Metabolic Syndrome in South African Patients with Severe Mental Illness: Prevalence and Associated Risk Factors

Shamima Saloojee¹*, Jonathan K Burns¹, Ayesha A Motala²

¹ Department of Psychiatry, Nelson R Mandela School of Medicine, University of KwaZulu - Natal, Durban, South Africa, ² Department of Diabetes and Endocrinology, Nelson R Mandela School of Medicine, University of KwaZulu - Natal, Durban, South Africa

* saloojees1@ukzn.ac.za

Abstract

Background
There is a surge of cardiovascular disease (CVD) in Africa. CVD is the leading cause of mortality among patients with severe mental illness (SMI) in developed countries, with little evidence from the African context.

Objective
To determine the prevalence and risk factors for MetS among South African patients with SMI.

Method
In a cross sectional study, individuals with SMI treated with antipsychotics and a control group without a mental illness, matched for age, gender and ethnicity were evaluated for MetS using the 2009 Joint Interim statement (JIS) criteria.

Results
Of the 276 study group subjects, 65.9% were male, 84.1% black African, 9.1% white, 5.4% of Indian descent and 1.5% coloured (mixed race) with a mean age of 34.7 years (±12.5). Schizophrenia was the most common diagnosis (73.2%) and 40% were taking first generation antipsychotics. The prevalence of MetS was 23.2% (M: 15.4%, F: 38.3%) in the study group and 19.9% (M: 11.9%, F: 36.3%) in the control group (p = 0.4). MetS prevalence was significantly higher in study subjects over 55 years compared to controls (p = 0.03). Increased waist circumference (p < 0.001) and low high density lipoprotein (HDL) cholesterol (p = 0.003) were significantly more prevalent in study subjects compared to controls. In study subjects, risk factors associated with MetS included age (OR: 1.09, 95% CI 1.06–1.12, p < 0.001), female gender (OR: 2.19, 95% CI 1.06–4.55, p = 0.035) and Indian descent (OR: 5.84, 95% CI 1.66–20.52, p = 0.006) but not class of antipsychotic (p = 0.26).
Conclusion

The overall MetS prevalence was not increased in patients with SMI compared to controls; however, the higher prevalence of the individual components (HDL cholesterol and waist circumference) suggests an increased risk for CVD, especially in patients over 55 years.

Introduction

Metabolic syndrome (MetS) gained prominence in the psychiatric literature in the past decade because the leading cause of premature mortality in patients with severe mental illness (SMI) from developed countries is reported to be cardiovascular disease (CVD) [1–3]. There is little doubt that MetS is a risk factor for diabetes mellitus and CVD [4], although the clinical utility and criteria by which MetS is defined is debatable [5,6]. Regarding the elevated risk of CVD in SMI, there have been several reports on the prevalence and associated risk factors for MetS in SMI globally [7–12]. Reported prevalence rates range from 9.3% in Indonesia [8] to 21% in Mexico [9], 27.5% in Japan [10], 57% in England [11] and 68% in Australia [12]. In a recent meta—analysis on data from 27 countries for the period 2003–2011, Mitchell et al. reported an overall prevalence of 32.5% in patients with schizophrenia and related disorders [13].

There is limited information regarding the prevalence of MetS in patients with SMI from Africa. The meta—analysis by Mitchell et al.[13] did not include any studies from Africa; also, only 0.001% of the patients enrolled in schizophrenia trials throughout the world are recruited from Africa [14]. Data for South Africa are limited to three studies [15–17]. A study of 84 long term in patients that included patients with cognitive and personality disorders reported a MetS prevalence of 32% [15] while the other two reported on the prevalence of MetS in patients taking a single antipsychotic [16,17]. From population studies in South Africa, the reported prevalence of MetS is 22.1% in rural [18] and 31.7% in urban black South African communities [19].

In many high income countries, more than 80% of antipsychotic prescriptions are for second generation antipsychotics (SGAs) and the metabolic side effects and magnitude of risk attributable to SGA medication is well established [20–22]. However, evidence comparing the metabolic side effects of individual older and cheaper, first generation antipsychotics (FGAs) which are still widely prescribed in Africa [23] is mostly derived from studies conducted prior to 1994, and is of low quality [24] prompting a call for more recent studies [24,25].

Regarding risk factors for MetS in SMI, reports on the gender distribution of MetS in SMI is variable, because although many studies report a higher prevalence in females [7,9,26,27] some report a higher prevalence in males [10,12,28]. More than two thirds of the studies in the meta —analysis by Mitchell et al. [13] did not report on ethnicity, and there is limited and mixed evidence for the increased prevalence of MetS among ethnic minorities with SMI from the United States (US) [29].

The sparse information regarding the prevalence and risk factors for MetS in South African patients with SMI is of concern, because Mensah et al. have shown that from 1990 to 2013 there was an 81% increase in CVD deaths in Sub Saharan Africa (SSA), with more women dying of CVDs (512 269) than men (445 445) [30].

