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Schizophrenia and the risk of cardiovascular diseases: A meta-analysis of thirteen cohort studies

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ABSTRACT

Background: Numerous studies have investigated the relationship between schizophrenia and the incidence of cardiovascular disease (CVD), but their results were not entirely consistent. Our study aimed to elucidate the association between schizophrenia and the risk of CVD by a meta-analysis of cohort studies.
Methods: PubMed, the Cochrane Library, and EMBASE databases were searched to identify relevant studies that met the prespecified inclusion criteria. We also reviewed reference lists from the retrieved articles. Relative risks (RRs) and 95% confidence intervals (CIs) were extracted and pooled using the fixed-effect or random-effects models.
Results: Thirteen studies involving 3,549,950 participants, with outcomes of CVD reported for 422,698, were included in the meta-analysis. The follow-up period ranged from 1.6 to 36.0 years. The meta-analysis found that the pooled RRs for schizophrenia compared with the reference group were 1.53 (95% CI: 1.27–1.86) for the incidence of CVD, 1.20 (95% CI: 0.93–1.53) for coronary heart disease (CHD), 1.71 (95% CI: 1.19–2.46) for stroke, and 1.81 (95% CI: 1.42–2.29) for congestive heart failure (CHF). Sensitivity analysis after the exclusion of a single cohort or using the unadjusted RRs yielded similar results to the primary overall estimations. No evidence of publication bias was observed.
Conclusions: Schizophrenia is associated with increased incidence of CVD, stroke and CHF, and might also increase the risk of CHD. Greater attention should be paid to schizophrenia patients to prevent the occurrence of CVD and to decrease the risk of cardiac morbidity.

1. Introduction

Schizophrenia is a chronic mental illness with a lifetime prevalence of 1% of the population worldwide (Freedman, 2003). Patients with schizophrenia are at two to three times higher risk of mortality than the general population (Laursen et al., 2007; Osby et al., 2000; Saha et al., 2007). In addition to unnatural deaths (e.g. accident, homicide, or suicide), the leading cause of excess mortality in schizophrenia patients is physical illness, including neoplastic disease, respiratory disease, and cardiovascular disease (CVD) (Brown et al., 2000; Laursen, 2011).

Numerous studies over the past decade have investigated the incidence of CVD-related death in schizophrenia patients (Brown et al., 2010; Capasso et al., 2008; Hennekens et al., 2005). As a result, the association between schizophrenia and risk of CVD is well known. The use of antipsychotic medications (Sacchetti et al., 2010) coupled with an unhealthy lifestyle (McCreadie and Scottish Schizophrenia Lifestyle Group, 2003; Kavanagh et al., 2002), which includes smoking, obesity, poor diet and sedentary behavior, may contribute to the higher morbidity resulting from CVD. In addition, many clinical medical conditions concomitant with schizophrenia could accelerate the progression of CVD and the incidence of major adverse cardiac events (Leucht et al., 2007). Several studies have examined the relationship between schizophrenia and risk of CVD (Bresee et al., 2010; Callaghan et al., 2009; Carney et al., 2006; Curkendall et al., 2004; Enger et al., 2004; Filik et al., 2006; Jakobsen et al., 2008; Lahti et al., 2012; Lin et al., 2008, 2010; McDermott et al., 2005; Shen et al., 2011; Tsai et al., 2012), including coronary heart disease (CHD), stroke, and congestive heart failure (CHF). While the majority of these studies have shown positive correlations, a few have demonstrated a significantly increased incidence of stroke but not of CHD in patients with schizophrenia (Carney et al., 2006; Curkendall et al., 2004). Thus, it

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has been hypothesized that schizophrenia may have different impacts on the vasculature of brain and heart.

The between-study inconsistencies in methodology, disease duration, follow-up duration, study population, and even participants' race, may explain why no absolute conclusions have been made about schizophrenia and CVD. As such, the study described herein aimed to evaluate the association between schizophrenia and the risk of CVD by a meta-analysis. Of note, the case-control study design is prone to recall and selection biases; additionally, due to various limitations in funding, patient consent, and availability of appropriate study participants, most of the case-control studies performed do not include a sufficient number of participants, which limits the strength and quality of the results. Thus, we included cohort studies in this meta-analysis to increase the accuracy and integrity of its results.

2. Methods

2.1. Search strategy

We have attempted to report this meta-analysis in accordance with the proposed Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guideline (Stroup et al., 2000). We systematically searched the PubMed, Cochrane Library, and EMBASE databases to identify citations of previously published (up to April 2012) relevant studies using the following search terms: (1) cardiovascular disease, coronary heart disease, congestive heart failure, coronary thrombosis, myocardial ischemia, myocardial infarction, coronary stenosis, cerebrovascular disorders, stroke; (2) schizophrenia; (3) cohort study, prospective study, follow-up study, longitudinal study. In addition, to ensure that no clinical trials were missed, we also conducted an extensive search of the ISI Web of Science citation database using cross-references from the eligible articles and relevant reviews. No language restriction was applied.

