use, fragmentation of physical and mental health care, disparities in quality of medical care) (24-28).

In order to help clinicians to identify and focus more on patients at increased risk for CVD, the concept of metabolic syndrome (MetS) has been introduced. MetS is defined by a combination of abdominal obesity, high blood pressure, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides and hyperglycemia (29-33). In the general population, these clustered risk factors have been associated with the development of CVD (29-33).

Although several definitions have been proposed for MetS, the most often cited are those formulated by the National Cholesterol Education Program (NCEP), i.e., the Adult Treatment Panel III (ATP-III) and adapted ATP-III criteria (ATP-III-A) (34,35), by the International Diabetes Federation (IDF) (36), and by the World Health Organization (WHO) (37). These definitions share similar diagnostic thresholds. However, abdominal obesity is central to the IDF definition, with provision of specific ethnic thresholds for waist circumference (38), while it is not a mandatory NCEP/ATP MetS criterion.

As a prevalent condition and a predictor of CVD across racial, gender and age groups, MetS provides a unique opportunity for identifying high-risk populations and preventing the progression of some of the major causes of morbidity and mortality (29-33).

In a previous meta-analysis (39), we demonstrated that almost one in three of unselected patients with schizophrenia meet criteria for MetS, one in two patients are overweight, one in five appear to have significant hyperglycemia (sufficient for a diagnosis of pre-diabetes) and at least two in five have lipid abnormalities. We also found a significantly lower cardio-metabolic risk in early schizophrenia than in chronic schizophrenia. Both diabetes and pre-diabetes appear uncommon in the early illness stages, particularly in drug naïve patients (40).

To the best of our knowledge, meta-analytic data comparing the cardio-metabolic risk in patients with schizophrenia across different stages (unmedicated, first-episode, multi-episode) versus matched healthy controls are currently lacking. Such data could raise awareness of conditions

that cause a significant burden of morbidity and mortality, and thereby help motivate preventive strategies and adherence to recommended therapies.

The primary aim of the current meta-analysis therefore was to compare the risk for MetS, abdominal obesity, hypertension, hyperlipidemia, and diabetes in unmedicated, first-episode, and multi-episode patients with schizophrenia versus healthy age- and gender- or cohort-matched controls. We also updated comparisons in MetS, abdominal obesity, hypertension, hyperlipidemia, and diabetes risks between unmedicated, first-episode, and multi-episode patients with schizophrenia.

METHODS

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard (41). The focus was on patients with schizophrenia, irrespective of age and clinical setting (inpatient, outpatient or mixed).

Inclusion criteria were: a DSM-IV-TR (42) or ICD-10 (43) diagnosis of schizophrenia (with or without related psychoses) and a MetS diagnosis according to non-modified ATP-III (34), ATP-III-A (35), IDF (36) or WHO (37) standards. We included case-control studies, prospective cohort studies, cross-sectional studies, and comparisons of study populations with age standardization. For comparison with healthy controls, only age- and gender-matched or cohort-matched studies were included. In the case of multiple publications from the same study, only the most recent paper with the largest sample was included.

Excluded were studies using non-standardized diagnoses of schizophrenia and/or MetS, limited to patients with known CVD, or limited to children and adolescents.

Two independent reviewers (DV and ADH) searched Medline, PsycINFO, Embase and CINAHL from database inception to March 1, 2013. The key word "schizophrenia" was cross-referenced with the following terms: "metabolic syndrome" OR "obesity" OR "lipids" OR "cholesterol" OR "hypertension" OR "diabetes". Manual searches were conducted using the reference lists from recovered articles. Prevalence rates of MetS, abdominal obesity, hypertension, hyperlipidemia and diabetes for patients and controls were abstracted by the same two independent reviewers. We also contacted authors for additional data and received information from 21 research groups (see Acknowledgements).

To examine the homogeneity of the effect size distribution, a Q-statistic was used (44). When the Q-statistic is rejected, the effect size distribution is not homogeneous, implying that the variability in the prevalence rates of the cardio-metabolic abnormalities between studies is larger than can be expected based on sampling error.

