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Associated illness severity in schizophrenia and diabetes mellitus: A systematic review

Benjamin I. Perry[a,b,*], Dhanya Salimkumar[c], Daniel Green[c], Anne Meakin[c], Andrew Gibson[b], Deepali Mahajan[d], Tayyeb Tahir[d], Swaran P. Singh[a,b]

[a] Department of Mental Health and Wellbeing, University of Warwick, Coventry, United Kingdom
[b] Coventry and Warwickshire Partnership NHS Trust, Coventry, United Kingdom
[c] Warwick Medical School, University of Warwick, United Kingdom
[d] Cardiff and Vale NHS Trust, Cardiff, Wales, United Kingdom

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ABSTRACT

Objective: We aimed to elucidate whether schizophrenia and type II diabetes mellitus may present with associated illness severity, in light of accumulating evidence to suggest both conditions have important shared inflammatory components with many shared inflammatory genetic factors.

Methods: We conducted a systematic review employing PRISMA criteria, searching EMBASE, Ovid MEDLINE, PsychInfo, Web of Science and Google Scholar to February 1st, 2017, for clinical studies assessing schizophrenia severity alongside dysglycaemia. A narrative synthesis was employed to discuss and compare findings between studies.

Results: Eleven observational studies were included in the analysis. Ten presented evidence in support of an association between schizophrenia severity and dysglycaemia. This association appeared particularly strong regarding negative symptomatology and impaired cognitive function, between which there may be some overlap. Studies examining positive symptomatology returned mixed results.

Conclusion: Whilst study design varied amongst the included studies, the results suggest that further work examining the effect of hyperglycaemia on schizophrenia severity may be relevant, particularly longitudinal studies assessing negative symptomatology and cognitive function. To the authors' knowledge, this is the first systematic review conducted to address this question.

1. Introduction

Schizophrenia is a life-shortening illness. Life expectancy amongst sufferers is reduced by 20%, with mortality rates twice as high as in the general population (Laursen et al., 2012). Unnatural causes such as accidents and suicide account for only a small portion of the increased mortality, with more than two-thirds explained by "natural causes" including physical illnesses such as diabetes mellitus (Inskip et al., 1998). The increasing use of antipsychotics since the 1950's led to a growing body of evidence showing a direct link between use of antipsychotics and development of diabetes and this causal link is now widely accepted. In 1952 however, even before the accidental discovery of chlorpromazine, historical publications suggested a possible relationship between diabetes and mental illnesses; including dementia praecox (Maudsley, 1985). Whilst definitions of both diabetes and schizophrenia differed considerably at that time, recent research suggests a direct link between schizophrenia and type II diabetes independent of medication, lifestyle, health habits and access to healthcare (Kohen, 2004). This is currently thought to be mediated via impaired glucose tolerance, hepatic insulin resistance and increased cerebral glucose requirement of schizophrenia patients (Van Nimwegen et al., 2008; Buchsbaum et al., 2007; Thakore, 2004). This work has perhaps culminated in recent meta-analyses (Perry et al., 2016; Pillinger et al., 2017) that found markers of early diabetes such as impaired glucose tolerance and insulin resistance are higher in patients with first-episode psychosis, with limited exposure to antipsychotic medication, than matched healthy controls.

Diabetes is now known to have an important inflammatory component. Poor glycaemic control has been found to be positively correlated with levels of inflammatory cytokines such as C-Reactive Protein (CRP), Tumour Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6) and 1β (IL-1β) in the circulating blood stream (Calle and Fernandez, 2012). Several studies have also shown the benefit of anti-inflammatory medication as a means of treatment for type II diabetes (Weisberg et al.,

* Corresponding author at: Caludon Centre, Coventry and Warwickshire Partnership NHS Trust, Coventry CV2 2TE, United Kingdom.
E-mail address: Benjamin.perry@covwarkpt.nhs.uk (B.I. Perry).

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2008; Staels and Fruchart, 2005). This evidence suggests that, despite a difference between systemic and neuroinflammation due to the action of the blood brain barrier, there may indeed be some cross-over. Cytokines are now thought to have the ability to cross the blood brain barrier (Banks, 2005), and there is evidence (Hawkins et al., 2007; Starr et al., 2003) that a hyperglycaemic state increases blood brain barrier permeability; thus active diabetes may relate to both a heightened systemic inflammatory response, but also increased susceptibility of the inflammatory cytokines to enter the CNS.

Likewise, there is a growing body of evidence pointing toward the significance of the pro-inflammatory state in many psychiatric disorders, such as bipolar disorder (Sharma et al., 2014), depression (Hurley and Tizabi, 2013), and more recently, schizophrenia; antipsychotics are noted for their immune-modulatory effect, and studies involving anti-inflammatory agents in the treatment of schizophrenia have shown promise (Muller et al., 2013). Furthermore, a longitudinal study using Avon Longitudinal Study of Parents and Children (ALSPAC) data found raised levels of CRP and IL-6 in childhood can predict development of psychotic illness in later life (Khandaker et al., 2014).

