

THE METABOLIC SYNDROME IN UNTREATED SCHIZOPHRENIA PATIENTS: PREVALENCE AND PUTATIVE MECHANISMS

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SUMMARY

The Metabolic Syndrome (MetS) is a constellation of commonly coexisting clinical markers. It is well established that MetS is more prevalent in schizophrenic (SCZ) patients medicated with atypical antipsychotics, however, questions still exist over whether schizophrenia itself can contribute directly to metabolic dysfunction.

We evaluated the antipsychotic-independent link between MetS and schizophrenia, by conducting a systematic literature search. Twelve papers were identified, from which 893 patients were evaluated. The mean prevalence of MetS was 10.8%, suggesting its incidence is not increased. However, some aspects of MetS may be increased, such as diabetes.

Hypothalamic-pituitary axis dysfunction, sympathetic nervous system dysfunction, proinflammatory states and several genetic mutations have been implicated in the observed metabolic dysregulation in schizophrenic patients, however much controversy exists in this area.

The huge cardiovascular burden makes it crucial to establish the causes and optimal management of MetS in schizophrenia.

Key words: schizophrenia - metabolic syndrome

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INTRODUCTION

The Metabolic Syndrome refers to a constellation of clinical markers which often coexist in patients, each representing an increased risk of developing cardiovascular (CV) disease. Several organisations have their own criteria for diagnosing MetS (Grundy et al. 2004, International Diabetes Federation 2005). These are largely overlapping, with the differences displayed in Table 1. MetS is generally accepted as an observed clinical syndrome, but controversy exists over whether a unifying pathogenic mechanism exists. Regardless of this, it has been shown that MetS represents a two-fold increase in CV risk, independently of diabetes (Mottillo et al. 2010). The prevalence of MetS varies between countries, which may be largely attributable to differences in diet and lifestyle (Cameron et al. 2004). In the developed world, rates are extremely high, with recent estimates in the USA of 32.3% in those over 20 years of

age (Ford et al. 2004) and 34.4% in the UK in 40-70 year olds (Khunti et al. 2010).

It is well established that the prevalence of MetS among schizophrenic patients is greatly increased compared to the general population (Saari et al. 2005). Though this effect is mostly attributed to use of atypical antipsychotic (AAP) medications (De Hert et al. 2012), questions also exist over whether schizophrenia itself can contribute more directly to metabolic dysfunction. Indeed, it was observed that metabolic disturbances were common in mental illness as early as 1880 (Maudsley 1880), and many years before the implementation of AAP medications (Braceland et al. 1945, Langfeldt 1952, Meduna et al. 1942). It has been predicted that approximately 50% of schizophrenics may develop MetS (Casey et al. 2004). In order to discern this, it is necessary to look at studies of patients who have not been treated with antipsychotics, and compare metabolic parameters with non-schizophrenic individuals.

Table 1. Diagnostic criteria for the metabolic syndrome

Parameter	Criterion
Waist circumference (cm)	ATPIII / ATPIIIA / AHA: >102 (M), >88 (F) IDF: ≥94 (M), ≥80 (F)
Blood pressure (mmHg)	≥130/85 (or undergoing treatment for HTN)
HDL (mmol/l)	<1.03 (M), <1.29 (F)
Triglycerides (mmol/l)	≥1.71
Glucose (mmol/l)	ATPIII: ≥6.1; ATPIIIA / IDF: ≥5.5 (or undergoing treatment for diabetes mellitus)

ATP – Adult Treatment Panel; ATPIII and ATPIIIA (NCEP 2002) require any three criteria to diagnose MetS. AHA – American Heart Association (Grundy et al. 2004). IDF – International Diabetes Federation; central obesity criterion and any two other criteria to diagnose MetS (International Diabetes Federation 2005).