The effect size used for the prevalence rate of all cardio-metabolic abnormalities under research was the proportion, but all analyses were performed converting proportions into logits. Logits are preferred over proportions because the mean proportion across studies underestimates the size of the confidence interval around the mean proportion (due to compression of the standard error as p approaches 0 or 1) and overestimates the degree of heterogeneity across effect sizes. This is especially the case when the observed proportions are <0.2 or >0.8 (45). However, for ease of interpretation, all final results were back converted into proportions. In case of heterogeneity and when information about moderator variables was available, we opted for a mixed effects model. In these analyses, several study characteristics were incorporated, including mean age of the study sample, type of treatment setting (outpatient versus inpatient), medication status (medicated versus drug-naïve), and disease status (first episode versus not first episode). A random effects model was adopted when the Q-statistics indicated that there was heterogeneity and moderator variables were lacking.

Lastly, we pooled data from individual studies to calculate the odds ratio (OR) and used Wald tests to statistically compare the prevalence of cardio-metabolic abnormalities between patients with schizophrenia (unmedicated, first-episode, multi-episode) and age-matched general population control subjects.

RESULTS

Our search generated 203 relevant studies, of which 136 (46-181) were included. Reasons for exclusion are presented in Figure 1.

The final dataset comprised 185,606 unique patients with schizophrenia. Forty-three studies were conducted amongst inpatients (n=12,499; 59.7% male; mean age = 38.9 years), 46 in outpatient settings (n=12,469; 61.0% male; mean age = 38.6 years) and 46 in mixed samples (n=160,638; 62.0% male; mean age = 38.7 years). Twelve studies examined individuals who were in their first episode (n=2,192; 62.0% male; mean age = 28.7 years); 18 studies examined drug-naïve patients (n=1,104; 61.0% male; mean age = 30.7 years).

In 28 studies, age and gender head-to-head or cohort-matched general population control data (n=3,898,739) were available (47,51,55,57,60,61,63,74,78,89,93,94,103, 117,119,122,134,135,138,148,150,152,156,158,165,171, 176). There were, however, insufficient data to compare the prevalence of cardio-metabolic abnormalities of first-episode and/or drug-naïve patients with age and gender head-to-head or cohort-matched general population control data.

The Q-statistic indicated that the distribution of the prevalence of abdominal obesity across individual studies was not homogeneous ($Q(51)=994.4$; $p<0.001$). Compared with multi-episode patients (N=46; n=19,043; mean age = 38.6 years), drug-naïve patients (N=5; n=444; mean age = 28.0 years) had a significantly reduced risk for abdominal obesity: 50.0% (95% CI=46.9%-53.1%) versus 16.6% (95% CI=