This study was therefore undertaken to determine the prevalence of MetS and associated risk factors in South African patients with SMI treated with antipsychotic medication.
Methods

We conducted a cross-sectional study in the psychiatric unit at King Edward VIII Hospital (KEH) in Durban, South Africa from February 2012 to December 2014. KEH is a 922 bedded general hospital with 20 psychiatric beds and serves a population of approximately 360 000 individuals. The psychiatric unit has two full time psychiatrists and provides a regional level service for other district hospitals without psychiatrists; but also serves as a district hospital because it is close to a large informal settlement without community mental health clinics. The study subjects were 18–65 year old patients with SMI of black, white, Asian Indian or coloured (mixed) ethnicity. In— or out—patients with schizophrenia, bipolar 1 mood disorder or schizoaffective disorder diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000) [31] criteria on antipsychotic medication for at least three months were included. Subjects who were taking a single antipsychotic only were assigned to the monotherapy group. Those subjects who were on two or more antipsychotics at the same time for at least six weeks and those who were taking antipsychotics combined with sodium valproate or an antidepressant were assigned to the polytherapy group. Control subjects were recruited by placing posters explaining the purpose and procedures for the study at the entrance, exit and other high traffic areas in the hospital. Hospital staff, health science students and members of the public who were physically healthy and who had no lifetime diagnosis or treatment for a mental illness were invited to participate in the study. Control and study subjects who were HIV positive or pregnant were excluded. Control subjects were matched for age gender and ethnicity with study subjects.

All consenting study and control subjects were interviewed and information regarding demographic and clinical characteristics was recorded on a specifically designed questionnaire. Study subject records were examined for diagnosis of mental illness and currently administered antipsychotic. At KEH, chlorpromazine and haloperidol are first line antipsychotic agents with risperidone and clozapine as alternatives. Olanzapine, quetiapine, aripiprazole and amisulpride are available only by special motivation.

Ethics Statement

This study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu—Natal. Written informed consent was obtained from all study and control subjects in English or Isizulu.

Anthropometric measurements were conducted as per the World Health Organization (WHO) (2000, 1995) protocols [32]. Weight in kilograms (kg) and height in centimetres (cm) were measured for calculation of the body mass index (BMI). BMI (kg/m²) was categorized as normal (< 25), overweight (25–29.9) and obese (> 30). Waist circumference was measured using a soft tape measure at the mid-point between the upper border of the iliac crest and the inferior margin of the last rib. Blood pressure was measured with the subject in the sitting position after a ten minute rest; two readings were taken with a minimum interval of ten minutes and the mean of the two readings was used to record the blood pressure. Venous blood sampling was performed after an overnight fast for plasma glucose and serum lipids (total cholesterol, total triglycerides, high density lipoprotein [HDL] cholesterol, low density lipoprotein [LDL] cholesterol). Plasma glucose, HDL and triglycerides were measured by the enzymatic method utilizing Beckman Coulter GLU, HDLD and TG reagent respectively on a Beckman Coulter DxC 600 instrument. LDL cholesterol was calculated by the Freidewald formula.

MetS was defined using the 2009 Joint Interim Statement (JIS) definition [4] and is diagnosed by the presence of any 3 of the following 5 risk factors: (i) increased waist circumference; waist circumference cut off points used: whites, blacks and coloureds: men ≥ 94 cm,
women ≥ 80 cm; Indians: men ≥ 90 cm, women ≥ 80 cm (ii) elevated blood pressure: systolic >130 mmHg (or on treatment) and/or diastolic >85 mmHg (or on treatment) (iii) elevated fasting plasma glucose ≥ 5.6 mmol/l (or on treatment) (iv) elevated fasting triglycerides ≥ 1.7 mmol/l (or on treatment) and (v) reduced HDL cholesterol ≤ 1.0 mmol/l men (or on treatment), ≤ 1.3 mmol/l women (or on treatment).

Statistical analysis
All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary).

The demographic and clinical characteristics of participants were summarized using means ± standard deviation (SD) or medians and interquartile ranges (IQR) for continuous variables and as proportions (%) for categorical variables. To compare differences in continuous demographic and clinical variables between the study and control groups and by class of antipsychotic medication, Student’s t-test, F-test, Wilcoxon-Mann-Whitney test and Kruskal-Wallis test were used depending on the data distribution. Fisher’s exact test was used to compare categorical variables. The difference in the prevalence of MetS and its individual components between the study and control groups and by class of antipsychotic medication was determined using Fisher’s exact test. To determine risk factors associated with MetS, multivariate logistic regression models were used were used. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to determine the independent risk factors associated with MetS. A p value < 0.05 was deemed to be statistically significant.

Results
Study group and control group
Table 1 shows the clinical and laboratory characteristics of the study and control subjects. There were 276 subjects with a SMI in the study group (M:F 182: 94) and majority were of black African ancestry (84.1%). There were no significant differences in the demographic characteristics between the two groups. In the study group, the majority (73.2%) had a diagnosis of schizophrenia with a mean duration of illness of 4.6 (±5.21) years. The most commonly prescribed antipsychotic alone or in combination with other antipsychotics was risperidone (33.9%), and the least commonly prescribed was olanzapine (3.67%). The mean BMI and waist circumference were high in both the study (27.6 ± 7.4 kg/m²; 92.8 ± 15cm, respectively) and control (27.1 ± 7.4 kg/m²; 87.8 ± 15.5cm, respectively) groups. Over half of the study group (55%) and control group (50%) were either overweight or obese.

Prevalence of MetS and individual components
The overall prevalence of MetS was 23.2% in the study group and 19.9% in the control group with no significant difference between the two groups (p = 0.4). In both groups the prevalence was higher in women. The prevalence of MetS in the oldest age group was significantly higher in the study group (71.4%) compared to the control group (40.7%) (p = 0.03). In the study group, subjects of Indian descent (60%) and those with schizoaffective disorder (36.4%) had a higher prevalence of MetS compared to African subjects (19.4%) and those with schizophrenia (20.8%) respectively (Table 2). Compared to men, women with schizophrenia (36.4% vs 15%, p = 0.001) and schizoaffective disorder (61.1% vs 19.2%, p = 0.005), but not bipolar disorder (23.8% vs 11.1%, p = 0.4) had a significantly higher prevalence of MetS.

