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Increased mortality among people with schizophrenia and other non-affective psychotic disorders in the community: A systematic review and meta-analysis

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ABSTRACT

Introduction: There is increasing evidence of excess mortality in schizophrenia but less information on other non-affective psychoses. We therefore generated standardised mortality ratios (SMRs) for community-dwelling people with schizophrenia and other non-affective psychoses, relative to the general population, and examined changes to the SMR over time.

Methods: We conducted a systematic review in which Pubmed, CINAHL, EMBASE, Google Scholar and PsycINFO were searched for publications that reported SMRs for all-cause mortality among community-dwelling people with schizophrenia and psychotic disorders. Meta-analyses of SMRs were conducted, pooled across genders and then separately by gender. Sub-group analyses were conducted for diagnostic group, global region, decade and risk of study bias.

Results: We were able to include 34 studies covering 1,724,906 participants. The gender pooled SMR for schizophrenia and psychotic disorders was 3.08 (95%CI 2.88–3.31). Schizophrenia and broader psychotic disorders had similar SMRs. Stratification by decade of observation suggests that the difference in SMR is not declining and may possibly be widening. Analyses showed high levels of heterogeneity.

Conclusions: The appearance of a static or widening mortality gap over time between people with schizophrenia and psychotic disorders and the general population is of concern. However, whether it is an increase over time is unclear, as there are insufficient studies to confirm this.

1. Introduction

The non-affective psychoses encompass a range of conditions including schizophrenia, schizophreniform, delusional and other non-organic psychotic disorders. These conditions have a significant burden of morbidity for the persons themselves, but also for carers, loved ones and the broader society (Millier et al., 2014). The estimated economic burden of schizophrenia in the United States alone is $155.7 billion (Cloutier et al., 2016). Schizophrenia is also associated with several risk factors including smoking (Gartner and Hall, 2015), poor diet (Dipasquale et al., 2013), sedentary behaviour (Rosenbaum et al., 2014) and cardio-metabolic adverse events associated with anti-psychotic medications (Mitchell et al., 2013) places people with schizophrenia at increased risk of cardiometabolic disease (Kisely et al., 2013). Epidemiological surveys suggest that rates of physical health comorbidities remain unchanged or are worsening (Morgan et al., 2014). Additionally, people with schizophrenia and other non-affective psychoses are less likely to receive timely medical treatment (Kisely et al., 2013; Lesage et al., 2015), and more likely to die by suicide (Popovic et al., 2014). These factors contribute to excess mortality in schizophrenia and other non-affective psychoses. While the life expectancy of the general population has been increasing, it does not appear to have improved for those living with schizophrenia and other non-affective psychoses (Lawrence et al., 2013).

Although there have been several recent systematic reviews and meta-analyses of mortality in people with schizophrenia and other non-

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affective psychoses, some gaps in the literature remain. For instance one recent meta-analysis examined years of life lost in people with schizophrenia (Hjorthøj et al., 2017), but not the more commonly used outcome of standardised mortality ratios (SMRs). The SMR is a form of indirect standardization used to compare mortality rates between populations with potential differences in baseline mortality. In reviews where SMRs have been reported, possible differences between schizophrenia and other non-affective psychoses were not compared (Saha et al., 2007; Walker et al., 2015). It is important to look at both schizophrenia specifically as well as non-affective psychoses more broadly as previous studies have shown different mortality rates between schizophrenia and other non-affective psychoses, with substantially higher rates for the latter group (Kisely et al., 2005; Lawrence et al., 2000). Not all studies separated results for community and hospital samples, the latter potentially less representative of the majority of people with schizophrenia (Raven, 2015; Saha et al., 2005). A final systematic review was restricted to nine English-language longitudinal studies (Lee et al., 2017).

We sought to address these limitations by systematically reviewing the literature on SMRs of community dwelling people with schizophrenia and other non-affective psychoses, compared to the general population, and conducting a meta-analysis to calculate SMRs and their change over time.

