Prevalence of diabetes, metabolic syndrome and metabolic abnormalities in schizophrenia over the course of the illness: a cross-sectional study
M De Hert*1, R van Winkel1, D Van Eyck1, L Hanssens2, M Wampers1, A Scheen3 and J Peuskens1

Address: 1University Psychiatric Center Katholieke Universiteit Leuven, Leuvense Steenweg 517, 3070 Kortenberg, Belgium, 2Department of Epidemiology and Public Health, University Liege, Belgium and 3Department of Diabetes and Metabolic Disorders, CHU Sart Tilman, University Liege, Belgium

Email: M De Hert* - Marc.de.hert@uc-kortenberg.be; R van Winkel - Ruud.van.Winkel@uc-kortenberg.be; D Van Eyck - Dominique.Van.Eyck@uc-kortenberg.be; L Hanssens - Linda.Hanssens@student.ulg.be; M Wampers - Martien.Wampers@uc-kortenberg.be; A Scheen - andre.scheen@chu.ulg.ac.be; J Peuskens - Jozef.Peuskens@uc-kortenberg.be
* Corresponding author

Abstract

Background: Patients with schizophrenia are at high risk of developing metabolic abnormalities.

Method: A prospective study focusing on metabolic disturbances in patients with schizophrenia, including an oral glucose tolerance test, is currently ongoing at our University Hospital and affiliate services. The prevalence of metabolic abnormalities at baseline was assessed in a cohort of 415 patients with schizophrenia. The sample was divided into 4 groups according to duration of illness: first-episode patients (<1.5 years), recent-onset patients (between 1.5 and 10 years), subchronic patients (between 10 and 20 years) and chronic patients (>20 years).

Results: Metabolic abnormalities were already present in first-episode patients, and considerably increased with increasing duration of illness. When compared to the general population matched for age and gender, much higher rates of the metabolic syndrome (MetS) and diabetes were observed for patients with schizophrenia. For MetS, the increase over time was similar to that of the general population. In contrast, the difference in the prevalence of diabetes in patients with schizophrenia and the general population dramatically and linearly increased from 1.6% in the 15–25 age-band to 19.2% in the 55–65 age-band.

Conclusion: Thus, the current data suggest that on the one hand metabolic abnormalities are an inherent part of schizophrenic illness, as they are already present in first-episode patients. On the other hand, however, our results suggest a direct effect of the illness and/or antipsychotic medication on their occurrence. The data underscore the need for screening for metabolic abnormalities in patients diagnosed with schizophrenia, already starting from the onset of the illness.
I. Background
Metabolic abnormalities have consistently been identified as a part of schizophrenic illness [1-4], but with the introduction of second generation antipsychotics and their possible association with metabolic abnormalities [5-7], the interest in this topic has been renewed.

Many studies have since then provided convincing evidence for a high risk of diabetes and other glucose abnormalities [5,8-12], the metabolic syndrome[13,14], and mortality due to elevated cardiovascular risk in patients with schizophrenia [15-18].

These metabolic abnormalities are of major clinical concern, not only because of their direct, somatic effects on morbidity and mortality, but also because of their association with psychiatric outcome, such as a higher prevalence of psychotic and depressive symptoms[19], a lower functional outcome [20], a worse perceived physical health [19] and lower adherence to medication [21].

The reasons that underlie the high prevalence of these metabolic abnormalities are much debated, especially when considering the possible role of second-generation, 'atypical' antipsychotics in the occurrence of these abnormalities. On the one hand, many studies have suggested a role of (certain) atypical antipsychotics in the occurrence of metabolic abnormalities, both case reports [22-26], cross-sectional or retrospective studies [27,28] as prospective studies [29,30]. On the other hand, other studies have provided evidence for an increased prevalence of central obesity [31] and glucose abnormalities such as impaired fasting glucose and insulin resistance [32] in drug-naïve first-episode patients, suggesting that metabolic abnormalities are an inherent part of schizophrenic illness.

Most probably, these two views represent a polarisation of clinical reality, as medical factors (weight, age,...), psychosocial factors (environmental stress, exercise, dietary habits,...), genetic factors (family history of diabetes, possible genetic overlap with psychiatric illness) and pharmacological factors (weight gain, medication-induced lipid and glucose abnormalities) are likely to interact in their influence on the occurrence of metabolic abnormalities, making it difficult to disentangle the influence of each individual risk factor.

Next to the interrelationship of the individual risk factors, the lack of insight into the development and course of these metabolic abnormalities makes an evaluation of the best possible strategy to assess and treat these abnormalities difficult. If metabolic abnormalities are already present in the first illness episode of psychotic patients and are an inherent part of psychiatric illness, would it be useful then to invest in prevention strategies? On the other hand, if metabolic abnormalities are caused by an interplay of many risk factors, could early detection and treatment of these risk factors result in a reduction of the prevalence of these metabolic abnormalities, and thus in a reduction of the excess mortality in patients with schizophrenia?