The growing body of work in both diabetes and schizophrenia, in terms of inflammation and neuroinflammation seems to be converging to a point, and may therefore have a role in explaining the link between the two conditions. Interestingly, genetic studies have found shared susceptibility genes encoding many implicated cytokines and other aspects of the immune response and inflammation, for both schizophrenia and type 2 diabetes (Lin and Shuldiner, 2010), raising the possibility of a genetically altered inflammatory response predisposing to both diabetes mellitus and schizophrenia, in at least a subset of patients.

Given this evidence and the potential implications for the understanding and management of both conditions, we aimed to conduct a systematic review of current clinical evidence, proposing that due to shared inflammatory pathways, the severity of comorbid diabetes and schizophrenia may be linked. We have been unable to locate a systematic review in current literature examining this research question.

2. Methodology

A systematic literature search was conducted to assess whether severity of schizophrenia may be associated with dysglycaemia.

OvidSP was used to search EMBASE (1947-present), Ovid MEDLINE (1946-present) and PsychInfo (1806-present) to November 24th, 2016. We also searched the first twenty pages of Google Scholar, alongside searching references of included studies for search keywords, to 24th November 2016. The search strategy was developed in association with an Information Specialist.

Our search strategy is presented below. MeSH headings (indicated with an asterisk) or their equivalent and text terms were used:

2.1. Schizophrenia*

grouped with: *Diabetes Mellitus*, Blood glucose*, Glucose, Glycaemic, Hyperglycaemia*, HbA1C, Glycosylated Haemoglobin, HbA1C, FPG.*

Grouped with:

Prognosis, Prognostic, Outcome, Severity, Marker, Progression*

The inclusion criteria were:

- Adults aged 18–65 with a diagnosis of schizophrenia, based upon a specific diagnostic classification (DSM/ICD.)
- Original clinical studies comparing glycaemic status with outcome/disease severity in schizophrenia.
- Severity is a broad term and defined as per study criteria, but may include measures of symptom severity, cognition or impaired function.

The exclusion criteria were:

- Studies with no biochemical measurement of glycaemic status
- Studies with no assessment of schizophrenia severity
- Studies focussed on the effect of antipsychotic medications on glycaemic status
- Studies with no relevance to study question

We applied the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines (Moher et al., 2009) for assessing search results.

Titles and/or abstracts of studies retrieved using the search strategy were screened independently by four authors (BP, DG, DS, AM) to identify studies that potentially met the inclusion criteria outlined above. Any discrepancies were resolved in consultation with the senior author (SS).

Studies adhering to inclusion criteria were then examined in full-text form with and formal inclusion/exclusion criteria were applied by three review authors (DG, DS, AM) independently. Risk of bias and quality appraisal was conducted using the STROBE checklist for cross-sectional studies (Von Elm et al., 2014). Disagreements between the review authors over the risk of bias in studies were resolved through discussion, with involvement of a third senior review author (SS).

The searches were re-run immediately prior to the final analyses on February 1st, 2017, and further studies retrieved for inclusion. Data were extracted by two reviewers from studies that met the inclusion criteria. Details included participant characteristics, diagnostic criteria, study design, outcomes measured and data for analysis.

We have summarised and compared studies using results tables. A meta-analytic approach to results synthesis was planned, though this was dependent on adequately low heterogeneity between included studies. Where a meta-analytic approach was not possible, a narrative discussion of the findings across studies was provided, structured around the association between dysglycaemia and schizophrenia disease severity.

3. Results

3.1. Study selection

Overall, eleven studies (Wysokinski, 2013; Takayanagi et al., 2012; Saatcioglu et al., 2016; Sicras-Mainar et al., 2015; Chen et al., 2013; Chen et al., 2014; Ogawa et al., 2011; De Nijs and Pet, 2016; Dickinson et al., 2008; Gonzalez, 2015; Pelayo-Teran, 2011) were selected for detailed analysis. Fig. 1 displays the PRISMA flow diagram. Many records were excluded at first instance, due to their aim of analysing and comparing the effect of antipsychotics on metabolic indices, which although relevant, is not the scope of this review. Studies excluded at full-text review were excluded due to having no assessment of schizophrenia disease severity, or no comparable measure of diabetic severity. Publication dates extend from 2008 to 2015.

Tables 1–3 demonstrate a comparison of the included studies. Table 1 denotes studies that report evidence to suggest that the dysglycaemia may be associated with schizophrenia severity, Table 2 denotes studies that have some data to support the association but also some non-significant findings, and Table 3 denotes studies that do support an association. It is evident that there are ten studies that present data to support evidence of an association, and one study that does not.

Firstly, we compare similarities and differences in methodology employed by the included studies before discussing their results. Due to the methodological heterogeneity between studies, a meta-analytic approach to the synthesis of results is not possible, thus a narrative synthesis will be employed, with statistical comparisons between studies employed where possible.

The studies were assessed for quality and risk of bias using the