For the individual components of MetS (Table 3), the most frequent abnormality in both the study and control groups was increased waist circumference (55.1% and 40.6%, study and control groups, respectively); the least frequent component was elevated serum triglycerides.
Table 1. Clinical and laboratory characteristics of patients with severe mental illness (study group) and control group.

|                            | Study group (n = 276) | Control group (n = 276) | p    |
|-----------------------------|-----------------------|-------------------------|------|
| Gender                      |                       |                         | 0.86 a |
| Male                        | 65.9(182)             | 67.0(185)               |      |
| Female                      | 34.1 (94)             | 33.0(91)                |      |
| Age(years)                  | 34.7 ± 12.5           | 34.7 ± 12               | 0.94 b |
| Age group(years)(% [n])     |                       |                         |      |
| 18–24                       | 25.72(71)             | 25.36(70)               |      |
| 25–34                       | 34.06(94)             | 34.78(96)               |      |
| 35–44                       | 17.03(47)             | 16.67(46)               |      |
| 45–54                       | 13.04(36)             | 13.41(37)               |      |
| ≥ 55                        | 10.15(28)             | 9.78(27)                |      |
| Ethnicity                   |                       |                         | 1.00 a |
| African                     | 84.1(232)             | 84.1(232)               |      |
| White                       | 9.1(25)               | 9.1(25)                 |      |
| Indian                      | 5.4(15)               | 5.8(16)                 |      |
| Coloured(mixed race)        | 1.5(4)                | 1.1(3)                  |      |
| Diagnosis                   |                       |                         |      |
| Schizophrenia               | 73.2(202)             |                         |      |
| Schizoaffective disorder    | 15.9(44)              |                         |      |
| Bipolar mood disorder       | 10.9(30)              |                         |      |
| First generation antipsychotic medication |             |                         |      |
| Zuclopenthixol Decanoate    | 14.12(50)             |                         |      |
| Chlorpromazine              | 10.17(36)             |                         |      |
| Fluorophotol Decanoate      | 7.91(28)              |                         |      |
| Haloperidol                 | 7.91(28)              |                         |      |
| Second generation antipsychotic medication |             |                         |      |
| Risperidone                 | 33.90(120)            |                         |      |
| Clozapine                   | 8.19(29)              |                         |      |
| Amisulpride                 | 5.93(21)              |                         |      |
| Aripiprazole                | 4.24(15)              |                         |      |
| Quetiapine                  | 3.96(14)              |                         |      |
| Olanzapine                  | 3.67(13)              |                         |      |
| Cigarette smokers           | 41.3(114)             | 34.8(96)                | 0.14 a |
| Body Mass Index (BMI) (kg/m²) | 27.6 ±7.4             | 27.1 ± 7.4              | 0.46 b |
| BMI category:               |                       |                         | 0.46 a |
| Normal: < 25               | 45.3(125/276)         | 50.2(138/275)           |      |
| Overweight: 25–29.9         | 26.5(73/276)          | 22.6(62/275)            |      |
| Obese: > 30                | 28.3(78/276)          | 27.3(75/275)            |      |
| Waist circumference (cm)    | 92.8 ± 15.0           | 87.8 ± 15.5             | <0.001 b |
| Blood pressure(mmHg):       |                       |                         |      |
| Systolic                    | 121.9 ± 16.2          | 121.8 ± 17.9            | 0.95 b |
| Diastolic                   | 76.2 ± 10.2           | 76.9 ± 12.6             | 0.45 b |
| Fasting plasma glucose (mmol/l) | 5.1 ± 1.2             | 5.1 ± 1.3               | 0.99 b |
| Serum lipids (mmol/l):      |                       |                         |      |
| Total cholesterol           | 4.1 ± 1.1             | 4.1 ± 1.0               | 0.96 b |
| Total triglycerides         | 1.1 ± 0.7             | 1.0 ± 0.7               | 0.40 b |
| High density lipoprotein cholesterol | 1.1 ± 0.3             | 1.2 ± 0.3               | 0.01 b |

(Continued)
(14.5% and 12.3%, respectively). The prevalence of low serum HDL cholesterol was significantly higher in the study group (52.5%) than the control group (39.9%) (p = 0.003).

Prevalence of MetS and antipsychotic medication

All study subjects were on antipsychotic medication (n = 276), with 127 subjects (46%) on monotherapy and 149 (54%) on polytherapy. Of the 149 subjects on polytherapy, 98 (35.5%) were taking an antipsychotic combined with sodium valproate, and 51 (15.5%) were taking two or more antipsychotics at the same time. Of the 98 subjects on sodium valproate 6 (2.2%) subjects were also taking an antidepressant (5 subjects were on a Selective Serotonin Reuptake Inhibitor and 1 was on a Serotonin Noradrenalin Reuptake Inhibitor) and only one subject was taking lithium.