To address these issues, the current study aimed to gather some insight into the development and course of metabolic abnormalities in schizophrenia, by assessing the presence of metabolic abnormalities in 4 cohorts of patients with schizophrenia: a cohort of first-episode patients with a duration of illness (DOI) of less than 1.5 years, a cohort of recent-onset patients with a DOI of 1.5 to 10 years, a cohort of subchronic patients with a DOI of 10 to 20 years and a cohort of chronic patients with a DOI of more than 20 years. It was hypothesized that metabolic abnormalities would already be present in first-episode patients, but that their prevalence would increase with DOI, in a rate that would be higher than that of the general population matched for age and gender.

2. Methods
All consecutive patients with a DSM-IV diagnosis of schizophrenia (SCH) or schizoaffective (SA), both out (26.3%) or inpatients, of the university psychiatric hospital St. Jozef (Kortenberg, Belgium) and its affiliate services, were asked to participate in an extensive screening and prospective follow-up study of metabolic parameters. The prospective inclusions started in November 2003. At baseline, patients received a full fasting laboratory screening (including a full lipid profile and measurement of glycated haemoglobin (HbA1c)), clinical measurements and an ECG. A 75 gr glucose load Oral Glucose Tolerance Test (OGTT) was performed in all patients. Patients were initiated on an overnight fast and were monitored during the OGTT. Insulin resistance was measured using fasting glucose and insulin concentrations with the HOMA method. All laboratory analyses were performed in the same laboratory.

The sample was divided into 4 groups according to duration of illness: first-episode patients (DOI<1.5 years), recent-onset patients (DOI<10 years), subchronic patients (DOI between 10 and 20 years) and chronic patients (DOI >20 years).

The presence of the MetS was assessed using the ATP-III criteria [33], the adapted ATP-III criteria (fasting glucose ≥ 100 mg/dl instead of 110 mg/dl) [34] and the recent IDF criteria (Table 1) [35]. For the diagnosis of diabetes and prediabetic abnormalities, the criteria of The American Diabetes Association were used (Impaired fasting glucose (IFG ≥ 100 mg/dl and Impaired Glucose Tolerance (IGT), glucose ≥ 140 mg/dl at 2 hours in the OGTT) [36].
Descriptive statistics were computed for the basic demographic and clinical variables as well as for the variables relevant for the evaluation of metabolic abnormalities. The influence of the presence/absence of the metabolic syndrome and the presence/absence of glucose abnormalities on continuous variables was assessed by means of an independent samples t-test. The association between categorical variables was evaluated by a chi-square test.

In a second approach, in order to allow a comparison with the general population, the sample was divided into ten-year age-bands (15–25; 25–35; 35–45; 45–55 and 55–65 year old patients). The population data for the comparison for MetS came from the Asklepios Study [38]. In this study cardiovascular risk factors were evaluated by a primary care physician in 2,524 healthy subjects between 35 and 55. The data for the comparison of the prevalence of diabetes was obtained from an online Belgian Government report [39]. This report is based on all epidemiological data on diabetes available in Belgium and an evaluation of sales of antidiabetic medication, all ages, and a survey of pharmacies. A weighted mean was calculated for the general population age-bands to control for gender differences (percentage of male patients in the current study sample times prevalence of diabetes/MetS for male subjects from the general population, plus percentage of female patients in the current study sample times prevalence of diabetes/MetS for female subjects from the general population). This weighted mean for the general population was then compared to the mean of the study sample per age band.

The study was approved by an ethical committee and all patients gave written informed consent.

## 3. Results

### 3.1. Subjects

The mean age of the patients was 37.7 years (std 11.3) and the mean duration of illness was 10.8 years (std 10.2). Of all patients, 67.2% of patients were male; 99% were white and Belgian natives. The studied population consisted of 415 patients with schizophrenia: 100 first-episode patients (24.1%), 130 recent-onset patients (31.3%), 106 subchronic patients (25.5%) and 79 chronic patients (19.0%). The demographic characteristics of the different cohorts are shown in Table 2.

On average, patients took 3.2 (std 2.0) different medications. Antipsychotics were combined with anticholinergics (16%), antidepressants (38%), benzodiazepines (36%), mood stabilisers (21%) and somatic medication (41%) (Table 3). Regarding somatic medication, 0.7% (3 patients) were being treated with metformin, 1.7% of patients took a statin (7 patients) and 10.1% (42 patients) took antihypertensive medication. 68% of all patients were smokers, with no significant differences between groups.

All but 2 patients were treated with antipsychotic medication at the time of assessment. First-generation antipsychotics were used by 19.3% (n = 80) of patients, second-generation antipsychotics by 91.1% (n = 378). The majority of patients were treated with one antipsychotic (n = 349, or 84.1%); 90.0% of this group received a second-generation antipsychotic, 10.0% a first-generation antipsychotic. Patients in the first-episode group were more likely to receive second-generation antipsychotics, to take a smaller number of different medications and to be on monotherapy (Table 3).