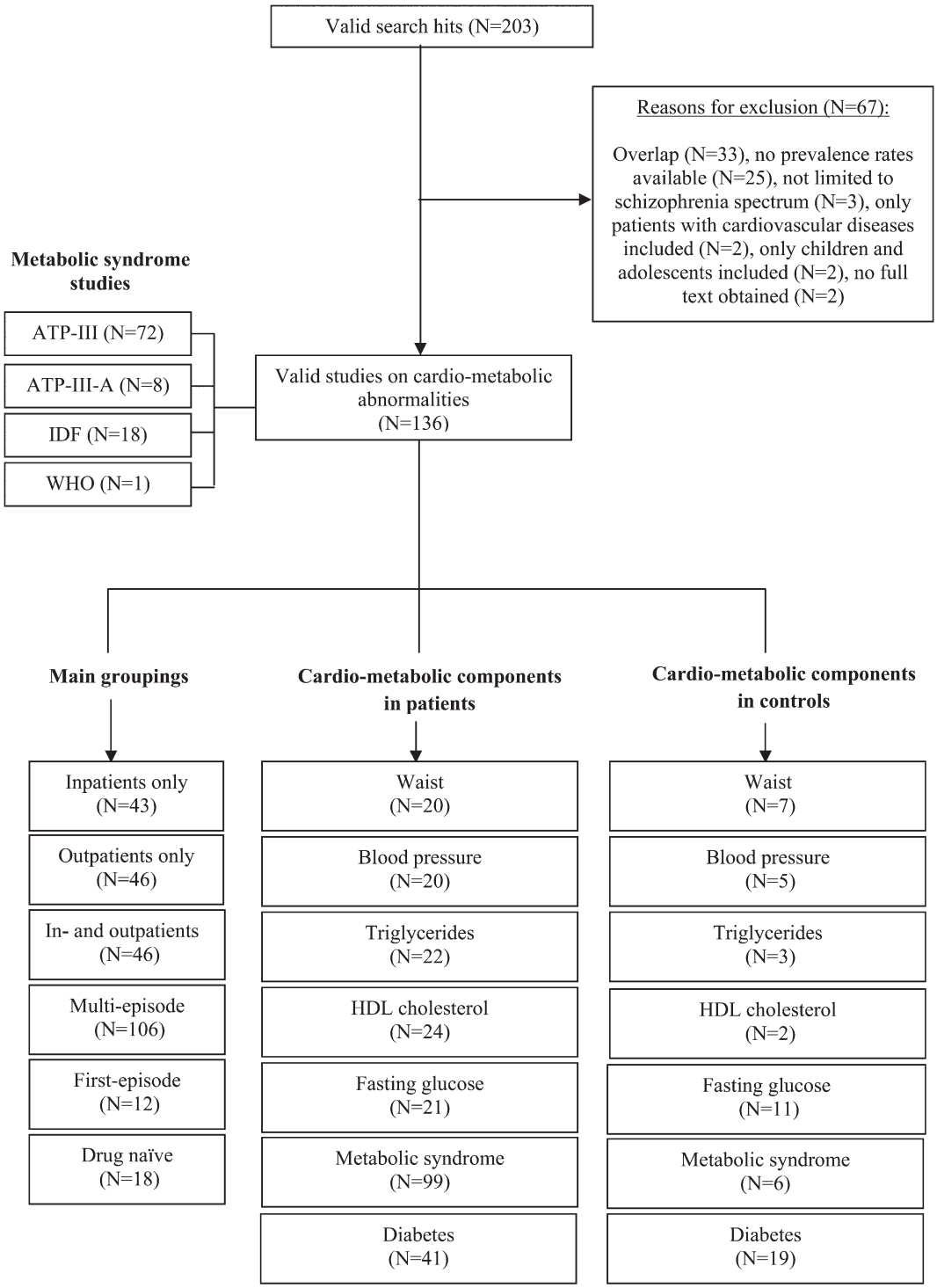

Figure 1 Quality of reporting of meta-analyses (Quorom) search results. ATP-III – Adult Treatment Panel III; ATP-III-A – Adult Treatment Panel III, adapted; IDF – International Diabetes Federation; WHO – World Health Organization; HDL – high-density lipoprotein

11.2%-24.0%) ($p<0.001$). Compared with matched general population control subjects (n=868), multi-episode patients (n=6,632) had a significantly increased risk of abdominal obesity when pooling data of the individual studies (N=5) (OR=4.43; CI=2.52-7.82; $p<0.001$). There were insufficient data to compare first-episode and drug-naïve patients with general population controls.

The Q-statistic indicated that the distribution of the prevalence of hypertension across individual studies was not homogeneous ($Q(56)=12262.5$; $p<0.001$). Fifty-seven