There was no significant difference (p = 0.9) in the prevalence of MetS in subjects on antipsychotic polytherapy (35/149, 23.5%) compared to those on monotherapy (29/127, 22.8%). In addition, no difference (p = 0.8) was observed in the prevalence of MetS in subjects on

Table 2. Prevalence of metabolic syndrome by demographic characteristics and diagnosis in the study and control groups.

|                          | Study group (n = 276) | Control group (n = 276) | p   |
|--------------------------|-----------------------|-------------------------|-----|
| Low density lipoprotein cholesterol | 2.5 ± 0.9             | 2.5 ± 0.8               | 0.80 b|

Data are mean ± SD and % (n), unless otherwise indicated p for significant differences between study and control group analysed using a Fisher’s exact test and, b Student’s t—test.
antipsychotic monotherapy (22.8%) compared to subjects taking antipsychotics combined with sodium valproate and antidepressant medication (24.5%) or those subjects taking two or more antipsychotics (21.6%, p = 0.9). Too few subjects were taking antipsychotics combined with antidepressants and sodium valproate only for a separate analysis.

Regarding the comparison of metabolic abnormalities in subjects taking FGAs vs SGAs; of the 127 subjects on monotherapy, 32 (11.6%) subjects were taking FGAs and 95 (34.4%) SGAs. No significant difference was observed in the clinical and demographic characteristics between subjects taking FGAs or SGAs as monotherapy (Table 4). There was no difference in the prevalence of MetS or its individual components between subjects on FGA vs SGA monotherapy (p = 0.26) (Table 5) or polytherapy (p = 0.2) (data for polytherapy not shown).

### Risk factors associated with MetS

In multivariate analysis, significant risk factors associated with MetS included age (OR: 1.09, 95% CI 1.06–1.12, p < 0.0001), female gender (OR: 2.19, 95% CI 1.06–4.55, p = 0.035) and Indian descent (OR: 5.84, 95% CI 1.66–20.52, p = 0.006) (Table 6).

### Discussion

In this study of South African patients with SMI taking antipsychotic medication there was a high but similar prevalence of MetS in the study (23.2%) and control group (19.9%); the prevalence of the individual components viz. increased waist circumference (p < 0.001) and low HDL cholesterol (p = 0.003) was higher in the study group. Significant risk factors for MetS in the study group included age, gender and Indian ethnicity. No significant difference (p = 0.9) was observed in the prevalence of MetS in subjects on monotherapy compared to those on polytherapy and in subjects taking FGAs or SGAs as monotherapy (p = 0.26).
Table 4. Demographic and clinical characteristics of subjects with severe mental illness by class of antipsychotic medication in subjects on monotherapy.

|                         | Subjects taking FGAs (n = 32) | Subjects taking SGAs (n = 95) | p          |
|-------------------------|--------------------------------|--------------------------------|------------|
| Gender                  |                                |                                | 0.7 a      |
| Male                    | 65.6(21)                       | 69.5(66)                       |            |
| Female                  | 34.4(11)                       | 30.5(29)                       |            |
| Age (years)             | 33.7 ±13.8                     | 33.3 ± 12.3                    | 0.9 b      |
| Diagnosis               |                                |                                | 0.5 a      |
| Schizophrenia           | 96.9(31)                       | 88.4(84)                       |            |
| Schizoaffective disorder| 3.1 (1)                        | 9.5 (9)                        |            |
| Bipolar mood disorder   | 0(0)                           | 2.1(2)                         |            |
| Body Mass Index (BMI) (kg/m²) | 26.6 ± 7.57     | 27.5 ± 6.31                    | 0.5 b      |
| BMI category:           |                                |                                | 0.5 a      |
| Normal: < 25            | 59.3(19)                       | 47.4(45)                       |            |
| Overweight: 25–29.9     | 18.8(6)                        | 23.2(22)                       |            |
| Obese: >30             | 21.9(7)                        | 29.5(28)                       |            |
| Waist circumference (cm)| 90.5 ± 15.4                    | 92.3 ± 16                      | 0.6 b      |
| Blood pressure (mmHg):  |                                |                                | 0.3 b      |
| Systolic                | 119.2 ± 11.3                   | 122.5 ± 17.9                   |            |
| Diastolic               | 72.6 ± 8.5                     | 76.6 ± 10.2                    | 0.04 b     |
| Fasting plasma glucose (mmol/l) | 5.2 ± 1.3             | 5.3 ± 1.4                      | 0.7 b      |
| Serum Lipids (mmol/l):  |                                |                                | 0.7 b      |
| Total cholesterol       | 4.2 ± 1.1                      | 4.2 ± 1.1                      |            |
| Total triglycerides     | 0.9 ± 0.4                      | 1.1 ± 0.7                      | 0.08 b     |
| High Density Lipoprotein cholesterol | 1.2 ± 0.3       | 1.1 ± 0.3                      | 0.2 b      |
| Low Density Lipoprotein cholesterol | 2.6 ± 1.0       | 2.6 ± 0.9                      | 0.7 b      |

Data are mean ± SD and % (n), unless otherwise indicated. FGA: first generation antipsychotic, SGA: second generation antipsychotic.

a Fisher’s exact test,
b Student’s t—test.

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Table 5. The prevalence of metabolic syndrome and individual components according to class of medication in subjects on antipsychotic monotherapy.

|                        | FGA (n = 32) | SGA (n = 95) | p a |
|------------------------|--------------|--------------|-----|
| Metabolic Syndrome     | 15.6(5)      | 25.3(24)     | 0.26|
| Elevated waist circumference (cm) | 62.5(20)     | 51.6(49)     | 0.28|
| Elevated blood pressure (mmHg): |                  |              |     |
| Systolic               | 6.25(2)      | 20(19)       | 0.07|
| Diastolic              | 6.25(2)      | 21.1(20)     | 0.06|
| Elevated fasting plasma glucose (mmol/l) | 18.8(6)       | 25.3(24)     | 0.45|
| Elevated serum triglycerides (mmol/l) | 3.1(1)        | 6.3(6)       | 0.5 |
| Low HDL –cholesterol (mmol/l) | 43.8(14)     | 52.6(50)     | 0.38|

Data are % (n). HDL: high density lipoprotein. FGA: first generation antipsychotic, SGA: second generation antipsychotic.

a z test.

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The prevalence in this study is in keeping with rates reported from Thailand (22.8%) [33], Mexico (21%) [9] and Spain (26.5%) [34], but lower than studies from England (57%) [11], the US (49.2%) [26], Australia (68%) [12], and the overall international prevalence of 32.5% reported by Mitchell et al. [13]. A review by Papanastasiou on the prevalence of MetS in schizophrenia [22], the position statement by De Hert [1] and meta-analysis by Mitchell et al. [13] found that many studies reported a two—fold higher prevalence of MetS in patients with SMI compared to the general population. However, no difference in the prevalence between SMI and control subjects was reported from Venezuela [35] and Mexico [9]. There are several possible explanations for the lower prevalence of MetS in the study group participants including the high proportion of young participants (25.6% of the study subjects were <25 years), male participants (66% male), the short mean duration of illness (4.6 years), the inclusion of participants with a first episode of SMI and the low proportions of participants taking FGA and SGA medication (chlorpromazine 10.2%, clozapine 8.2% and olanzapine 3.7%) that are associated with the highest risk for MetS [36].

The high prevalence of increased waist circumference in subjects with SMI in this study is compatible with findings of other studies [1,13,21,22]. In a recent report, more than 80% of patients taking antipsychotic medication had central obesity [11]. This places patients with SMI at increased risk for diabetes mellitus, given that central obesity correlates better with insulin resistance than total body obesity (BMI) [37]. The prevalence of diabetes mellitus is reported to be approximately 12% in patients with SMI and two to three fold higher than that in the general population [38]. However, we did not find a high prevalence of dysglycemia in patients with SMI confirming an earlier study from this district which reported a low prevalence (3.85%) of type 2 diabetes mellitus in a group of chronic hospitalized patients with SMI [39]. Although genetic and lifestyle factors may also account for abnormal glucose homeostasis and frank diabetes with antipsychotic treatment, it is likely that the low prevalence of diabetes mellitus in this study is due to the underutilization of antipsychotics with a higher liability for diabetes mellitus such as clozapine, olanzapine and quetiapine [40]. Prospective studies in African patients with SMI are required to further clarify the risk of dysglycemia.

In this study, 18.5% of patients were prescribed two or more antipsychotics, and 35.5% were on antipsychotics combined with sodium valproate. There is little empirical support for either practice but both are common internationally [41] with rates of 2–70% [42] and 16–35% [43] respectively. Although it has been shown that combining psychotropic medications results in the potentiating of the metabolic side effects of each of the individual medications [44], the results of this study support and extend the evidence for no independent association between

| Study group | Control group |
|-------------|--------------|
| **Odds Ratio (95% CI)** | **Odds Ratio (95% CI)** |
| Female gender | 2.19(1.06–4.55) | 1.31(0.57–3.00) |
| Age | 1.09(1.06–1.12) | 1.07(1.03–1.10) |
| Ethnicity: |  |  |
| Indian | 5.84(1.66–20.52) | 3.80(1.12–12.89) |
| White and mixed race | 0.51(0.03–8.77) | 1.68(0.55–5.13) |
| Body Mass Index (kg/m²) | 1.13(1.07–1.19) | 1.16(1.09–1.23) |

*adjusted values.

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MetS and the prescription of two or more antipsychotics [45] or antipsychotics combined with sodium valproate [46].

Furthermore, an additional analysis showed that there was no difference in the prevalence of MetS between subjects taking FGAs and SGAs as monotherapy (p = 0.26) or polytherapy (0.2). As reported in the literature, possible explanations include the probability that there is no class effect for the metabolic adverse effects of antipsychotics in view of the substantial heterogeneity within each class [21,25,47]; and the current classification of antipsychotics is arbitrary [21]. Taking into account that subjects in this naturalistic study were not randomized to either class of medication and that the comparison by class of antipsychotic medication is a within group analysis, it is also likely that the sample size is insufficient to detect a difference between FGAs and SGAs. However, describing the metabolic side effects of FGAs is still relevant because although many SGA medications are now off patent, two of the three oral antipsychotics on the 19th WHO Model List of Essential Medicines (April 2015) are FGAs [48].

In a multivariate analysis, significant risk factors associated with MetS were age, female gender and Indian descent. The association of age with MetS that we observed in subjects and controls concurs with that reported in the literature [13,22,28]. However, the higher prevalence of MetS in subjects with SMI under 25 years (11.3%) compared to controls (5.7%) is of concern and consistent with recent reports of the development of MetS in young patients with SMI [49].

The significant association of female gender with MetS in this study confirms the findings of the landmark CATIE study, one of the largest antipsychotic effectiveness studies to date [26], by contrast, the meta-analysis by Mitchell et al. [13] reported no significant gender difference, while a Korean study found that the risk of MetS was four fold higher in males with schizophrenia [28]. The increased risk for MetS in women compared to men that we observed in the study group may reflect a regional predisposition to obesity and MetS in women because a higher prevalence of obesity and MetS in South African women has been confirmed in epidemiological studies [18,19]. Culturally acceptable attitudes to larger body size may be influencing this phenomenon [50]. Our findings may also be explained by an increased susceptibility to the side effects of antipsychotic medication in women with SMI [51], because in contrast to all the other risk factors for MetS in this study, the increased risk for MetS in women compared to men in the control group, was not statistically significant (p = 0.53). However, even though South African women have a higher prevalence of individual risk factors for CVD such as obesity, diabetes mellitus and HDL cholesterol, a recent study has shown a higher 10 year Framingham risk for CVD in men [52].