### 3.2. Metabolic abnormalities according to duration of illness

First-episode patients had a normal BMI and BMI segmentation (normal, overweight and obese). With increasing DOI, weight also significantly increased. Similarly, there was a significant increase in waist circumference (Tables 2 and 4). In all groups, there was a high prevalence of family history of both metabolic (diabetes and lipid abnormalities) as well as cardiovascular disorders.

MetS was prevalent in all groups but significantly increased with increasing DOI, as did the individual crite-
ria, except for low HDL (Table 4 and Figure 2). The frequency of elevated waist and glucose abnormalities was more than doubled in patients with a duration of illness of more than 10 years, when compared to first-episode patients. Female compared to male patients were significantly more often overweight or obese and more frequently met the waist circumference criterium, according to both ATP III and IDF criteria ($\chi^2 = 30.6$ and $\chi^2 = 16.36$, $p < .0001$).

In the total sample, 6.3% ($n = 26$) met criteria for diabetes, another 23.4% ($n = 97$) had prediabetic abnormalities, defined as impaired fasting glucose (IFG; fasting glucose $\geq 125$ mg/dl) and/or impaired glucose tolerance (IGT; glucose $\geq 200$ mg/dl at 120 minutes in the OGTT). Of the patients meeting criteria for diabetes, 12 (46.2%) met criteria with fasting values, 14 (53.8%) met criteria at 120 min in the OGTT and 4 (15.4%) met criteria both fasting and at 120 min in the OGTT. This means that when the current sample would have only been screened with a fasting glucose assessment, as suggested by the American Psychiatric Association/American Diabetes Association 37, only 12 of the 26 diabetes cases (46.2%) would have been identified. The prevalence of glucose abnormalities differed significantly between the different patient cohorts. The prevalence of diabetes increased from 3% in the first-episode and recent-onset group to 16.5% in the chronic group (Table 5 and Figure 2). The mean values of parameters evaluated in the OGTT did not differ significantly between groups. Diabetes and glucose abnormalities were more frequent in patients treated with clozapine ($\chi^2 = 29.17$, $p < .0012$). The distribution of glucose abnormalities over antipsychotic treatment regimes is shown in table 6.

As expected, the prevalence of the metabolic syndrome, regardless of the definition used, was significantly higher in diabetic subjects (ATP-III 76.7%, ATP-III A 80.0%, IDF 80.0%) compared to patients with prediabetic abnormalities (ATP-III 35.8%, ATP-III A 49.5%, IDF 54.1%) and patients without glucose abnormalities (ATP-III 17.5%, ATP-III A 17.7%, IDF 21.9%). Patients with MetS were more likely to meet criteria for diabetes or prediabetic abnormalities in all definitions of the MetS applied.

All parameters evaluated in the OGTT (glucose and insulin values fasting, at 30 minutes, at 60 minutes and 120 minutes) as well as HOMA-IR and glycated haemoglobin
A1c were significantly different between patients with or without the metabolic syndrome regardless of the definition (p < .0001), with higher values in patients with MetS. Similar highly significant differences were found on all fasting serum lipid values and calculated lipid risk factors for cardiovascular disease (cholesterol, triglycerides, HDL, LDL, CHOL/HDL and LDL/HDL) (p < .0001).

Table 3: Medication in different groups.

|                        | FE       | <10 yr   | 10 to 20 yr | >20 yr   | p        |
|------------------------|----------|----------|-------------|----------|----------|
| Anticholinergic        | 8% (8)   | 13.1% (17)| 16.0% (17)  | 31.5% (25)| 0.0002   |
| Benzodiazepine         | 36% (36) | 23.8% (31)| 44.4% (46)  | 44.3% (35)| 0.0003   |
| Antidepressant         | 23% (23) | 42.3% (55)| 44.3% (47)  | 43.0% (34)| 0.0043   |
| Mood stabiliser        | 9% (9)   | 20.8% (27)| 30.2% (72)  | 25.3% (20)| 0.0019   |
| Antipsychotic          |          |          |             |          | 0.0001   |
| Only first generation  | 3% (3)   | 4.6% (6)  | 9.5% (10)   | 20.5% (16)|          |
| Only second generation | 94% (94)| 87.7% (113)| 74.5% (79)  | 60.3% (47)|          |
| Combination            | 3% (3)   | 7.6% (10) | 16.0% (17)  | 19.2% (15)|          |
| Second generation AP   | 97% (97) | 94.6% (123)| 90.5% (96)  | 78.5% (62)| 0.0001   |
| Second generation (N=400 prescriptions) |          |          |             |          | 0.0001   |
| Amisulpride (n = 32)   | 5% (5)   | 5.8% (6)  | 16.0% (17)  | 5.9% (4)  |          |
| Aripiprazole (n = 4)   | 3% (3)   | 0.7% (1)  | 0% (0)      | 0% (0)    |          |
| Clozapine (n = 74)     | 3% (3)   | 15.5% (20)| 29.1% (30)  | 30.9% (21)|          |
| Risperidone (n = 98)   | 32% (32)| 20.2% (26)| 23.3% (24)  | 23.5% (16)|          |
| Quetiapine (n = 53)    | 10% (10)| 10.7% (25)| 10.7% (11)  | 10.3% (7) |          |
| Olanzapine (n = 139)   | 47% (47)| 31.1% (32)| 31.1% (32)  | 29.4% (20)|          |

