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Review

Schizoaffective disorder and metabolic syndrome: A meta-analytic comparison with schizophrenia and other non-affective psychoses

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ABSTRACT

People with psychotic disorders, including schizophrenia (SCZ), schizoaffective disorder (SD), or other non-affective psychoses (ONAP), have a higher risk of metabolic syndrome (MetS) than general population. However, previous meta-analyses failed to explore if people with SD are more likely to suffer from MetS than SCZ and ONAP.

We carried out a systematic review and meta-analysis comparing rates of MetS in SD with those in SCZ or ONAP. We searched main electronic databases for relevant articles published up to January 2015, and for unpublished data, contacting corresponding authors, to minimize selective reporting bias. Odds ratios (ORs) based on random effects models, with 95% confidence intervals (CIs), and heterogeneity (I^2), were estimated. We performed leave-one-out, quality-based, and subgroups analyses to check findings validity. Testing for publication bias, Egger's test estimates were reported.

We included 7616 individuals (1632 with SD and 5984 with SCZ/ONAP) from 30 independent samples. SD, as compared with SCZ/ONAP, had a random-effect pooled OR (95%CI) for MetS of 1.41 (1.23–1.61; $p < 0.001$; $I^2 = 5\%$). No risk of publication bias was found ($p = 0.85$). Leave-one-out, sensitivity, and subgroups analyses confirmed the association.

To our knowledge, this is the first meta-analysis comparing MetS comorbidity between individuals with SD and those with SCZ or ONAP. SD subjects are more likely to suffer from MetS, with consistent findings across the studies included. However, the role of explanatory factors of this association, and the relative contribution of MetS subcomponents, deserve further research.

1. Introduction

In the last decade a bulk of evidence showed that individuals who suffer from psychotic disorders, including schizophrenia (SCZ), schizoaffective disorder (SD), or other non-affective psychoses (ONAP- i.e., schizophreniform, delusional, brief psychotic, and psychotic NOS disorders), are more likely to have rates of cardiovascular risk factors and metabolic disorders (dyslipidemia, diabetes, obesity) higher than in the general population (Birkenaes et al., 2006; Osborn et al., 2006; Osby et al., 2014; Vancampfort et al., 2013). In particular, metabolic syndrome (MetS), also known as insulin resistance syndrome (Reaven, 1988) and metabolic syndrome X (Reaven, 1993), have attracted considerable attention and concerns due to its high comorbid prevalence in people with psychotic disorders (De Hert et al., 2009; Mitchell et al., 2013). MetS is a complex disease characterized by a cluster of cardiovascular risk factors (Alberti et al., 2009; Grundy et al., 2005), with prevalence rates ranging between 20 and 30% in adult populations (Grundy, 2008). About one third of adults with SCZ and related disorders, with differences possibly related to various phases of the disease and treatment status, is affected by comorbid MetS (Mitchell et al., 2013). Geographical variations have been identified with high MetS comorbid rates among people with psychotic disorders especially in North America (Cohn et al., 2004; Correll et al., 2010), Northern Europe (Boden et al., 2013; Foldemo et al., 2014), and Australia (Galletly et al., 2012; Tirupati and Chua, 2007). However, previous meta-analytic findings (e.g., Bartoli et al., 2013a, b; Mitchell et al., 2013; Osborn et al., 2008; Vancampfort et al., 2013) indiscriminately pooled data of individuals with SCZ, SD, and ONAP, failing to explore potential

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differences on MetS rates across different psychotic disorders. Indeed, psychotic disorders may not necessarily show the same likelihood of MetS, resulting in different rates of metabolic abnormalities (e.g., Khatana et al., 2011; van Winkel et al., 2008). Previous research has descriptively reported on the association between SD and cardiovascular and metabolic abnormalities (e.g., Bobes et al., 2012), showing that people with SD might be more prone to disorders such as obesity, dyslipidemia, and glucose intolerance/diabetes (Khatana et al., 2011; Kilbourne et al., 2007; Regenold et al., 2002), with higher rates of comorbid MetS (Basu et al., 2004; John et al., 2009). However, recent evidence on the cumulative effects of psychotic and affective symptoms on healthy behaviors and lifestyle (Centorrino et al., 2012; Khatana et al., 2011), allow hypothesizing that SD may be a mental condition particularly at risk of MetS as compared with other psychotic disorders. To our knowledge, no meta-analysis has been conducted comparing MetS rates across different psychotic disorders. With a view to overcome some of the limitations of studies to date, we carried out a systematic review and meta-analysis comparing MetS rates in SD with those in SCZ and ONAP.

