

# Metabolic Syndrome and Mental Disorders: A Literature Review

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## ABSTRACT

**Background:** People with mental disorders have higher mortality rates in comparison with the general population. The occurrence of metabolic syndrome is greater in people with mental disorders than in the general population. A review of the research literature was carried out with regard to metabolic syndrome, its prevalence in the general population, and among those with psychiatric disorders.

**Materials and methods:** Literature search was conducted with the ensuing search terms, keywords, and phrases—"metabolic syndrome," "severe mental illness," "mental disorder," "schizophrenia," "bipolar disorder," "substance use," "prevalence," "alcohol dependence," and "physical activity." The search was executed in databases such as PubMed, ProQuest, and Google Scholar.

**Review results:** Considerable debate exists regarding the causes for the high prevalence of metabolic disturbances in patients with mental disorders; however, gaps remain in relevant aspects, inspiring further studies in specific smaller groups of psychiatric patients to evaluate the impact of each variable on the risk for developing metabolic syndrome. From this review, we surmise that there are several factors that influence the amplified prevalence of metabolic syndrome among patients with mental disorders. Rather than a sole causative factor, there are multiple factors associated with metabolic syndrome, such as sociodemographic variables, clinical variables, and level of physical activity.

**Conclusion:** The research literature supports the requisite for timely identification of metabolic syndrome in people with mental disorders and initiation of suitable interventions.

**Clinical significance:** It is of paramount significance that guidelines pertinent to the Indian context are developed for the monitoring and screening of psychiatric patients for metabolic syndrome and physical health in general.

**Keywords:** Metabolic syndrome, Physical activity, Psychiatric disorders, Psychotropics.

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## BACKGROUND

People diagnosed with mental disorders experience a great encumbrance of mortality at both the individual and population level.<sup>1</sup> It is well known that people with mental disorders have higher mortality compared with the general population. Severe mental illness is associated with a threefold increased risk of early death and it curtails life expectancy by roughly 10–20 years.<sup>2</sup> The increased rates of mortality cannot be explained only by increased rates of unnatural causes of death like accidents and suicide.<sup>2</sup> More than 60% of this mortality is due to physical illness, cardiovascular disease, and stroke.<sup>1,3</sup> Factors predisposing people with severe mental illness to cardiovascular disease include unhealthy lifestyles and antipsychotic medications as well as their reduced likelihood to receive standard levels of medical care.<sup>4</sup> Metabolic syndrome is closely allied with major mental illnesses. The prevalence of metabolic syndrome is greater in people with mental disorders than in the general population.<sup>5</sup>

The research literature was appraised with regard to metabolic syndrome, its prevalence in the general population, and among those with psychiatric disorders. A literature search was steered with the following search terms, keywords, and phrases—"metabolic syndrome," "severe mental illness," "mental disorder," "schizophrenia," "bipolar disorder," "substance use," "prevalence," "alcohol dependence," and "physical activity." The search was executed in the following databases—PubMed, ProQuest, and Google Scholar.

This review commences with an overview of metabolic syndrome. Next, the evolution of the concept of metabolic syndrome and criteria used to define metabolic syndrome are

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reviewed. The review subsequently centers on the prevalence of metabolic syndrome in the general population as well as in patients with mental disorders. Various factors associated with metabolic syndrome are elucidated.

## AN OVERVIEW OF METABOLIC SYNDROME

Metabolic syndrome is a complex, lifestyle-dependent illness defined by a constellation of interrelated biochemical and clinical factors that directly increase the risk of cardiovascular disease.<sup>6</sup> Metabolic syndrome is a rising public health and clinical challenge worldwide.<sup>6</sup> This could be a result of increasing urbanization, rise of obesity, and sedentary life habits.<sup>6</sup> Metabolic syndrome has a strong genetic as well as environmental influence.<sup>4</sup> Some debates