Table 4: Metabolic syndrome and criteria prevalence.

|                        | FE       | <10 yr   | 10 to 20 yr | >20 yr   | p        |
|------------------------|----------|----------|-------------|----------|----------|
| MS ATP-III             | 17% (17) | 21.5% (28)| 34.9% (37)  | 36.7% (29)| 0.0026   |
| Criteria:              |          |          |             |          |          |
| Waist (M>102, F>88)    | 18% (18) | 32.3% (42)| 45.3% (48)  | 44.3% (42)| 0.0001   |
| BP (≥ 130/85)          | 43% (43) | 34.6% (45)| 57.5% (61)  | 64.7% (51)| 0.0001   |
| HDL (M<40 mg/dl, F<50 mg/dl) | 26% (26) | 27.7% (36)| 31.1% (33)  | 31.6% (26)| ns       |
| TG (≥ 150 mg/dl)       | 33% (33) | 36.1% (47)| 50.9% (54)  | 46.8% (37)| 0.0252   |
| Glucose (≥ 110 mg/dl)  | 3% (3)   | 2.3% (3)  | 11.3% (12)  | 20.2% (16)| 0.0001   |
| MS ATP-III A (AHA)     | 18% (18) | 24.6% (32)| 39.6% (42)  | 44.3% (35)| 0.0001   |
| Criteria:              |          |          |             |          |          |
| Waist (M≥94, F≥80)     | 18% (18) | 32.3% (42)| 45.3% (48)  | 44.3% (42)| 0.0001   |
| BP (≥ 130/85)          | 43% (43) | 34.6% (45)| 57.5% (61)  | 64.7% (51)| 0.0001   |
| HDL (M<40 mg/dl, F<50 mg/dl) | 26% (26) | 27.7% (36)| 31.1% (33)  | 31.6% (26)| ns       |
| TG (≥ 150 mg/dl)       | 33% (33) | 36.1% (47)| 50.9% (54)  | 46.8% (37)| 0.0252   |
| Glucose (≥ 100 mg/dl)  | 8% (8)   | 16.9% (22)| 27.4% (29)  | 40.5% (32)| 0.0001   |
| MS IDF                 | 17% (17) | 28.5% (37)| 42.4% (45)  | 49.4% (39)| 0.0001   |
| Criteria:              |          |          |             |          |          |
| Waist (M ≥ 94, F ≥ 80)| 38% (38) | 55.4% (72)| 73.6% (78)  | 70.9% (56)| 0.0001   |
| BP (≥ 130/85)          | 43% (43) | 34.6% (45)| 57.5% (61)  | 64.7% (51)| 0.0001   |
| HDL (M<40 mg/dl, F<50 mg/dl) | 26% (26) | 27.7% (36)| 31.1% (33)  | 31.6% (26)| ns       |
| TG (≥ 150 mg/dl)       | 33% (33) | 36.1% (47)| 50.9% (54)  | 46.8% (37)| 0.0252   |
| Glucose (≥ 100 mg/dl)  | 8% (8)   | 16.9% (22)| 27.4% (29)  | 40.5% (32)| 0.0001   |
The mean lipid values were lower in the first-episode group, although not statistically significant, in contrast to the frequency of abnormal lipid values that differed significantly for total cholesterol, triglycerides, LDL, CHOL/HDL and LDL/HDL (Table 7).

3.3. Comparison to the general population
The division of the study sample into age-bands resulted in a group of 98 patients in the 15–25 age-band, 127 in the 25–35 age-band, 99 in the 35–45 age-band, 71 in the 45–55 age-band and 20 in the oldest age-band (55–65).

Recent data on the prevalence of MetS according to ATP III and IDF criteria in the population were available for the age-bands 35–45 and 45–55 years old [38]. When compared to the calculated weighted mean prevalence for the general population, the prevalence of MetS was considerably higher in patients. The increase with age of the prevalence of MetS was similar in patients and the general population (Figure 3).

For diabetes, data were available on the prevalence for all the age-bands that were investigated in the present study [39]. In the age-band 15–25, a five times higher prevalence of diabetes was found when compared to the general population. With increasing age, the absolute difference between patients and the general population dramatically and linearly increased from 1.6% in the 15–25 age-band to 19.2% in the oldest age-band (Figure 4). The prevalence of diabetes per age-band, however, was 4 to 5 times higher in patients (15–25: 5.0; 25–35: 3.6; 35–45: 5.5; 45–55: 5.3 and 55–65: 4.3).
from 1.6% in the 15–25 age-band to 19.2% in the 55–65 age-band. The prevalence of diabetes per age-band was 4 to 5 times higher in patients with schizophrenia.