Racial differences in the risk for MetS has been documented in patients with SMI previously [29]. However, the elevated risk for MetS that we observed in South Africans of Indian descent with SMI compared to Africans with SMI has to the best of our knowledge not been documented previously. A likely explanation for the high prevalence of MetS in native and migrant Indians include a genetic predisposition to diabetes mellitus and a tendency for higher visceral fat deposition at lower BMI’s than other ethnic groups [53]. We did not confirm the findings of Ader et al [54] who found that African Americans were more susceptible to the metabolic side effects of antipsychotic medication but our findings were in keeping with those of Keenan et al [55] who found a lower risk for MetS in African American subjects with SMI after adjusting for age and gender. This substantiates the need for further studies on the association of ethnicity and MetS among those with SMI in and outside the US.

The limitations of this study include the cross sectional, observational study design that resulted in disproportionate medication groups, lack of information on lifestyle factors and the recruitment of participants from a single site which limits the generalizability of the results.
Conclusion
The results of this study show that 1 in 5 African patients with SMI taking either FGA or SGA medication met the criteria for MetS, and 1 in 2 was overweight or obese. Moreover, the development of MetS in females, individuals of Indian descent and young patients under the age of 25 years on treatment with antipsychotics is of concern. Our results emphasise the need for nationwide, cardiovascular and metabolic risk preventative and screening programmes that must include individuals with a mental illness. This study provides evidence for the integration of physical health programmes into mental health services in South Africa.

Author Contributions
Conceived and designed the experiments: SS JKB AAM. Performed the experiments: SS. Analyzed the data: SS JKB AAM. Wrote the paper: SS JKB AAM.

References
1. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RIG, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology. Eur Psychiatry. 2009; 24: 412–424. doi: 10.1016/j.eurpsy.2009.01.005 PMID: 19682863
2. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. Am Heart J. 2005; 150: 1115–1121. doi: 10.1016/j.ahj.2005.02.007 PMID: 16338246
3. Laursen TM, Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. Curr Opin Psychiatr. 2012; 25: 83–88. doi: 10.1097/YCO.0b013e3283503fca
4. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International. Circulation. 2009; 120: 1640–1645. doi: 10.1161/CIRCULATIONAHA.109.192644 PMID: 19805654
5. Gale EAM. The myth of the metabolic syndrome. Diabetologia. 2005; 48: 1679–1683. doi: 10.1007/s00125-005-1873-5 PMID: 16025251
6. Kahn R. Metabolic syndrome-what is the clinical usefulness? Lancet. 2008; 371: 1892–1893. doi: 10.1016/S0140-6736(08)60731-X PMID: 18501420
7. Bressington DT, Mui J, Cheung EFC, Petch J, Clark AB, Gray R. The prevalence of metabolic syndrome amongst patients with severe mental illness in the community in Hong Kong—a cross sectional study. BMC Psychiatry. 2013; 13: 87. doi: 10.1186/1471-244X-13-87 PMID: 23506322
8. Marthoenis M, Aichberger MC, Puteh I, Syahrial S, Schouler-Ocak M. Metabolic syndrome among psychiatric inpatients with schizophrenia in Indonesia. Asian J Psychiatr. 2015; 15: 10–14. doi: 10.1016/j.ajp.2015.04.004 PMID: 25910596
9. Díaz-Domínguez DA, de la Rosa-Donlucas F, Romans-Demaria L, Grajales-Almeida JR, Sauer-Vera T, Sotelo-Monroy GE. Prevalence of Metabolic Syndrome and Associated Risk Factors in Hospitalized Patients with Schizophrenia in Mexico. Int J Ment Health. 2013; 42: 95–104. doi: 10.2753/IMH0020-7411420405
10. Sugawara N, Yasui-Furukori N, Sato Y, Umeda T, Kishida I, Yamashita H, et al. Prevalence of metabolic syndrome among patients with schizophrenia in Japan. Schizophr Res. 2010; 123: 244–250. doi: 10.1016/j.schres.2010.08.030 PMID: 20850274
11. Gardner-Sood P, Lally J, Smith S, Atakan Z, Ismail K, Greenwood KE, et al. Cardiovascular risk factors and metabolic syndrome in people with established psychotic illnesses: baseline data from the IMPaCT randomized controlled trial. Psychol Med. 2015; 45: 2619–2629. doi: 10.1017/S0033291715000562 PMID: 25961431
12. Tirupati S, Chua L-E. Obesity and metabolic syndrome in a psychiatric rehabilitation service. Aust N Z J Psychiatry. 2007; 41: 606–610. doi: 10.1080/00048670701392841 PMID: 17558623
13. Mitchell AJ, Vancamport D, Sweers K, Van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders—a systematic review and meta-analysis. Schizophr Bull. 2013; 39: 306–318. doi: 10.1093/schbul/sbr148 PMID: 22207632
14. Purgato M, Adams C, Barbui C. Schizophrenia trials conducted in African countries: a drop of evidence in the ocean of morbidity? Int J Ment Health Syst. 2012; 6: 9. doi: 10.1186/1752-4458-6-9 PMID: 22768830

15. Maaroganye K, Mohapi M, Rheedr P. The prevalence of metabolic syndrome and its associated factors in long-term patients in a specialist psychiatric hospital in South Africa. Afr J Psychiatry. 2013; 16: 414–423. doi: 10.4314/ajpsy.v16i6.53

16. Faasen N, Niehaus DJH, Koen L, Jordaan E. Undiagnosed metabolic syndrome and other adverse effects among clozapine users of Xhosa descent. South African J Psychiatry. 2014; 20: 54–57.