subsist, whether metabolic syndrome is a true syndrome or a combination of unrelated phenotypes. A syndrome is a group of factors that happen more often together than by inadvertent occurrence alone and often the cause is uncertain. Metabolic syndrome is not an absolute risk factor, since it does not take into consideration several factors that determine absolute risk, such as age, sex, low-density lipoprotein cholesterol levels, and cigarette smoking. Nevertheless, patients with metabolic syndrome have twice the possibility of developing cardiovascular disease over the next 10 years compared to those without metabolic syndrome. The risk over a lifetime is indisputably even higher. Moreover, metabolic syndrome has a fivefold increase in risk for type 2 diabetes mellitus (T2DM). The most widely recognized metabolic risk factors are raised blood pressure, atherogenic dyslipidemia, and elevated plasma glucose. Additionally, individuals with these characteristics commonly show a pro-thrombotic state and a proinflammatory state. Atherogenic dyslipidemia entails of a combination of lipoprotein abnormalities that include elevated serum triglyceride and apolipoprotein B, increased small low-density lipoprotein particles, and a reduced level of high-density lipoprotein cholesterol. Most persons with metabolic syndrome have insulin resistance and abdominal obesity. These conditions appear to contribute to the increase of metabolic risk factors, although the mechanisms underlying these influences are not entirely understood.<sup>7</sup> Recent studies found single nucleotide polymorphisms such as MC4R rs17782312 and IRS1 rs2943634, which may explain part of the genetic variation in metabolic syndrome.<sup>8</sup> There is a need for sensitizing all healthcare personnel to the physical health issues of persons with severe mental illnesses.<sup>9</sup>

### Evolution of the Criteria for Metabolic Syndrome

Metabolic syndrome initially started as a concept rather than a diagnosis.<sup>10</sup> The concept of metabolic syndrome had its origin in 1920 when Kylin, a Swedish physician, demonstrated the association of elevated blood pressure, elevated blood glucose, and gout, as cited by Emanuela et al.<sup>11</sup> Vague et al. described that visceral obesity was commonly associated with the metabolic abnormalities found in cardiovascular disease and T2DM.<sup>12</sup> The field moved onward significantly following the Banting Lecture 1988 given by Reaven,<sup>13</sup> who described “a cluster of risk factors for diabetes mellitus and cardiovascular disease” and termed it “Syndrome X.” His main contribution to this field was the concept of insulin resistance. However, he omitted visceral obesity from the definition, which was later incorporated as a vital abnormality. In 1989, Kaplan renamed this syndrome “The Deadly Quartet” implying the combination of truncal obesity, hypertension, glucose intolerance, and hypertriglyceridemia.<sup>14</sup> In 1992, it was retitled as “The Insulin Resistance Syndrome.”<sup>15</sup> In 2005, Eckel et al. have published an extensive review on the evolution of the concept and criteria of metabolic syndrome.<sup>16</sup>

In 1998, the WHO and the National Diabetes data group emphasized insulin resistance as the major principal risk factor. They stated that diagnosis of metabolic syndrome required insulin resistance and two additional markers among the following: obesity, hypertension, high triglyceride level, reduced HDL cholesterol level, or microalbuminuria.<sup>17–19</sup>

In 2001, another set of major criteria was proposed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).<sup>20</sup> The ATP III criteria did not necessitate demonstration of insulin resistance and no single factor was mandatory for the diagnosis.<sup>7</sup> ATP III required the presence of

three of the following five factors for arriving at the diagnosis: abdominal obesity (highly correlated with insulin resistance), elevated blood pressure, elevated triglyceride, reduced high-density lipoprotein cholesterol, and elevated fasting glucose (impaired fasting glucose or T2DM). In the absence of diabetes or cardiovascular disease, the metabolic syndrome is a predictor of these conditions.

In 2005, both the International Diabetes Federation (IDF)<sup>21</sup> and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)<sup>22</sup> dropped the WHO’s emphasis on insulin resistance, but made abdominal obesity essential as one of five factors required for the diagnosis of metabolic syndrome, with special emphasis on the role of waist measurement as a feasible screening tool.<sup>7</sup>

Recently, IDF<sup>21</sup> and AHA/NHLBI<sup>22</sup> developed a consensus opinion that abdominal obesity should not be a considered essential for diagnosis, but is one of the five criteria. The presence of any three of five risk factors (elevated waist circumference; elevated triglycerides  $\geq 150$  mg/dL, reduced HDL cholesterol  $< 40$  mg/dL in males and  $< 50$  mg/dL in females; elevated blood pressure—systolic  $> 130$  and/or diastolic  $\geq 85$  mm Hg; elevated fasting glucose  $\geq 100$  mg/dL) establishes a diagnosis of metabolic syndrome.<sup>7</sup> Elevated waist circumference had population- and country-specific definitions.<sup>7</sup>