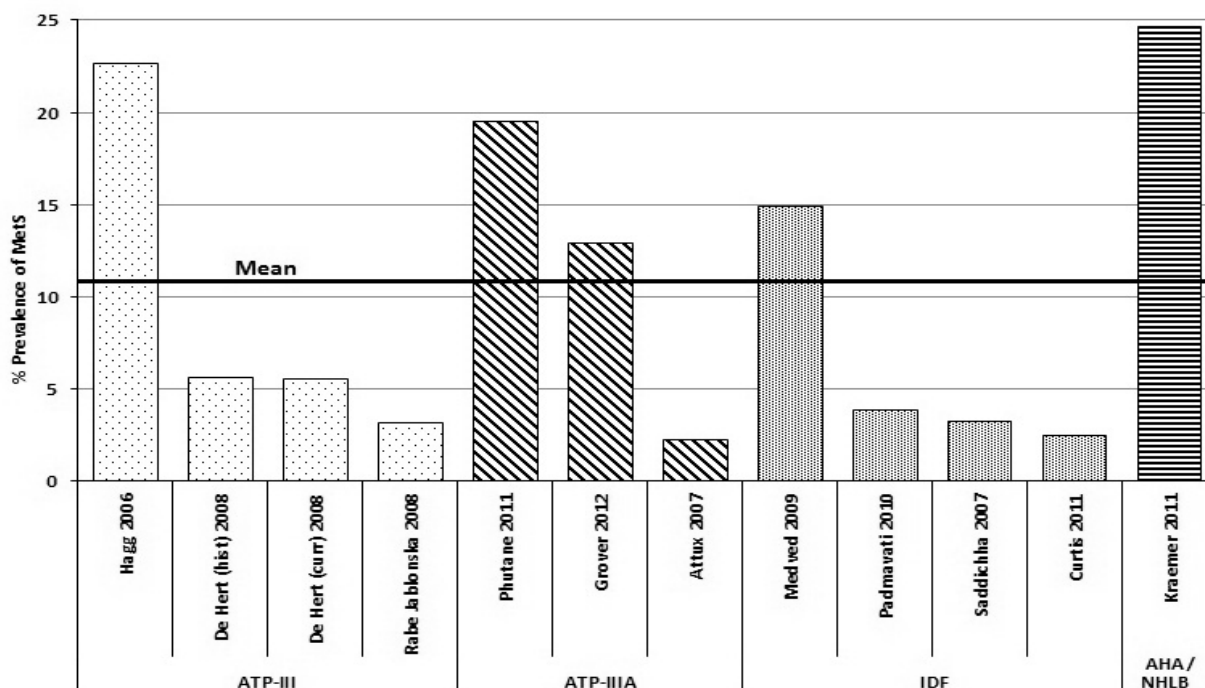


Figure 1. Prevalence of MetS sorted according to diagnostic criteria. Mean prevalence of MetS across all 12 studies (n=893) found to be 10.8% (Attux et al. 2007, Curtis et al. 2011, Grover et al. 2012, Hägg et al. 2006, De Hert et al. 2008, Kraemer et al. 2011, Medved et al. 2009, Padmavati et al. 2010, Phutane et al. 2011, Rabe-Jabłońska & Pawełczyk 2008, Saddichha et al. 2007)

METHODS AND RESULTS

We sought to evaluate the link between MetS and SCZ which is independent of AAPs. A systematic literature search of PubMed was conducted using the MeSH search terms “schizophrenia” and “metabolic syndrome”, yielding 408 results from the past 10 years (2002-2012). Abstracts were assessed to exclude irrelevant papers, and papers were analysed to identify those specifically investigating drug-naïve and first episode patients. Twelve papers met our criteria, from which 893 patients were evaluated. An average prevalence of MetS across these studies came to 10.8% (Figure 1). We have shown that there are very few data to suggest that the incidence of MetS is increased in first episode and drug naïve adult patients with SCZ.

Rates of MetS prevalence vary greatly between countries (Cameron et al. 2004), and it is therefore difficult to compare these studies to population data. Only 3 of the studies compared their rates to control populations, such as data from national surveys (Padmavati et al. 2010, Phutane et al. 2011, Rabe-Jabłońska & Pawełczyk 2008). All of these determined that the rates of MetS in antipsychotic naïve and first episode schizophrenic patients did not significantly differ from controls. Indeed, Padmavati et al. (2010) found that rates of MetS and mean BMI in schizophrenic patients were in fact significantly lower than healthy age and sex matched controls.

DISCUSSION

Despite finding no increase in the overall prevalence of the metabolic syndrome, there may, however, be reason to suspect that SCZ does increase some components of MetS, such as diabetes. Following the observation that the prevalence of type 2 diabetes mellitus was increased in relatives of those with schizophrenia (Mukherjee et al. 1989) it was shown that fasting glucose tolerance and insulin sensitivity were impaired in first episode, drug naïve schizophrenics compared to matched controls (Ryan et al. 2003). However, more recent studies have failed to replicate this (Arranz et al. 2004, Zhang et al. 2004). Comparable first episode, drug naïve schizophrenic populations were shown to have increased central adiposity when compared to controls (Thakore et al. 2002). These studies have promoted interest in identifying a common inherited susceptibility to type 2 diabetes and schizophrenia, and several potential loci have been identified (Gough & O’Donovan 2005). Furthermore, selection of untreated patients biases towards those in the early stages of disease, providing little information about chronic effects of SCZ on CV health.

PUTATIVE MECHANISMS

Many putative contributory mechanisms have been proposed for the observed metabolic dysregulation in SCZ patients (Figure 2). The majority of investigations