2. Methods

2.1. Design

This systematic review was registered with PROSPERO (CRD42016053531), an international database of prospectively registered systematic reviews. We followed guidelines for conducting and reporting meta-analyses of observational studies in epidemiology (MOOSE) (Stroup et al., 2000) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

2.2. Search strategy

We conducted searches of electronic databases (Pubmed including Medline, CINAHL, EMBASE, Google Scholar and PsycINFO) using a search string devised with the assistance of a research librarian. We used a combination of keyword and title/abstract terms combined with Boolean operators, for example: (schizophren* OR psychotic disorder* OR severe mental disorder*) AND (mortality, death*, survival analysis). Databases were searched from inception to October 2017. The full search strings and their results are provided in Supplementary table S1.

Grey literature sources included a manual search of reference lists of review articles, reports, editorials and resource texts, and an online search to identify additional non-peer reviewed data sources. We also examined the Global Health Data Exchange (GHDx), a repository of international epidemiological data hosted by the IHME (http://ghdx.healthdata.org). Where possible, project investigators were contacted to clarify details of study methodology and to obtain additional information such as estimates of uncertainty.

2.3. Inclusion and exclusion criteria

For inclusion in the review and subsequent meta-analysis, studies had to meet the following criteria: 1. Sample comprised people with schizophrenia and/or psychotic disorder diagnosed according to a DSM or ICD classification or by validated instruments that could be mapped to ICD/DSM criteria (e.g. ICD-10 codes F20-F29); 2. Sample was community based; this included samples recruited from the general population or community-dwelling clinical samples recruited during an acute psychiatric admission to hospital. For example, studies in common residential settings within the community (e.g. old age nursing homes, homeless) were included however studies in institutional settings (e.g. prisons, refugee camps or long stay psychiatric facilities) were excluded; 3. Reported risk of 'all-cause mortality'; 4. Mortality risk was expressed as a standardised mortality ratio (SMR) of deaths among schizophrenia and psychotic disorder cases compared to age- and sex specific rates of death in the general population. We chose to use SMRs exclusively because they are readily interpretable and commonly reported in the literature. An initial analysis of the search results showed that SMR was indeed the most common measure and studies reporting other measures of relative risk without a corresponding SMR were few; and 5. Data collection or follow up of cohort ended no earlier than 1980, corresponding with the introduction of ICD9 and DSM III that improved diagnostic accuracy. No limitations were placed on language of publication or age group of samples.

2.4. Study selection criteria

Potentially eligible studies identified through database and grey literature searches were screened independently by two researchers (JD, AD) based on relevance of title and abstract. Positive results were then screened against selection criteria based on full-text publication (JD, AD). Results of full text screening were verified by a third member of the research team (PO). Discrepancies were resolved through consultation with the review team.

2.5. Data extraction

Data were extracted and validated by three researchers (AD, JD, PO) with disagreements arbitrated by the review team. Information describing study characteristics included setting, World Health Organization (WHO) geographic regions (World Health Organization, 2015), sample size, study design and data sources. SMRs were abstracted by sex, mortality type, nested diagnostic group (schizophrenia or non-affective psychoses more broadly) and diagnostic classification system. Where studies reported estimates for multiple time intervals and/or age groups, only estimates for the total period of observation and cohort were included in the meta-analysis. Only one estimate per study was included in each meta-analysis, unless studies reported estimates for multiple, independent cohorts. To reduce risk of double counting, community and register based studies from the same country were examined; where recruitment period overlapped by more than 10%, the study with the most recent end of follow up was included.

2.6. Quality assessment

Study quality and risk of bias were assessed using a modified form of the Newcastle-Ottawa Scale (NOS) (Mata et al., 2015). The modified NOS comprises five binary scored criteria to assess quality and risk of bias; 1) representativeness of the sampling strategy, 2) sample size, 3) response rate and characteristics of non-respondents, 4) use of a verified instrument for ascertainment of personality disorders and 5) quality of descriptive statistics. For the purposes of analysis studies were dichotomized according to those scoring more than or equal to four on the five-point scale. Detailed descriptions of assessment criteria and scoring rules are provided in the Supplementary material.

2.7. Data analysis

A random effects meta-analytic model was chosen to generate pooled SMR estimates, to allow for undocumented residual variance in true effects between studies. In addition to overall SMRs we stratified results by sex, and conducted subgroup analyses based on diagnosis, region, decade of follow-up and study quality.

Heterogeneity was investigated using the I^2 statistic to determine whether differences in reported estimates were greater than could be expected by chance. I^2 values are based on Cochrane's heterogeneity statistic (Q) but incorporate degrees of freedom to control for low or