The NCEP ATP III and IDF criteria have both been widely used in the studies reviewed here. Grover et al. have conducted studies among individuals with mental disorders using both these criteria in various psychiatric disorders.<sup>23–27</sup> There is collective belief that NCEP ATP III definition of the metabolic syndrome is not best suited for the identification of risks for T2DM or coronary heart disease, as it does not identify metabolic syndrome correctly in South Asians. A crucial limitation is that the globally recognized cut-off points of waist circumference (men  $> 102$  cm; women  $> 88$  cm) for the diagnosis of abdominal obesity do not apply to South Asians. A study also shows a high odds ratio for the presence of cardiovascular risk factors was associated with waist circumference levels of  $> 90$  cm for men and  $> 80$  cm for women.<sup>28</sup>

Deepa et al. studied the prevalence of metabolic syndrome in the general population using WHO, ATP III, and IDF criteria; they noted higher prevalence rates of metabolic syndrome using the IDF criteria, with only a small difference in rate with the WHO criteria; however, there was a significant under-characterization using ATP III criteria.<sup>29</sup>

### Metabolic Syndrome in the General Population—Prevalence and Associated Factors

Metabolic syndrome is an escalating public health problem as reflected by the estimated prevalence ranging from 34.7% in a study from the United States<sup>30</sup> to 11.2% in a study from Chennai, India.<sup>31</sup> Several meta-analyses documented that people with severe mental illnesses have an increased risk for developing metabolic syndrome compared with the general population.<sup>22–24</sup>

Research data from studies indicate that glucose intolerance, atherogenic dyslipidemia, endothelial dysfunction, and subclinical inflammation are relatively high among Asian Indians than Caucasians.<sup>32</sup> Also these manifestations are seen at an early age and are more severe in Asian Indians than Caucasians.<sup>32</sup> Metabolic syndrome and cardiovascular risk in Asian Indians and South Asians are amplified by their higher body fat mass, intra-abdominal fat mass, truncal subcutaneous fat mass, and ectopic fat deposition.<sup>33</sup>

The prevalence of metabolic syndrome in Asian Indians varies according to the region, the extent of urbanization, lifestyle patterns, and cultural and socioeconomic factors.<sup>34</sup> Recent data show that about one-third of those living in urban India's major cities have metabolic syndrome. High prevalence of metabolic syndrome (~12%) has been shown by Misra et al., in intracountry rural-to-urban migrant population belonging to low socioeconomic strata residing in urban slums.<sup>28</sup>

Deepa et al. conducted an epidemiological study among 2,350 Asian Indians and identified metabolic syndrome in 546 subjects (23.2%) based on the WHO criteria, 430 subjects (18.3%) based on the ATP III criteria, and 607 subjects (25.8%) as per the IDF criteria.<sup>29</sup> The prevalence of metabolic syndrome, irrespective of the criteria used, increased with age until the age of 69 and decreased thereafter in all three groups. It is of note that even among subjects in the age group of 20–29 years, there was a 5.1–8.9% prevalence of metabolic syndrome, which meant that they will have sustained exposure to the atherosclerotic risk factors.<sup>29</sup>

Another Indian study by Sawant et al. found a prevalence of 19.52% among 548 subjects.<sup>34</sup> The prevalence was twofold in males as compared to females. This study also revealed the amplified prevalence of metabolic syndrome in 41–60 years' age group, suggesting that this group is at an amplified risk of developing coronary artery disease.<sup>34</sup>

### Prevalence of Metabolic Syndrome in Patients with Mental Disorders

In a study conducted by Teixeira et al. in Brazil among various psychiatric groups, highest prevalence rates of metabolic syndrome were noted among subjects with depression (48.1%) followed by bipolar disorder (38%) and schizophrenia and schizoaffective disorder (31.8%).<sup>35</sup> Mattoo and Singh in 2007 studied the prevalence of metabolic syndrome in psychiatric inpatients in North India using the IDF criteria and found a higher prevalence of metabolic syndrome in psychiatric inpatients (37.8%) than that in the general population.<sup>36</sup> They showed presence of metabolic syndrome in 40.9 and 41.9% patients in the diagnostic subgroups schizophrenia and other psychotic disorders, respectively.<sup>36</sup>

A meta-analysis of studies on metabolic syndrome in schizophrenia and related disorders showed that the overall rate of metabolic syndrome was 32.5%, and there were only minor differences according to the different definitions of metabolic syndrome, treatment setting (outpatient vs inpatient), by country of origin, and no substantial difference between genders.<sup>37</sup> A retrospective analysis conducted by Bermudes et al. in 2003 in the United States among psychiatric inpatients with primary psychotic and mood disorders used the NCEP ATP III criteria to diagnose metabolic syndrome and found a prevalence of 38.6% among their subjects.<sup>38</sup> Studies have shown a prevalence of metabolic syndrome in schizophrenia ranging from 15.7 to 68% and have also reported that the prevalence is higher in patients with schizophrenia compared to a healthy control group.<sup>36,39–41</sup> However, Padmavati et al. found a 3.9% prevalence of metabolic syndrome among never-treated chronic schizophrenics and concluded that in the absence of antipsychotic drug treatment, schizophrenia alone is not a factor contributing to the high prevalence of metabolic abnormalities.<sup>42</sup>