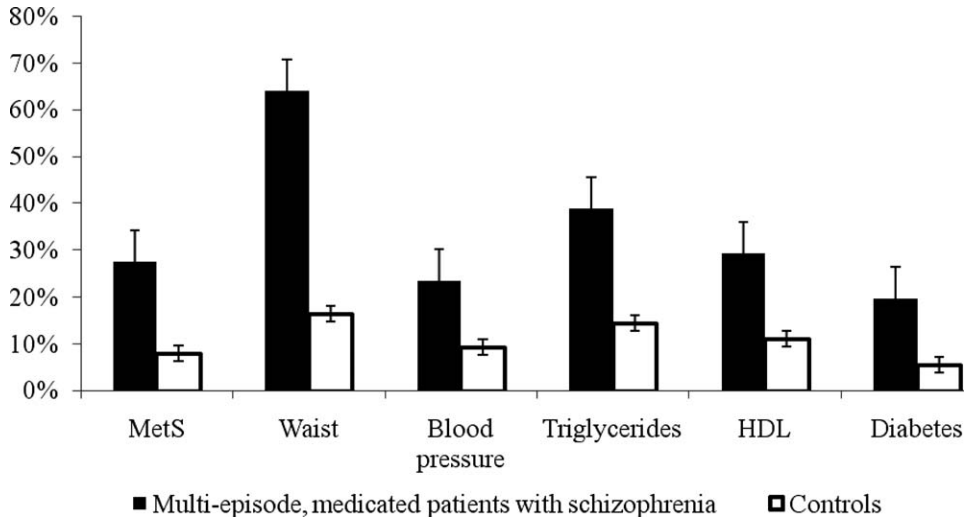

Figure 2 Overview of the prevalence of cardio-metabolic abnormalities in multi-episode medicated patients with schizophrenia versus age- and gender- or cohort-matched controls. MetS – metabolic syndrome; HDL – high-density lipoprotein cholesterol.

studies reported on hypertension (n=113,286; 61.9% male; mean age = 38.8 years). The prevalence of hypertension was 36.3% (95% CI=30.9%-42.1%). Multi-episode patients (37.3%, 95% CI=32.5%-42.3%; N=47; n=112, 167; 62.0% male; mean age = 41.7 years) did not differ (p=0.64) from first-episode (41.1%, 95% CI=20.7%-65.1%; N=1; n=488; 60.0% male; mean age = 26.6 years) and drug-naïve (31.6%, 95% CI=21.3%-44.0%; N=8; n=631; 63.0% male; mean age = 28.3 years) patients. Compared with matched general population control subjects (n=732,965), multi-episode patients (n=2,410) had a significantly increased risk of hypertension when pooling data of the individual studies (N=4) (OR=1.36; CI=1.21-1.53; p<0.001).

The Q-statistic indicated that the distribution of the prevalence of hypertriglyceridemia across individual studies was not homogeneous (Q(57)=1641.2; p<0.001). Fifty-eight studies reported on hypertriglyceridemia (n=20,996; 61.0% male; mean age = 38.5 years). The prevalence of hypertriglyceridemia was 34.5% (95% CI=30.7%-38.5%). There was no significant difference between drug-naïve (N=7; n=538; 60.8% male; mean age = 27.6 years) and first-episode (N=5; n=1,150; 58.0% male; mean age = 30.4 years) patients, with a prevalence of 23.3% (95% CI=15.4%-33.6%) and 10.5% (95% CI=5.8%-18.2%), respectively. In contrast, multi-episode patients (N=46; n=19,152; 61.2% male; mean age = 41.1 years) had a significantly increased prevalence (39.0%, 95% CI=9.9%-44.0%) compared to drug-naïve and to first-episode patients (p<0.001). Compared with matched general population control subjects (n=6,016), multi-episode patients (n=647) had a significantly increased risk of hypertriglyceridemia (OR=2.73; CI=1.95-3.83; p<0.001) (N=2).

The Q-statistic indicated that the distribution of the prevalence of abnormally low HDL cholesterol levels across individual studies was not homogeneous (Q(57)=1118.4; p<0.001). Fifty-eight studies reported on low HDL cholesterol levels (n=20,907; 61.2% male; mean age = 38.6 years). The prevalence rate was 37.5% (95% CI=34.3%-40.8%). There was no significant difference between drug-naïve (N=7; n=538; 61.7% male; mean age = 27.5 years) and first-episode (N=5; n=1,306; 57.2% male; mean age = 28.5 years) patients, with 24.2% (95% CI=17.4%-32.5%) and 16% (95% CI=10.4%-23.9%), respectively. In contrast, multi-episode patients (N=46, n=19,063; 61.5% male; mean age = 41.2 years) had a significantly increased prevalence (41.7%, 95% CI=38.3%-45.2%) compared to drug-naïve and to first-episode patients (p<0.001). Compared with general population control subjects (n=6,016), multi-episode patients (n=647) had a significantly higher risk for low HDL cholesterol levels (OR=2.35; CI=1.78-3.10; p<0.001) (N=2).