2. Methods

The current systematic review and meta-analysis was conducted according to the Meta-analysis Of Observational Studies in Epidemiology (*MOOSE*) guidelines (Stroup et al., 2000). The study protocol was registered in the International Prospective Register of Systematic Reviews (*PROSPERO* – registration number: *CRD42014015678*).

2.1. Definitions

With minor differences (Malaspina et al., 2013) between DSM-IV-TR (American Psychiatric Association, 2000) and the recently released DSM-5 criteria (American Psychiatric Association, 2013), SD is defined as an uninterrupted period of illness during which there is a major mood episode (major depressive or manic) concurrent with psychotic symptoms. During the lifetime duration of the illness, delusions or hallucinations occur for at least two weeks in the absence of prominent mood symptoms. Mood episodes are present for the majority of the total duration of the active and residual portions of the illness. Similarly to other psychotic disorders, SD is generally characterized by a compromised psychosocial functioning (Correll, 2011) and high levels of psychological distress (Carrà et al., 2011).

MetS involves a cluster of cardiovascular risk factors, including abdominal obesity, high blood pressure, fasting plasma glucose and triglycerides, and low HDL-cholesterol. Several definitions with different cut-offs have been proposed, e.g., according to the diagnostic criteria of the Adult Treatment Panel (ATP) III (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001)), the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), also named adapted ATP III (ATP IIIa) (Grundy et al., 2005), and the International Diabetes Federation (IDF) (Alberti et al., 2005, 2006). Most recent recommendations (Alberti et al., 2009) attempted to *harmonize* these criteria, defining MetS as the co-occurrence of at least three of the following conditions:

- abdominal obesity, defined as a high waist circumference according to population- and country-specific characteristics;
- triglycerides ≥150 mg/dL (1.7 mmol/L), or current drug treatment for elevated triglycerides;
- HDL-C <40 mg/dL (1.0 mmol/L) in males and <50 mg/dL (1.3 mmol/L) in females, or drug treatment for reduced HDL-C;
- blood pressure ≥130/80 mmHg, or antihypertensive drug treatment in a patient with a history of hypertension;
- elevated levels of fasting glucose ≥ 100 mg/dL, or relevant drug treatment.

2.2. Search strategy

We searched PubMed, EMBASE, PsycINFO (via ProQuest) electronic databases for articles published up to January, 2015. Two different sets of search phrases were implemented, adapting search terms, according to different bibliographic databases, index terms, and relevant disorders (eTable 1). There were no language restrictions and in addition web search engines were used in order to check if all relevant studies were included. References were managed using *EndNote Web* Software.

2.3. Eligibility criteria

We included any observational study which estimated MetS prevalence (*i*) in a sample of people suffering from SD *and* (*ii*) in a sample of people with any other psychotic disorder (SCZ or ONAP). We excluded duplicated studies and those involving samples with a mean age <18 years, as well as conference abstracts and dissertations.

2.4. Data extraction

Two authors (CC and MC) completed the preliminary screening based on titles and abstracts. Studies were then retrieved in full text and final eligibility according to inclusion criteria was independently assessed by two authors (FB and GC). Differences in suitability for inclusion were resolved by discussion and consensus, involving all authors. We built a data extraction template, including key items for all eligible studies, i.e., year of publication, country, years of data collection, characteristics of recruited populations, sample size, mean age, setting, percentage of men and women, methods to assess MetS, and main results. If multiple sets of diagnostic criteria had been used to estimate MetS rates in SD and SCZ/ONAP samples, we followed a structured approach to different classifications, with ATP IIIa ranked higher than ATP III and IDF (Alberti et al., 2009). We benefited from a professional scientific translation service for papers in languages other than English and Italian. When reported information was unclear or insufficient, the relevant corresponding author was contacted (FB). Finally, in order to reduce the risk of selective reporting bias and to include also unpublished findings, one investigator (FB) contacted for clarification corresponding authors of studies not explicitly reporting MetS rates of people with SD as compared with SCZ/ONAP.

2.5. Data analysis

Meta-analyses of the association between SD, as compared with SCZ and ONAP, and MetS, were carried out generating pooled odds ratios (ORs), with related 95% confidence intervals (CIs), using inverse variance models with random effects. Statistical significance was set at $p < 0.05$ and conventional forest plots were used to summarize the results. Testing for publication bias, we reported Egger's bias coefficients with 95%CI and relevant p-value (Egger et al., 1997). Heterogeneity was estimated using the I^2 statistic, with values of 25%, 50%, and75%, taken to indicate low, moderate, and high levels of heterogeneity, respectively (Higgins et al., 2003; Higgins and Thompson, 2002). In addition, we carried out leave-one-out analysis to ensure that no single study unduly influenced the estimate (Sutton et al., 2000; Wallace et al., 2009). Furthermore,