### 4.2. Prevalence of metabolic abnormalities and its implications for clinical practice

The data confirm that metabolic abnormalities are highly prevalent in a relatively young sample of schizophrenic patients treated with antipsychotics. Two large scale naturalistic studies in Belgium however revealed that the screening and diagnosis of these abnormalities in patients treated with antipsychotics still have not become routine practice, and that therefore, these abnormalities frequently remain untreated [40,41]. The data also suggest that when these patients would have been screened according to the current American Psychiatric Association/American Diabetes Association guidelines, relying only on fasting glucose, more than half of patients with diabetes (14 out of 26 or 53.8%) would not have been detected and thus, would not have been adequately treated. This is in line with the findings of Adam and Tarigan [42], and underscores the need for a more thorough screening in high-risk populations. Clearly, schizophrenic patients treated with antipsychotics ought to be considered at high risk of developing diabetes [43], as is confirmed by the current data.

Although considered costly and inconvenient by some [44,45], the use of OGTT’s as a screening method for patients diagnosed with schizophrenia should therefore be encouraged, and certainly for very high risk patients presenting with IFG [46,47] or MetS. Moreover, the current data underscore the need for screening for metabolic abnormalities in patients diagnosed with schizophrenia, already starting from the onset of the illness, as suggested in the literature [12,47-49].

### 4.3. Evolution over time: expression of vulnerability or iatrogenic effect?

The current data suggest a greater vulnerability to develop metabolic abnormalities for patients diagnosed with schizophrenia when compared to the general population. A higher prevalence of metabolic abnormalities was already present in the age-band between 15 and 25 years old and increased with increasing age and duration of illness, which suggests a direct impact of the illness and/or negative metabolic side-effects of antipsychotic medication. The suggestion of a direct impact of the illness of schizophrenia and/or its pharmacological treatment on the development of metabolic abnormalities is in line with another Belgian study (BEST, i.e. "Belgian Evaluation of Screening and Treatment of high risk patients based on waist and age") [50]. This study was recently performed in 8,587 middle-aged (40–75 years) individuals without any cardiovascular history, consecutively selected by general practitioners upon a moderately increased waist circumference (≥ 80 cm in women and ≥ 94 cm in men). In this survey, 25% of the non-diabetic population had the metabolic syndrome according to NCEP-ATP III criteria, thus a much lower prevalence than the 36.7% observed in the subgroup of patients with the longest duration of the ill-

### Table 5: Glucose abnormalities.

|                  | FE     | <10 yr | 10 to 20 yr | >20 yr | p     |
|------------------|--------|--------|-------------|--------|-------|
| All abnormalities| 12% (12) | 22.3% (29) | 36.8% (37) | 44.5% (43) | 0.0001 |
| IFG, IGT         | 9% (9)  | 20% (26) | 30.2% (32) | 38.0% (30) |       |
| Diabetes         | 3% (3)  | 2.3% (3)  | 6.6% (7)   | 16.5% (13) |       |
| Fasting abnormalities |     |        |             |        |       |
| IFG              | 8% (8)  | 16.9% (22) | 27.3% (29) | 40.5% (32) | 0.0001 |
| Diabetes         | 6% (6)  | 16.1% (21) | 24.5% (26) | 32.9% (26) |       |
| Abnormalities at 120 min in OGTT | | | | | |
| IGT              | 7% (7)  | 9.2% (12) | 22.6% (24) | 35.4% (28) | 0.0001 |
| Diabetes         | 6% (6)  | 6.9% (9)  | 17.9% (19) | 24.0% (19) |       |
ness. This difference is striking since the subjects of BEST were older (61 vs 50 years) and had a much higher BMI (31.8 vs 26.6 kg/m²) when compared to the patients with chronic schizophrenia in our sample, obviously due to selection criteria. Furthermore, in the subgroup with the longest duration of illness, the prevalence of diabetes (16.5%) was almost similar to that observed in the non-psychiatric population of the BEST study (18%), despite a 10 year younger age and a 5 kg/m² lower BMI. These findings support a deleterious metabolic effect of the illness of schizophrenia itself and/or antipsychotic medication.

Interestingly, the increase of the prevalence of the MetS with age was similar to that of the general population, meaning that although there was a higher prevalence of the MetS in patients with schizophrenia, the difference in prevalence with the general population remained more or less stable. In contrast, the difference in the prevalence of diabetes in patients with schizophrenia and the general population dramatically and linearly increased from 1.6% in the 15–25 age-band to 19.2% in the 55–65 age-band. The interpretation of these findings is difficult and needs to be done with caution, especially given the cross-sectional nature of the current study. They seem to suggest that the development of diabetes is not necessarily secondary to the development of MetS and that there could be an inherent vulnerability to diabetes in patients with schizophrenia, possibly aggravated by the metabolic side-effects of (some) antipsychotic medications. The finding that patients who were treated with clozapine were more likely to develop diabetes compared to patients treated with other antipsychotics is in line with this interpretation.