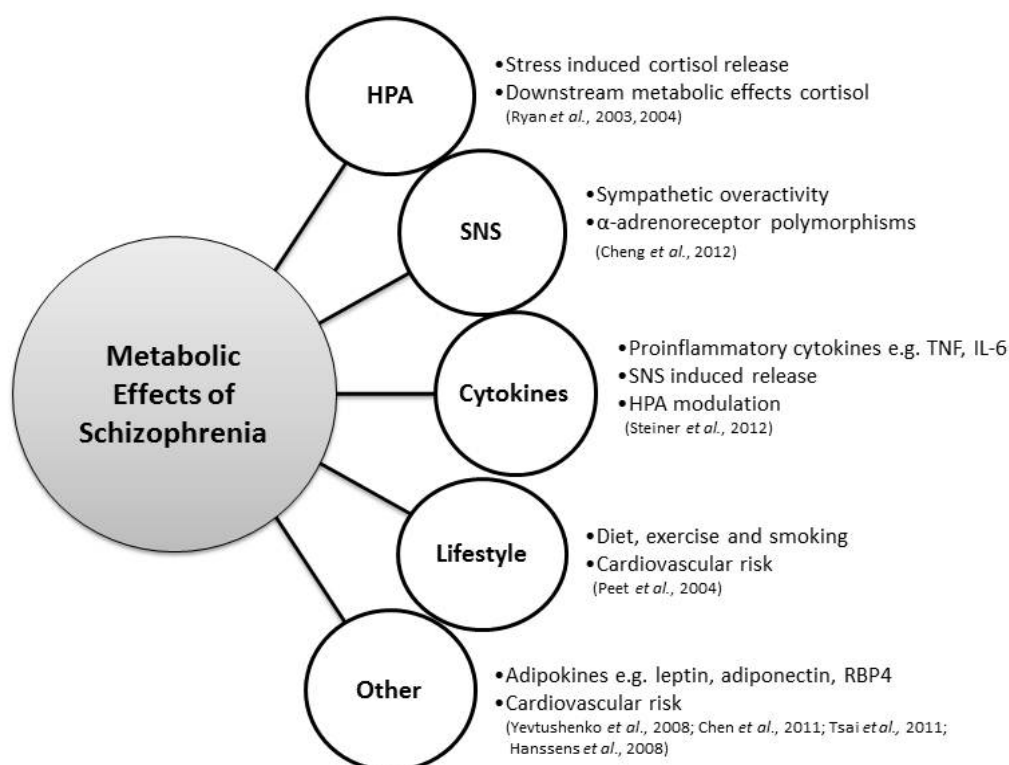


Figure 2. Summary of proposed mechanisms for MetS pathogenesis in SCZ (Chen *et al.* 2011, Cheng *et al.* 2012, Hanssens *et al.* 2008, Peet 2004, Ryan *et al.* 2003, 2004, Steiner *et al.* 2012, Tsai *et al.* 2011, Yevtushenko *et al.* 2008)

into the mechanisms have been in those who have been treated with antipsychotics, a known cause of metabolic dysregulation.

The most commonly proposed mechanism for SCZ-induced metabolic dysfunction is hypothalamic-pituitary axis dysfunction. It has been suggested that stress-induced ACTH release drives metabolic derangement (Ryan *et al.* 2004), and indeed, cortisol levels have been shown to be elevated in first episode SCZ patients (Ryan *et al.* 2003). Given the widespread effects of cortisol on metabolism it is easy to envisage how chronic hypercortisolaemia may cause the central obesity, lipid and glycaemic derangements that constitute the components of the metabolic syndrome. Exactly how psychological stress may precipitate hypothalamic dysregulation remains to be elucidated.

Sympathetic nervous system over-activity has been implicated, through studies linking α -adrenoreceptor polymorphisms to MetS severity in SCZ (Cheng *et al.* 2012). Mechanistically, excess catecholamine action bears many similarities to the putative cortisol-induced dysregulation, through widespread antagonism of insulin-mediated effects on metabolism, and may also represent an upstream cause of excess cortisol.

It has been observed that cytokines such as IL-1 and IL-6 are elevated in schizophrenia. Some groups have proposed that a proinflammatory state may represent a common pathogenic mechanism, with these cytokines impairing cerebral metabolism and predisposing to schizophrenia, and peripherally causing the observed metabolic features (Steiner *et al.* 2012).

There has also been interest recently in several adipokines, such as leptin (Chen *et al.* 2011, Tsai *et al.* 2011, Yevtushenko *et al.* 2008) and adiponectin (Hanssens *et al.* 2008), and RBP4 (Chen *et al.* 2011). At this point, however, the extent to which these can be ascribed to pathogenic mechanisms of SCZ or reactions to AP therapy has not been demonstrated.

It is also conceivable that behavioural consequences of SCZ may contribute to MetS development and CV risk. Specifically, smoking is more common in SCZ patients, and diet and exercise habits are also more likely to be unhealthy. Furthermore, the observation that the CV outcomes in SCZ patients in developing countries are better than those in developed nations, which may be a consequence of differences in diet, in particular due to having a high polyunsaturated: saturated fat ratio and low sugar intake (Peet 2004).

CONCLUSION

There is a huge cardiovascular burden on schizophrenic patients, with an almost doubled risk of mortality from CV disease (De Hert *et al.* 2009). Those with mental illness may be less likely to seek medical help, contributing to mortality from CV disease. The diagnostic criteria for MetS are easy to assess in a clinical setting, and provide a useful indicator of future CV risk. It is crucial, therefore, to establish the risk and aetiology of MetS and CV risk in schizophrenia, and to implement aggressive screening and management of risk factors.

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