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Cause, consequence or coincidence: The relationship between psychiatric disease and metabolic syndrome

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ABSTRACT

It is now well established that severe mental illness (SMI) is associated with a reduced lifespan and increased risk of cardiovascular disease (CVD). Individuals with SMI often have abnormalities of lipid metabolism, glucose homeostasis, an increased prevalence of obesity and hypertension. They also have an increased prevalence of Metabolic Syndrome (MetS). The reasons for this are not entirely clear, but are likely to be multifactorial. Whilst there have been numerous studies investigating the prevalence of MetS in patients with SMI, many have been in small, mixed population samples, that have not been adequately controlled for the background population from which they have been drawn. This is important because of the wide range of prevalence estimates that have been reported, and variations of MetS prevalence with ethnicity. The negative impact of treatment with second-generation antipsychotic (SGA) drugs on the risk of MetS also appears clear in most populations, although the mechanisms accounting for this increased risk are yet to be clarified. Despite this high prevalence of CVD risk factors in patients with SMI, most studies report a poor implementation of screening for CVD risk factors at baseline, and following initiation of treatment with SGAs. Not all patients with SMI are susceptible to the adverse effects of SGAs, but in those that are, switching to an anti-psychotic that is less likely to cause metabolic disturbance, starting statin therapy and a reduction in CVD risk factors through changes in lifestyle may all be important strategies.

1. Introduction

Severe mental illness (SMI) is associated with a substantially reduced life expectancy.[1,2] The complexity of defining SMI has been outlined by the Director of the US National Institute of Mental Health,[3] and in the United States (US) a practical and pragmatic approach has been used[4]; SMI therefore comprises psychotic and affective disorders that lead to functional impairment that affect major life activities. The increased risk of premature cardiovascular disease (CVD) in individuals with SMI is particularly notable, and this has been attributed, in part, to a high prevalence of metabolic syndrome (MetS). The latter condition, also termed Syndrome X by Reaven,[5] is characterised by a clustering of several CVD risk factors that include central obesity, dyslipidaemia, hypertension and impaired glucose tolerance. Reaven has argued that insulin resistance (IR) is the central metabolic defect in MetS. Bjorntorp noted that stress-related cortisol secretion is often enhanced in individuals with central obesity and that this may lead to IR and the other features of MetS.[6] His team further observed that the hypothalamic-pituitary adrenal (HPA) axis may be stimulated by several socio-economic and psychosocial factors, which include: alcohol, smoking and traits of psychiatric disease.[7] Therefore, the relationship between major psychiatric conditions such as schizophrenia and bipolar disorder (BD), and risk of MetS and cardiovascular disease (CVD) may be due to:

1) SMI being a cause of MetS, due to the direct effects of psychiatric disease, or its treatment,[8,9] on the metabolic and hormonal milieu,[10] or on patterns of behaviour that increase the risk of the components of MetS;[11,12]
2) SMI being a consequence of the potential impact of the MetS,[13] and particularly obesity,[14] on mental wellbeing,[15] or

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Abbreviations

AHA	American Heart Association
ATPIII	National Cholesterol Education Programme, Adult Treatment Panel-III
ATPIIIa	adapted ATP-III
AUD	Alcohol use disorder
BD	Bipolar disorder
BMI	Body mass index
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
CVR	Cardiovascular risk
DM	Diabetes mellitus
FES	First episode schizophrenia
HDL-C	High-density lipoprotein-cholesterol
HRLQ	Health related quality of life
HOMA	Homeostasis model assessment
HPA	Hypopituitary-pituitary-adrenal
ICD	International Classification of Diseases
IDF-AHA/NHLBI	International Diabetes Federation-American Heart Association/National Heart Lung and Blood Institute
IDF	International Federation of Diabetes
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IR	Insulin-resistance
IS	Insulin-sensitivity
JIS	Joint Interim Statement
LDL-C	Low-density lipoprotein-cholesterol
MDD	Major depressive disorder
MI	Myocardial infarction
MetS	Metabolic Syndrome
MTHFR	methylenetetrahydrofolate reductase
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PCOS	Polycystic ovary syndrome
PHQ-9	Patient Health Questionnaire-9
PPARs	Peroxisome Proliferator-Activated Receptors
PTSD	Post-traumatic stress disorder
QUICKI	Quantitative insulin check index
ROC	Receiver operating characteristic
SGAs	Second-generation antipsychotics
SMI	Severe mental illness
SSRI	Selective serotonin uptake inhibitor
TG	Triglycerides
TPH2	Tryptophan hydroxylase 2
UA	Uric acid
US	United States
VPA	Valproic acid
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-to-Hip Ratio

3) Individuals being affected by SMI and MetS co-incidentally because of shared common risk factors, that may include a genetic predisposition,[16] sleep disorders,[17] or stress,[18] that predispose to both psychiatric disease and metabolic abnormalities.[19]

These putative mechanisms are not mutually exclusive; the relationships may be bidirectional and self-reinforcing (see Fig. 1). For example, whilst depression can predispose to CVD; CVD may also lead to depression, and several socio-economic and behavioural correlates of both conditions may further influence this relationship.[20]

In this review, these possible complex relationships are explored further, together with the reported prevalence of MetS in different SMIs (schizophrenia, schizoaffective disorder, bipolar disorders, depression, stress related disorders and substance dependency) and different global population samples. The interpretation of prevalence estimates of MetS in populations with psychiatric disease is complicated. This is particularly the case with respect to historical and global data, because of the different criteria

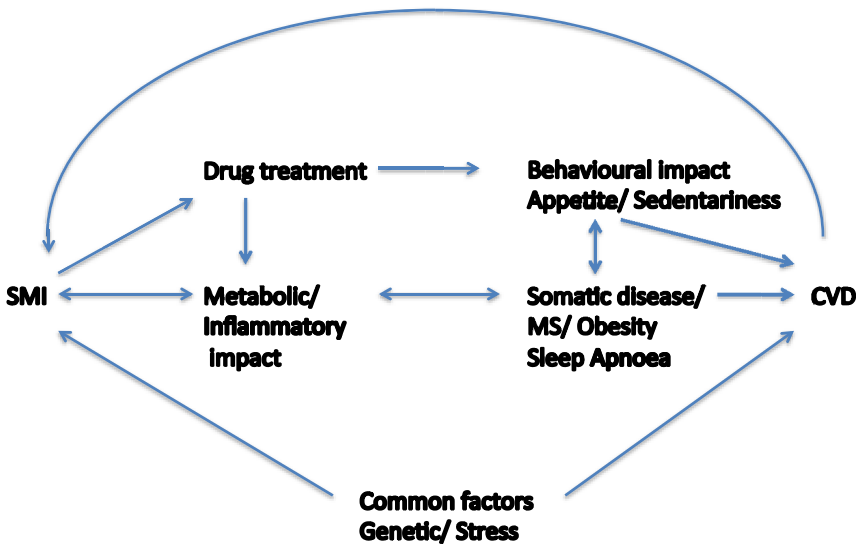

Fig. 1. Interactions between factors related to severe mental illness (SMI) and cardiovascular disease (CVD) risk factors, including Metabolic Syndrome (MS).

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