4.4. Methodological issues
This study also has some limitations. First and most importantly, it is a cross-sectional study. Therefore, one has to be cautious when interpreting the differences between patient groups, since cohort effects could (in part) explain the differences in the presence of metabolic abnormalities between patient groups. However, cohort effects are most likely to reduce differences between patients to the null in the present study, as the prevalence of diabetes and obesity has been rising rapidly in children, adolescents and young adults worldwide [51,52]. Second, this study was restricted to one site, indicating that the interpretation of the results needs to be done with caution, since large regional differences in metabolic parameters have been reported in the literature [53]. Third, patients were not equally spread over the different age-bands, with especially a low number of patients in the oldest age-band (n = 20) which could have biased our findings in this specific age-band. Fourth, insufficient patients were included in the present study to allow a dichotomization according to gender over the different age-bands, although a significant influence of gender on the occurrence of metabolic abnormalities was found in

Table 6: Glucose abnormalities in relation to antipsychotic treatment.

|                   | Diabetes (n = 26) | Prediabetes (n = 97) | Normal values (n = 292) |
|-------------------|------------------|---------------------|------------------------|
| Only FGA (n = 35) | 8.6% (3)         | 25.7% (9)           | 65.7% (23)             |
| Combination FGA + SGA (n = 45) | 2.2% (1)     | 28.9% (13)          | 68.9% (31)             |
| Combination SGA (n = 19) | 5.3% (1)       | 21.0% (4)           | 73.7% (14)             |
| Only 1 SGA (n = 314) | 6.7% (21)   | 22.6% (71)          | 70.7% (222)            |
| Amisulpride (n = 26) | 0% (0)        | 3.9% (1)            | 96.1% (25)             |
| Aripsiprazole (n = 3) | 0% (0)        | 0% (0)              | 100% (3)               |
| Clozapine (n = 54) | 9.3% (5)       | 42.6% (23)          | 48.1% (26)             |
| Risperidone (n = 75) | 6.6% (5)      | 22.7% (17)          | 70.7% (53)             |
| Quetiapine (n = 44) | 11.4% (5)     | 9.1% (4)            | 79.5% (35)             |
| Olanzapine (n = 112) | 5.4% (6)      | 23.2% (26)          | 71.4% (80)             |

Table 7: Abnormal lipid values.

|                   | FE | <10 yr | 10 to 20 yr | >20 yr | p     |
|-------------------|----|--------|-------------|--------|-------|
| CHOL (≥ 190 mg/dl) | 27% (27) | 45.4% (59) | 61.3% (65) | 60.8% (48) | 0.0001 |
| TG (≥ 150 mg/dl)  | 33% (33) | 36.1% (47) | 50.9% (54) | 46.8% (37) | 0.0252 |
| HDL (M<40 mg/dl; F=50 mg/dl) | 26% (26) | 27.7% (36) | 31.1% (33) | 31.6% (26) | ns |
| LDL (≥ 115 mg/dl) | 28% (28) | 45.4% (59) | 54.7% (58) | 53.2% (42) | 0.0005 |
| CHOL/HDL (≥ 4)    | 30% (30) | 42.3% (55) | 53.8% (57) | 49.4% (39) | 0.0043 |
| LDL/HDL (≥ 3)     | 14% (14) | 23.1% (30) | 33.0% (35) | 32.9% (26) | 0.0050 |
the present study and was also reported in the literature [54, 55].

5. Conclusion
Metabolic abnormalities were already present in first-episode patients, but their prevalence considerably increased with increasing duration of illness. When compared to the general population matched for age and gender, higher rates of the MetS and diabetes were observed for patients with schizophrenia. For the MetS, the increase of the prevalence was similar to that of the general population. In contrast, the difference in the prevalence of diabetes in patients with schizophrenia and the general population dramatically and linearly increased from 1.6% in the 15–25 age-band to 19.2% in the 55–65 age-band. The prevalence of diabetes per age-band was 4 to 5 times higher in patients with schizophrenia. Thus, the current data suggest that on the one hand metabolic abnormalities are an inherent part of schizophrenic illness, as they are already present in first-episode patients. On the other hand, however, the current data suggest a direct effect of the illness and/or antipsychotic medication on the development of metabolic abnormalities, so that prevention strategies, identification of risk factors, early detection through adequate screening and treatment of metabolic abnormalities could well be of eminent importance in these patients. The current data underscore the need for screening for MetS, diabetes and lipid abnormalities in patients diagnosed with schizophrenia, already starting from the onset of the illness.

Competing interests
The author(s) declare that they have no competing interests.