17. Chiliza B, Asmal L, Oosthuizen P, van Nieuwerkerk E, Erasmus R, Kidd M, et al. Changes in body mass and metabolic profiles in patients with first-episode schizophrenia treated for 12 months with a first-generation antipsychotic. Eur Psychiatry. 2015; 30: 277–283. doi: 10.1016/j.eurpsy.2014.11.013 PMID: 25577186

18. Motala AA, Esterhuizen T, Pirie FJ, Omar MAK. The prevalence of metabolic syndrome and determination of the optimal waist circumference cutoff points in a rural South African community. Diabetes Care. 2011; 34: 1032–1037. doi: 10.2337/dc10-1921 PMID: 21330644

19. Peer N, Lombard C, Steyn K, Levitt N. High prevalence of metabolic syndrome in the Black population of Cape Town: the Cardiovascular Risk in Black South Africans (CRIBSA) study. Eur J Prev Cardiol. 2015; 22: 1036–1042. doi: 10.1177/2047487314549744 PMID: 25208906

20. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: A systematic review and meta-analysis. Schizophr Res. 2010; 123: 225–233. doi: 10.1016/j.schres.2010.07.012 PMID: 20692814

21. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2012; 8: 114–126. doi: 10.1038/nrendo.2011.156

22. Papanastasiou E. The prevalence and mechanisms of metabolic syndrome in schizophrenia: a review. Ther Adv Psychopharmacol. 2012; 3: 33–51. doi: 10.1177/2045125312464385

23. Rukat A, Musisi S, Ströhle A, Mundt AP. Prescription Patterns of Psychotropic Medications for the Treatment of Psychotic Disorders in the Largest Mental Health Institutions of Uganda. J Clin Psychopharmacol. 2014; 34: 1–6. doi: 10.1097/JCP.0000000000000168

24. Dold M, Samara MT, Li C, Tardy M LS. Haloperidol versus first-generation antipsychotics for the treatment of schizophrenia and other psychotic disorders. Cochrane Database Syst Rev. 2015; Art. No.: CD009831. doi: 10.1002/14651858.CD009831

25. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009; 373: 31–41. doi: 10.1016/S0140-6736(08)61764-X PMID: 19058842

26. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al. 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. doi: 10.1016/j.schres.2005.07.014 PMID: 16137860

27. Hägg S, Lindblom Y, Mjörndal T, Adolfsson R. High prevalence of the metabolic syndrome among a Swedish cohort of patients with schizophrenia. Int Clin Psychopharmacol. 2006; 21: 93–98.

28. Lee NY, Kim SH, Jung DC, Kim EY, Yu HY, Sung KH, et al. The prevalence of metabolic syndrome in Korean patients with schizophrenia receiving a monotherapy with aripiprazole, olanzapine or risperidone. Prog Neuro-Psychopharmacology Biol Psychiatry. 2011; 35: 1273–1278. doi: 10.1016/j.pnpbp.2011.03.022

29. Carliner H, Collins PY, Cabassa LJ, McNallen A, Joestl SS, Lewis-Fernández R. Prevalence of cardiovascular risk factors among racial and ethnic minorities with schizophrenia spectrum and bipolar disorders: A critical literature review. Compr Psychiatry. 2014; 55: 233–247. doi: 10.1016/j.comppsych.2013.09.009 PMID: 24269193

30. Mensah G, Roth G, Sampson U, Moran A, Feigin V, Forouzanfar M, et al. Mortality from cardiovascular diseases in sub-Saharan Africa, 1990–2013: a systematic analysis of data from the Global Burden of Disease Study 2013: cardiovascular topic. Cardiovasc J Afr. 2015; 26: S6–S10. doi: 10.5830/CVJA-2015-036 PMID: 25962950

31. American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: Author.

32. WHO. Physical Status: the Use and Interpretation of Anthropometry. Report of a WHO Expert Committee. Technical Report Series No. 854. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. Technical Report Series No. 854. 1985. pp. 1–452, 854
33. Srisurapanont M, Likhitsathian S, Boonyanaruthee V, Charnsrip C, Jarusurasin N. Metabolic syndrome in Thai schizophrenic patients: a naturalistic one-year follow-up study. BMC Psychiatry. 2007; 7: 14. doi: 10.1186/1471-244X-7-14 PMID: 17448257

34. Arango C, Bobes J, Aranda P, Carmena R, Garcia-Garcia M, Rejas J. A comparison of schizophrenia outpatients treated with antipsychotics with and without metabolic syndrome: Findings from the CLAMSORS study. Schizophr Res. 2008; 104: 1–12. doi: 10.1016/j.schres.2008.05.009 PMID: 18606526

35. Baptista T, Serrano A, Uzcátegui E, ElFakih Y, Rangel N, Carrizo E, et al. The metabolic syndrome and its constituting variables in atypical antipsychotic-treated subjects: Comparison with other drug treatments, drug-free psychiatric patients, first-degree relatives and the general population in Venezuela. Schizophr Res. 2011; 126: 93–102. doi: 10.1016/j.schres.2010.10.014 PMID: 21071179

36. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. Lancet. 2013; 382: 951–962. doi: 10.1016/S0140-6736(13)60733-3 PMID: 23810019

37. Ritchie SA, Connell JMC. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. Nutr Metab Cardiovasc Dis. 2007; 17: 319–326. doi: 10.1016/j.numecd.2006.07.005 PMID: 17110092

38. Holt RIG, Mitchell AJ. Diabetes mellitus and severe mental illness: mechanisms and clinical implications. Nat Rev Endocrinol. 2011; 11: 79–89. doi: 10.1038/nrendo.2014.203 PMID: 25445848

39. Lasich AJ, Paruk N, Ramparsad J. A survey of the prevalence of diabetes type 2 amongst schizophrenic patients in a chronic care treatment facility. Afr J Psychiatry. 2007; 10: 143–146. doi: 10.4314/ajpsy.v10i3.30246

40. Coccurello R, Moles A. Potential mechanisms of atypical antipsychotic-induced metabolic derangement: Clues for understanding obesity and novel drug design. Pharmacol Ther. 2010; 120: 210–251. doi: 10.1016/j.pharmthera.2010.04.008 PMID: 20493213

41. Gallego JA, Bonetti J, Zhang J, Kane JM. Prevalence and correlates of antipsychotic polypharmacy: A systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res. Elsevier B.V.; 2012; 138: 18–28. doi: 10.1016/j.schres.2012.03.018

42. Fisher MD, Reilly K, Isenberg K, Villa KF. Antipsychotic patterns of use in patients with schizophrenia: polypharmacy versus monotherapy. BMC Psychiatry. 2014; 14: 341. doi: 10.1186/s12888-014-0341-5 PMID: 25433495

43. Horowitz E, Bergman LC, Ashkenazy C, Moscona-Hurvitz I, Grinvald-Fogel H, Magnezi R. Off-label use of sodium valproate for schizophrenia. PLOS ONE. 2014; 9: 1–7. doi: 10.1371/journal.pone.0092573

44. Chang HH, Yang YK, Gean PW, Huang HC, Chen PS, Lu RB. The role of valproate in metabolic disturbances in bipolar disorder patients. J Affect Disord. Elsevier B.V.; 2010; 124: 319–323. doi: 10.1016/j.jad.2009.12.011

45. Correll CU, Frederickson AM, Kane JM, Manu P. Does antipsychotic polypharmacy increase the risk for metabolic syndrome? Schizophr Res. 2008; 104: 91–96. doi: 10.1016/j.schres.2006.08.017 PMID: 17070017

46. Zuo S, Fries BE, Szafrana K, Regal R. Valproic Acid as a Potentiator of Metabolic Syndrome In Institutionalized Residents on Concomitant Antipsychotics: Fat Chance, or Slim to None? 2015; 40: 126

47. Falleti B, Mauri M, Shaw K, Wetterling T, Doble A, Giudicelli A, et al. The METEOR study. Int Clin Foley DL, Mackinnon A, Watts GF, Shaw JE, Magliano DJ, Castle DJ, et al. Cardiometabolic risk indicators that distinguish adults with psychosis from the general population, by age and gender. PLOS ONE. 2013; 8: e82606. doi: 10.1371/journal.pone.0082606 PMID: 24367528

48. World Health Organization. WHO Model List of Essential Medicines—19th List (April 2015). 2015; 1–53.

49. Foley DL, Mackinnon A, Watts GF, Shaw JE, Magliano DJ, Castle DJ, et al. Cardiometabolic risk indicators that distinguish adults with psychosis from the general population, by age and gender. PLOS ONE. 2013; 8: e82606. doi: 10.1371/journal.pone.0082606 PMID: 24367528

50. Draper CE, Davidowitz KJ, Goedecke JH. Perceptions relating to body size, weight loss and weight-loss interventions in black South African women: a qualitative study. Public Heal Nutr available CJ02015. 2015; 1–9. doi: 10.1017/S1368980015001688

51. Seeman MV. Secondary effects of antipsychotics: Women at greater risk than men. Schizophr Bull. 2009; 35: 937–948. doi: 10.1093/schbul/sbn023 PMID: 18400811

52. Peer N, Lombard C, Steyn K, Gaziano T, Levitt N. Comparability of total cardiovascular disease risk estimates using laboratory and non-laboratory based assessments in urban-dwelling South Africans: the CRIBSA study. S Afr Med J. 2014; 104: 691–696. PMID: 25363056

53. Palaniappan L, Wong E, Shin J, Fortmann S, Lauderdale DS. Asian Americans Have Greater Prevalence of Metabolic Syndrome Despite Lower Body Mass Index. Int J Obes. 2011; 35: 393–400.
54. Ader M, Garvey WT, Phillips LS, Nemeroff CB, Gharabawi G, Mahmoud R, et al. Ethnic heterogeneity in glucoregulatory function during treatment with atypical antipsychotics in patients with schizophrenia. J Psychiatr Res. 2008; 42: 1076–1085. doi: 10.1016/j.jpsychires.2008.01.004 PMID: 18295798

55. Keenan TE, Yu A, Cooper LA, Appel LJ, Guallar E, Gennusa JV, et al. Racial patterns of cardiovascular disease risk factors in serious mental illness and the overall U.S. population. Schizophr Res. 2013; 150: 211–216. doi: 10.1016/j.schres.2013.07.022 PMID: 23916188