The Q-statistic indicated that the distribution of the MetS prevalence across individual studies was not homogeneous (Q(106)=1470.4; p<0.001). One hundred and seven studies reported on MetS (n=28,729; 60.6% male; mean age = 38.8 years). The prevalence was 31.1% (95% CI=28.9%-33.4%). There was no significant difference between drug-naïve (N=11; n=733; 60.0% male; mean age = 29.2 years) and first-episode (N=6; n=1,039; 60.1% male; mean age = 30.1 years) patients, with 10.0% (95% CI=7.0%-14.2%) and 15.9% (95% CI=10.5%-23.3%), respectively. In contrast, multi-episode patients (N=46; n=26,957; 60.6% male; mean age = 38.8 years) had a significantly increased prevalence (34.2%, 95% CI=31.9%-36.6%) compared to drug-naïve and to first-episode patients (p=0.007). Compared with age- and gender- or cohort-matched general population control subjects (n=6,632), multi-episode medicated patients (n=868) had a significantly higher risk for MetS (OR=2.35; CI=1.68-3.29; p<0.001) (N=4).

The Q-statistic indicated that the distribution of the prevalence of diabetes across individual studies was not homogeneous (Q(42)=3718.8; p<0.001). Forty-one studies reported on diabetes (n=161,886; 61.3% male; mean age=40.1 years). The prevalence was 9.0% (95%CI=7.3%-11.1%). Multi-episode patients (9.5%, 95% CI=7.3%-12.2%; N=29; n=116,751; 60.0% male; mean age = 43.8 years) did not differ (p=0.56) from first-episode (8.7%, 95% CI=5.6%-13.3%; N=5; n=1033; 61.0% male; mean age = 32.4 years) and drug-naïve (6.4%, 95% CI=3.2%-12.5%; N=5; n=346; 66.0% male; mean age = 29.2 years) patients. Compared with matched general population control subjects (n=3,891,899), multi-episode patients (n=106,720) had a significantly higher risk for diabetes (OR=1.99; CI=1.55-2.54; p<0.001) (N=15).

Figure 2 presents an overview of the mean prevalence for all investigated cardio-metabolic parameters in multi-episode medicated patients with schizophrenia versus healthy controls.

DISCUSSION

To the best of our knowledge, this meta-analysis is the first to demonstrate that medicated multi-episode patients with schizophrenia are at a more than fourfold increased risk for abdominal obesity compared to age- and gender- or cohort-matched general population controls (OR=4.43). The odds ratio of risk for low HDL cholesterol (OR=2.35), MetS (OR=2.35) and hypertriglyceridemia (OR=2.73) was more than double. Compared to general population controls, multi-episode patients with schizophrenia also have almost twice the risk (by odds) for diabetes (OR=1.99), while the odds for hypertension was 1.36. Our data also confirm previous findings (40) that chronic, medicated patients with schizophrenia have a significantly increased risk for developing cardio-metabolic abnormalities compared with first-episode and drug-free patients. No significant differences in blood pressure and diabetes between chronic, medicated, first-episode and drug-free patients were, however, found. A possible reason might be that we were not able to control for use of antihypertensive and glucose lowering drugs.

We wish to acknowledge some limitations in our primary database that should be considered when interpreting the results. First, there was considerable heterogeneity, which could only be partly controlled by stratification for disease stage. Second, there was a very limited number of studies comparing first-episode and unmedicated patients with controls and hence these analyses were not possible. Third, there was marked variation in the sample size of the included studies. Fourth, we were not able to adjust for type and duration of antipsychotic treatment.

Next to a low socio-economic status (8), behavioural factors (16-23), side effects of antipsychotic and concomitantly used medications, and fragmentation of health care (24-28), various inflammatory processes could contribute to the increased cardio-metabolic risk observed in patients with schizophrenia (182). In a recent review, Steiner et al (183) highlighted the alterations in the immune system of patients with schizophrenia. Increased concentrations of interleukin (IL)-1, IL-6, and transforming growth factor-beta appear to be state markers, whereas increased levels of IL-12, interferon-gamma, tumor necrosis factor-alpha, and soluble IL-2 receptor appear to be trait markers of schizophrenia. The mononuclear phagocyte system and microglial activation are also involved in the early course of the disease. The mechanisms whereby inflammatory mediators initiate a wide range of cardio-metabolic abnormalities are being elucidated, but the causes of the vulnerability to chronic low-grade inflammation are still speculative, especially as increased body mass index (BMI) and obesity are in and of themselves associated with increased inflammation (182,183).

Since patients with schizophrenia are a high-risk group for developing cardio-metabolic abnormalities, they should be routinely screened for CVD risk factors at key stages (184,185). This can be achieved by establishing a risk profile based on consideration of cardio-metabolic factors (abdominal obesity, dyslipidemia, hypertension, hyperglycemia), but also through consideration of a patient's personal and family history, covering diabetes, hypertension, CVD (myocardial infarction or cerebrovascular accident, including age at onset) and behavioural factors (e.g., poor diet, smoking and physical inactivity) (186-189). This risk profile should afterwards be used as a basis for ongoing monitoring, treatment selection and management.

Guidelines from the WPA (189) recommend that monitoring should be conducted at the initial presentation and before the first prescription of antipsychotic medication and (for patients with normal baseline tests) repeated at 6 weeks (for blood glucose) and 12 weeks after initiation of treatment, and at least annually thereafter for all parameters. The 6-week blood sugar assessment to rule out precipitous diabetes onset has, however, been recommended in Europe, but not in the US (189). In light of the high rates of metabolic abnormalities observed in all settings, we propose that minimum monitoring should include waist circumference. Optimal monitoring should also include fasting glucose, triglycerides and HDL-cholesterol and hemoglobin A1C (HbA1c). HbA1c has the advantage of not requiring a fasting sample in those taking antipsychotic medication and was recently shown to identify patients with pre-diabetes and diabetes not captured by assessments of fasting glucose (190,191). Moreover, a recent study found that the optimal testing protocol to detect diabetes was a HbA1c threshold $\geq$5.7%, followed by conventional testing with an oral glucose tolerance test (OGTT) and fasting blood glucose in patients who test positive (192).

Psychiatrists should, regardless of the medication prescribed, monitor and chart waist circumference of every patient with schizophrenia at every visit, and should encourage patients to monitor and chart their own weight (189). The WPA (189) states that these physical health monitoring tests

are simple, easy to perform and inexpensive, and therefore can/should be implemented in the health care systems of developed as well as developing countries. In a recent study (193), we demonstrated that the optimal clinical predictors of diabetes in severe mental illness were BMI, waist/hip ratio, height, age, and duration of illness. No single clinical factor was able to accurately rule in a diagnosis of diabetes, but three variables could be used as an initial screening (rule-out) test, namely BMI, waist/hip ratio and height. A BMI <30 had a 92% negative predictive value in ruling out diabetes. Of those not diabetic, 20% had a BMI <30. It is therefore recommended that clinicians use HbA1, fasting glucose and OGTT when testing for diabetes in patients with schizophrenia, especially high risk patients, based on the above clinical factors.

In addition to optimal screening and follow-up, the WPA (189) recommends that psychiatrists, physicians, physical therapists and other members of the multidisciplinary team should help educate and motivate patients with schizophrenia to improve their lifestyle through use of behavioural interventions, including smoking cessation, dietary measures, and exercise. In two recent, multi-centre studies (194,195) we showed that many, although not all, patients with schizophrenia were either unaware of the need to change their lifestyle or did not possess the knowledge and skills required to make appropriate lifestyle changes. Therefore, it is useful that family members and caregivers be offered education regarding the increased cardio-metabolic risk of patients with schizophrenia and ways to mitigate this risk.

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