Authors' contributions
Study planning and design: M. De Hert, L. Hanssens, A. Scheen, J. Peuskens
Data collection and statistical analysis: M. De Hert, R. van Winkel, D. Van Eyck, M. Wampers

Drafting report: all

Acknowledgements
This study was made possible by a grant of outcomes research of BMS

References
1. Meduna L, Gerty F, Urse V: Biochemical disturbances in mental disorders. Arch Neurol Psychiatry 1942;38:52.
2. Raphael TP: Blood sugar studies in dementia praecox and manic depressive insanity. Arch Neurol Psychiatry 1921;5:687-709.
3. Homel P, Casey D, Allison DB: Changes in body mass index for individuals with and without schizophrenia, 1987-1996. Schizophr Res 2002, 55:277-284.
4. Allison DB, Fontaine KR, Heo M, Mentore JL, Cappelleri JC, Chandler LP, Weiden PJ, Cheskin LJ: The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999, 60:215-220.
5. Jin H, Meyer JM, Jeste DV: Atypical antipsychotics and glucose dysregulation: a systematic review. Schizophr Res 2004, 71:195-212.
6. Allison DB, Casey DE: Antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry 2001, 62 Suppl 7:22-31.
7. Jin H, Meyer JM, Koro CE: The effects of antipsychotic therapy on serum lipids: a comprehensive review. Schizophr Res 2004, 70:1-17.
8. Jin H, Meyer JM, Jeste DV: Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. Ann Clin Psychiatry 2002, 14:59-64.
9. Haupt DW, Newcomer JW: Hyperglycemia and antipsychotic medications. J Clin Psychiatry 2001, 62 Suppl 27:15-26; discussion 40-1.
10. Debyen Aj, De Hert M: [Drug-induced diabetes mellitus: the example of atypical antipsychotics]. Rev Med Liege 2005, 60:455-460.
11. Newcomer JW: Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 2005, 19 Suppl 2:1-19.
12. De Nayer A, De Hert M, Scheen A, Van Gaal L, Peuskens J: Conference report: Belgian consensus on metabolic problems associated with second-generation antipsychotics. Int J Psy Clin Pract 2005, 9:130-137.
13. Heiskanen T, Niskanen L, Lyytikainen R, Saarinen PI, Hinikka J: Metabolic syndrome in patients with schizophrenia. J Clin Psychiatry 2003, 64:575-579.
14. Basu R, Brar JS, Chengappa KN, John V, Parepally H, Gershon S, Schlicht P, Kupfer DJ: The prevalence of the metabolic syndrome in patients with schizoaffective disorder--bipolar subtype. Bipolar Disord 2004, 6:314-318.
15. Brown S: Excess mortality of schizophrenia. A meta-analysis. Br J Psychiatry 1997, 171:502-508.
16. Brown S, Inskip H, Barracough B: Causes of the excess mortality of schizophrenia. Br J Psychiatry 2000, 177:212-217.
17. Osby U, Correa N, Brandt L, Ekborg A, Sparen P: Mortality and causes of death in schizophrenia in Stockholm county, Sweden. Schizophr Res 2000, 45:21-28.
18. Osby U, Correa N, Brandt L, Ekborg A, Sparen P: Time trends in schizophrenia mortality in Stockholm county, Sweden: cohort study. Br J Psychiatry 2000, 321:483-484.
19. Dixon L, Postrado L, Delahanty J, Fischer PJ, Lehman A: The association of medical comorbidity in schizophrenia with poor physical and mental health. J Nerv Ment Dis 1999, 187:496-502.
20. Lyketsos CG, Dunn G, Kaminsky MJ, Breakey WR: Medical comorbidity in psychiatric inpatients: relation to clinical outcomes and hospital length of stay. Psychosomatics 2002, 43:24-30.
21. Weiden PJ, Mackell JA, McDonnell DD: Obesity as a risk factor for antipsychotic noncompliance. Schizophr Res 2004, 66:51-57.
22. Peuskens H, De Hert M, Van Eyck D, Peuskens J: A case of reversible olanzapine-induced diabetes after switching to risperidone. Adv Schiz Clin Psych 2004, 1:31-33.
23. Church CO, Stevens DL, Fugate SE: Diabetic ketoacidosis associated with aripiprazole. Diabet Med 2005, 22:1404-1409.
24. Sanchez-Barranco P: New onset of diabetes mellitus with ziprasidone: a case report. J Clin Psychiatry 2005, 66:296-269.
25. McCall M, Bourgeois JA: Olanzapine-induced hyperglycemic hyperosmolar nonketotic coma: a case report. J Clin Psychopharmacol 2004, 24:670-673.
26. Mithat B, Alpaslan T, Bulent C, Cengiz T: Risperidone-associated transient diabetic ketoacidosis and diabetes mellitus type 1 in a patient treated with valproate and lithium. Pharmacopsychiatry 2005, 38:105-106.
27. Caro JJ, Ward A, Levintow C, Robinson K: The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. J Clin Psychiatry 2002, 63:1135-1139.
28. Gianfrancesco F, White R, Wang RH, Nazzriah HA: Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. J Clin Psychopharmacol 2003, 23:328-335.
29. Lindenmayer JP, Czobor P, Vakula J, Citrome L, Shieftman B, McEvoy JP, Cooper TB, Chakos M, Lieberman JA: Changes in glucose and cholesterol levels in patients with schizophrenia treated with
typical or atypical antipsychotics. Am J Psychiatry 2003, 160:290-296.
30. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2003, 353:1209-1223.