Among depressive disorder patients, a prevalence rate of 17.1% was reported by Mattoo et al.,<sup>36</sup> while Solia et al.<sup>40</sup> reported a prevalence of 39.5%. Prevalence rates of 8.6–40.5% were seen among patients of bipolar affective disorder in studies

by Mattoo et al.<sup>36</sup> and Solia et al.<sup>40</sup> Another study by Mattoo et al. in 2011 in North Indian population showed a prevalence of metabolic syndrome among alcohol use disorder of 24.6%.<sup>43</sup> A meta-analysis conducted in 2015 showed a 21.8% pooled prevalence of metabolic syndrome among individuals with alcohol use disorder.<sup>44</sup>

### Variables Associated with Metabolic Syndrome in Patients with Mental Disorders

#### *Sociodemographic Variables*

Among the various studies conducted on metabolic syndrome in mental illness, sociodemographic variables, such as age, gender, marital status, area of domicile, and education/employment, were studied by most researchers.<sup>23,25,26,36,38,40,45–49</sup> Old age had a modest impact on the rate of metabolic syndrome.<sup>37</sup> A meta-analysis found that gender is a significant predictor of metabolic syndrome, with a higher prevalence among females.<sup>4</sup> However, some studies did not find a significant gender variation in the prevalence of metabolic syndrome.<sup>25,36,38,40,50</sup> Certain studies highlighted the marital status as a correlate of metabolic syndrome. Alosaimi et al.<sup>50</sup> reported a greater prevalence of metabolic syndrome among divorcees, whereas Solia et al.<sup>40</sup> reported a higher prevalence among those never married. In a study on patients with schizophrenia, Bajaj et al.<sup>46</sup> reported that rural patients are more likely to have metabolic syndrome in contrast to Ganesh et al.,<sup>4</sup> who reported a significantly lower prevalence of metabolic syndrome in the rural population. Certain studies have revealed that individuals with higher levels of education were at a higher risk of developing metabolic syndrome.<sup>23,46</sup>

#### *Clinical Variables: Diagnosis, Duration of Illness, and Psychotropic Medications*

The association between metabolic syndrome and various diagnostic groups has been reviewed under the heading prevalence of metabolic syndrome in patients with mental disorders. Variables like duration of psychiatric illness and exposure to psychotropic medication are reviewed here.

De Hert et al. in a prospective cross-sectional study calculated the prevalence of metabolic syndrome across four clusters of illness duration and demonstrated a strong association: the longer the participants had had psychosis, the higher the rates of metabolic syndrome.<sup>51</sup> Another study also concurred with regard to the influence of illness duration, indicating that 46.9% of patients with metabolic syndrome had disease duration between 6 and 10 years.<sup>50</sup> The duration of psychiatric disorders is often an indirect means or a proxy of duration of exposure to psychotropic medication and is interconnected to patient age, both of which can influence metabolic syndrome.<sup>37,52</sup> Meta-analyses found that the duration of psychiatric disorders was the strongest predictor of metabolic syndrome.<sup>37,53</sup>

Atypical antipsychotics have been widely studied with regard to their association with obesity, hyperglycemia and dyslipidemia, and physiological changes (like abnormalities of glucose regulation).<sup>38</sup> Solia et al. studied the association of treatment with various antipsychotic medications and the duration of their use.<sup>40</sup> Patients using antipsychotics in general, especially olanzapine and clozapine, have been consistently found to have a higher risk of metabolic syndrome compared to antipsychotic naive individuals.<sup>5</sup> A recent Indian study reported that the risk of metabolic syndrome is higher when the dose of clozapine is high.<sup>54</sup> In contrast, the metabolic syndrome risk was significantly lower with aripiprazole

than other antipsychotics (amisulpride being an exception).<sup>5</sup> An Indian study done by Chadda et al. showed antipsychotic-induced changes on metabolic parameters became evident after 2 weeks and reached a maximum at 3 months of treatment. Saddichha et al. reported an increase in the prevalence of metabolic syndrome from 3.3% at baseline to 31.8% at the end of 6 weeks' treatment with olanzapine or risperidone.<sup>55</sup> Later, the same group reported a five times higher prevalence of metabolic syndrome in patients on antipsychotics, compared to healthy controls. Treatment-induced metabolic syndrome was highest with olanzapine (20–25%), followed by risperidone (9–24%), and was least with haloperidol (0–3%).<sup>56</sup> A study from Thailand reported that around 20% of schizophrenia patients on treatment went on to develop metabolic syndrome at 1-year follow-up after having subsyndromal metabolic syndrome components at baseline.<sup>57</sup>

### Level of Physical Activity

Clinical experience and multiple studies confirmed that patients with severe mental illness are physically less active.<sup>45,58–60</sup> Identification of metabolic syndrome needs to be further underscored as the overall functioning is impaired due to it.<sup>61</sup> Studies have compared the association of physical activity in mental illness and metabolic syndrome.<sup>38,40,62</sup> However, research on this theme is scarce in India. Measurement of physical activity in large population groups is customarily undertaken using self-reported recall, often in the form of a questionnaire, either by telephone or household interview. Nevertheless, there has been no standardized protocol for assessing physical activity in psychiatric patients. A less prevalence of metabolic syndrome has been reported to be linked with moderate to vigorous physical activity by studies in the general population that used both objective and subjective measures.<sup>63,64</sup> Bermudes et al. studied the role of physical activity and the prevalence of the metabolic syndrome in psychiatric inpatients with mood disorders and primary psychotic disorders.<sup>38</sup> They did not find a significant association with physical activity and metabolic syndrome; however, a validated tool was not administered for the evaluation of physical activity.<sup>38</sup> Some authors have assigned scores based on the intensity of physical activity such as absent, mild: <4 hours/week, moderate: 4 hours/week, and intense: >4 hours/week.<sup>40,65</sup> Lifestyle factors such as sedentary habits and high carbohydrate and fat intake are common in patients with severe mental illness.<sup>38</sup>

The World Health Organization (WHO) developed the Global Physical Activity Questionnaire (GPAQ) to measure the physical activity habits of populations using a standardized protocol.<sup>66</sup> This questionnaire encompasses multiple components of physical activity, such as frequency, intensity, and duration, and assesses three domains in which physical activity is performed (occupational, transport-related, and physical activity during discretionary or leisure time).<sup>66,67</sup> Bull et al. have shown good reliability and validity of GPAQ in assessing physical activity across nine countries including India.<sup>67</sup>

### SUMMARY

From this review, it is apparent that studies on the international front are many, but there are relatively less Indian studies on the prevalence of metabolic syndrome in mental illnesses. The number of studies found in South India over this topic are especially sparse. This review indicates that, the prevalence of metabolic syndrome in patients with mental disorders ranges from 3.9 to 68%, in comparison to the range in the general population

(11.2–34.7%). Based on this review, no clear pattern emerges with regard to the association between sociodemographic variables and metabolic syndrome in patients with mental disorders. This review also emphasizes the influence of illness duration and use of psychotropic medications, particularly antipsychotics, in the risk of developing metabolic syndrome. This review highlights the fact that patients with severe mental illness are less physically active and level of physical activity is closely associated with metabolic syndrome. Emphasis needs to be laid on the importance of inclusion of physical activity into psychiatric treatment and rehabilitation programs. Assessment of level of physical activity is best done using a validated scale.

The prevalence of metabolic syndrome and its components among patients with psychiatric disorders is cause for concern. While considerable debate exists regarding the causes for the high prevalence of metabolic disturbances in patients with mental disorders, gaps remain in relevant aspects, encouraging further studies in specific subgroups of psychiatric patients to evaluate the impact of each variable on the risk for developing metabolic syndrome. From this review, we infer that there are several associated factors that influence the increased prevalence of metabolic syndrome, among patients with mental disorders. Rather than a single causative factor, there are multiple factors associated with metabolic syndrome.

The research literature supports the requisite for early identification of metabolic syndrome in people with mental disorders and initiation of suitable interventions. It is of paramount importance that guidelines specific to the Indian context are developed for the screening and monitoring of psychiatric patients with reference to metabolic syndrome and physical health in general. Appropriate screening for physical illness and promotion of physical activity and physical well-being among patients with mental disorders are likely to contribute to a better overall outcome. The fact that metabolic syndrome is widely prevalent among individuals with mental illness, and studies in this part of the country are scarce, underscores the need for further research on this topic.

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