2.2. Eligibility and exclusion criteria

Two investigators (Fan and Shen) independently carried out the review and evaluation of potentially relevant studies to determine adherence to preselected inclusion criteria (see below). Any disagreements were resolved by discussion. The reviewers were blinded to the potentially relevant study's publishing journal and affiliated institution. The meta-analysis inclusion criteria were: (1) application of a cohort study design (prospective cohort or historical cohort); (2) **reporting of** original **research data**; (3) assignment of schizophrenia as the baseline exposure; (4) reporting of the clinical endpoints of the incidence of CVD, CHD, stroke, or CHF; (5) direct reporting of relative risk (RR), odds ratio (OR), or hazard ratio (HR) with their corresponding 95% confidence intervals (CIs), or sufficient raw data so that the variables could be calculated.

2.3. Data extraction

The following data were extracted from each of the cohort studies that met the inclusion criteria: study characteristics (study name, authors, publication year, study site, follow-up years, study design, number of participants), baseline demographics of participants (mean age or age range, sex), clinical outcome (CVD, stroke, CHD, CHF), diagnostic methods of schizophrenia, and statistical adjustments for confounding factors. In this meta-analysis, CVD was defined as CHD, stroke, cardiac arrest, heart failure, or peripheral artery diseases. CHD was defined as acute myocardial infarction, angina pectoris, or any other ischemic heart disease. If any additional information was needed the authors of original articles were contacted directly.

2.4. Statistical analysis

STATA 11 (StataCorp, College Station, TX, USA) was used for all statistical analyses. The RR served as a common measure of the association between schizophrenia and risk of CVD, CHD, stroke, or CHF. The HR was directly regarded as RR, and the OR as RR. The multivariate-adjusted RRs with 95% CIs that were presented in the respective study were used. If unavailable, the raw data were used to calculate these values. The RRs, with their corresponding standard errors (SEs) were calculated according to their respective 95% CIs or p-values and then logarithmically transformed to stabilize variance and normalize distribution. The potential between-study heterogeneity was assessed using the χ^2-based Q statistical test and the I^2 test (DerSimonian and Laird, 1986; Lau et al., 1997). Heterogeneity was considered significant when I^2 was $>50\%$ and p was <0.10. When no heterogeneity existed, the results from the individual studies were combined using the fixed-effects model with the Mantel-Haenszel method (Mantel and Haenszel, 1959). Otherwise, the summary estimates were presented using the random-effects model with the DerSimonian-Laird method (DerSimonian and Laird, 1986).

Because study designs, geographic region, and follow-up duration were not consistent among the enrolled studies, we further conducted subgroup analyses to explore possible explanations for the related heterogeneity and to assess the potential impact of these factors on the occurrence of clinical outcomes. In addition, we conducted a sensitivity analysis by omitting each trial one at a time from the analysis, and thereafter computed the overall estimates for the remaining studies. We also carried out a sensitivity analysis by using the unadjusted RRs (if supplied) of the studies to investigate whether the primary overall results would be changed. The subgroup analysis was only performed for CHD due to the insufficient numbers of studies reporting the other outcomes.

Publication bias was estimated using the STATA procedure of 'Metabias,' which is based on two different approaches: the Begg's adjusted-rank correlation test (Begg and Mazumdar, 1994) and the Egger's regression asymmetry test (Egger et al., 1997). A p-value <0.05 was considered indicative of statistically significant publication bias.

3. Results

3.1. Literature search

Fig. 1 shows a flow diagram of the selection process for relevant studies. From the initial literature search, we identified 608 potentially relevant items. After the extended screening, only 13 cohort studies were found to be eligible for this meta-analysis (Bresee et al., 2010; Callaghan et al., 2009; Carney et al., 2006; Curkendall et al., 2004; Enger et al., 2004; Filik et al., 2006; Jakobsen et al., 2008; Lahti et al., 2012; Lin et al., 2008, 2010; McDermott et al., 2005; Shen et al., 2011; Tsai et al., 2012).

3.2. Study characteristics

The baseline characteristics of the 13 eligible studies are presented in Table 1. These studies were published between 2004 and 2012 and represented a total of 3,549,950 participants. CVD outcomes were reported for 422,698 of the total participants. One study did not concretely report the number of patients enrolled in the cohort (Filik et al., 2006). Three studies did not provide information on the incidence of CVD (Curkendall et al., 2004; Filik et al., 2006; McDermott et al., 2005). Of the 13 enrolled studies, four were conducted in Taiwan, China, three in the United States, three in

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