31. Thakore JH, Mann JN, Vlahos I, Martin A, Reznik R: Increased visceral fat distribution in drug-naive and drug-free patients with schizophrenia. Int J Obes Relat Metab Disord 2002, 26:137-141.
32. Ryan MC, Collins P, Thakore JH: Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. Am J Psychiatry 2003, 160:284-289.
33. Expert Panel on Detection and Evaluation of Treatment of High Blood Cholesterol in Adults: Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001, 285:2486-2497.
34. Grundy SM, Cleeman JL, Merz CN, Brewer HB, Clark LT, Hunninghake DB, Pasternak RC, Smith SCJ, Stone NJ: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004, 110:227-239.
35. IDF: The IDF Consensus Worldwide Definition of the Metabolic Syndrome. [http://www.idf.org].
36. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003, 26:555-530.
37. American Diabetes Association, American Psychiatric Association: Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004, 27:596-601.
38. Rietzschel ER, De Buyzere ML, De Bacquer D, Langlois M, Bekaert S, Scheen A, Peuskens J: Metabolic syndrome, a map of the cardiovascular damage. Results from the asklepios study in 2528 apparently healthy 35-55 year old subjects. Abstracts Conference European Society of Cardiology. Eur Heart J 2005, 110.
39. Capet F, Debalville R, Van Oyen H, Tafforeau J: Diabetes. Huidige toestand in België en elementen voor een gezondheidsbeleid. Edited by: Volkgezondheid WI. Available at: http://www.ipj.fgov.be/epidemio/morbidat/nl/zie/ziek04t.pdf, 1999.
40. Hanssens L, De Hert M, Wampers M, Reginster JY, Peuskens J: Pharmacological treatment of ambulatory schizophrenic patients in Belgium. Clinical Practice and Epidemiology in Mental Health 2006, in press.
41. Wampers M, De Hert M, Van Eyck D, Peuskens J: Somatic medication in hospitalised schizophrenic patients in Belgium. Schizophr Res 2004, 67 (Abstracts Winter Workshop on Schizophrenia).
42. Adam JM, Tarigan NP: Comparison of The World Health Organization (WHO) two-step strategy and OGTT for diabetes mellitus screening. Acta Med Indones 2004, 36:3-7.
43. Lean ME, Pajonk FG: Patients on atypical antipsychotic drugs: another high-risk group for type 2 diabetes. Diabetes Care 2003, 26:1597-1605.
44. Sern MP, Williams K, Haffner SM: Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? Ann Intern Med 2002, 136:575-581.
45. Lorenzo C, Okoloeze M, Williams K, Sern MP, Haffner SM: The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. Diabetes Care 2003, 26:3135-3139.
46. Thakore JH: Metabolic syndrome and schizophrenia. Br J Psychiatry 2005, 186:455-456.
47. van Winkel R, De Hert M, Van Eyck D, Hanssens L, Wampers M, Scheen A, Peuskens J: Screening for diabetes and other metabolic abnormalities in patients with schizophrenia and schizoaffective disorder: evaluation of incidence and screening methods. J Clin Psychiatry 2006 in press.
48. Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM, Kane JM, Lieberman JA, Schooller NR, Covell N, Stroup S, Weissma EM, Wirshing DA, Hall CS, Pogach L, Pi-Sunyer X, Bigger JT, Friedman A, Kleinberg D, Yevich SJ, Davis B, Shon S: Physical health monitoring of patients with schizophrenia. Am J Psychiatry 2004, 161:1334-1349.
49. Scheen A, Van Gaal L, Brochet C, De Backer G, Vissers E, Vandenhoven G: High prevalence of diabetes mellitus and metabolic syndrome in the BEST study ("Belgian Evaluation of Screening and Treatment of high risk patients based on waist and age"). Diabetologia 2005, 48 (Suppl 1):A122, 325.
50. Vivian EM: Type 2 diabetes in children and adolescents—the next epidemic? Curr Med Res Opin 2006, 22:297-306.
51. Robenstien AH: Obesity: a modern epidemic. Trans Am Clin Climatol Assoc 2005, 116:103-11; discussion 112-3.
52. Ford ES, Mokdad AH, Giles WH, Galuska DA, Serdula MK: Geographic variation in the prevalence of obesity, diabetes, and obesity-related behaviors. Obes Res 2005, 13:118-122.
53. De Hert M, van Winkel R, Van Eyck D, Hanssens L, Wampers M, Scheen A, Peuskens J: Prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotic medication. Schizophr Res 2006, 83:87-93.
54. McEvoy JP, Meyer JM, Golf DC, Nasrallah HA, Davis SM, Sullivan L, Meltzer HY, Hsiao J, Scott Stroup T, Lieberman JA: Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res 2005, 80:19-32.

Published with BioMed Central and every scientist can read your work free of charge

*BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime.*

Sir Paul Nurse, Cancer Research UK

Your research papers will be:
* available free of charge to the entire biomedical community
* peer reviewed and published immediately upon acceptance
* cited in PubMed and archived on PubMed Central
* yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp