Associated Illness Severity in Schizophrenia and Diabetes Mellitus: A Systematic Review

Benjamin I Perry; Dhanya Salimkumar; Daniel Green; Anne Meakin; Andrew Gibson; Deepali Mahajan; Tayyeb Tahir; Swaran P Singh

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.

Keywords:

Schizophrenia; Psychotic disorders; Diabetes Mellitus; Inflammation

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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., 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) (Sharma et al, 2014), depression (Hurley and Tizabi, 2013), and more recently, schizophrenia; anti-psychotics 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:

*Schizophrenia**
grouped with: *Diabetes Mellitus*, Blood glucose*, Glucose, Glycaemic, Hyperglycemia*, 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.

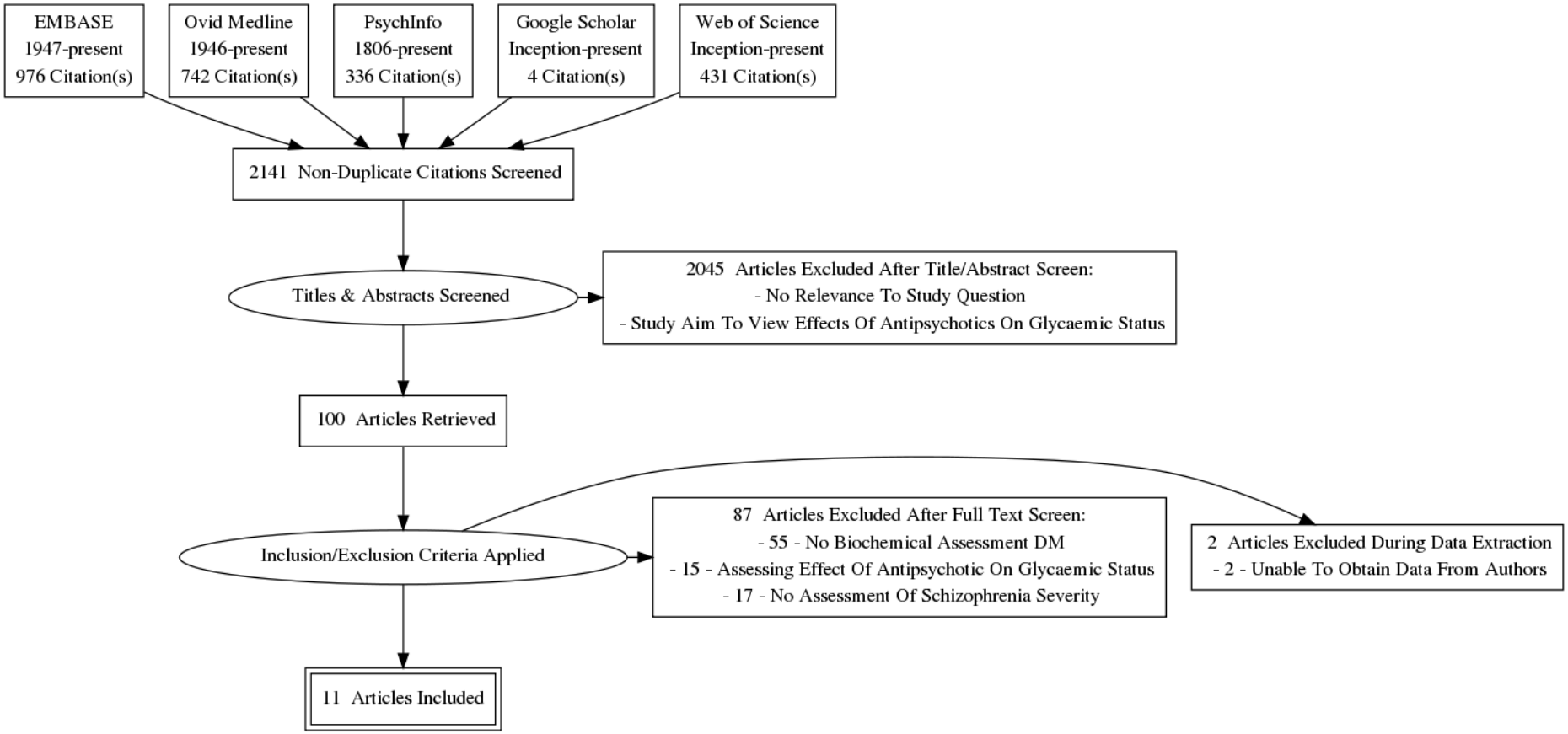

Figure 1: PRISMA flow diagram

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 et al., 2016, Dickinson et al., 2008, Gonzalez, 2015, Pelayo-Teran, 2011) were selected for detailed analysis. Figure 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, 2 and 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 STROBE Checklist for Cross-Sectional Studies; results of which are displayed in Table 4. This checklist was used for the cohort and case-control studies after deliberation, as the results from these studies were compared in a cross-sectional fashion.

3.2 Study Design

The experimental design differed amongst our included studies. All but one were observational, including six cross-sectional, three cohort and one case-control study. The remaining study was a meta-analysis carried out on two distinct samples that are not

represented by our other included studies. Cross-sectional studies have been included after deliberation as they meet inclusion criteria, and meet relevance to the study question. The case control and cohort studies were analysed in a cross-sectional fashion, to allow for comparisons between studies.

3.3 Sample Size

Sample size distribution varied widely across the included studies, ranging from n=38 (Ogawa et al., 2011) to n=1289 (Takayanagi et al., 2012). The median absolute deviation across studies was 85.

3.4 Demographics

Mean age across studies was 36.7, with a mean range of 31.7-53.9. Four studies (Dickinson et al., 2008, Ogawa et al., 2011, Saatcioglu et al., 2016, Takayanagi et al., 2012) specified an upper age limit of 65, one a limit of 50 (de Nijs et al., 2016), and another specified an upper age limit of 42 (Chen et al., 2013).

All studies reviewed included both male and female study participants, though there was a higher representation of male participants (mean 67.8%), potentially reflecting the known slight-male dominant epidemiology of schizophrenia. Ethnicity varied across studies.

3.5 Assessment of Disease Severity

All studies, as per inclusion criteria, specified biochemical investigation as a measure of glycaemic status. Six studies used fasting plasma glucose (FPG) as the sole biochemical marker. Three studies utilised glycosylated haemoglobin (HbA1c) solely. The remaining two studies used a combination of measurements.

All studies utilised a research based assessment tool as a measure of schizophrenia severity. Most of included studies measure symptom severity using the Positive and Negative Syndrome Scale (PANSS), which has previously shown to have high reliability and stability in assessing both positive and negative symptoms. Five studies used PANSS solely. Two studies (Wysokinski, 2013, Gonzalez, 2015) used PANSS in combination with various other measures including, the Calgary Depression Scale for Schizophrenia (CDSS), Clinical Global Impressions scale (CGI) , Marder factor and Negative Symptoms Assessment for

Motivation scale (NSA). One study (Saatcioglu et al., 2016) used the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Positive and Negative Symptoms (SAPS/SANS), CDSS and Personal and Social Performance Scale (PSP). Another (Ogawa et al., 2011) used the Japanese equivalent of the BPRS as well as Global Assessment of Functioning (GAF) whereas the largest study in our analysis (Dickinson et al., 2008) only employed the use of the Repeatable Battery for the Assessment of Neuropsychological Status scale in the measurement of the cognitive effects of schizophrenia (RBANS).

3.6 Inclusion Criteria

One study (Wysokinski, 2013) employed ICD-10 criteria for paranoid schizophrenia only and one (Ogawa et al., 2011) did not specify what criterion was used but that participants did have a medical diagnosis of schizophrenia. All other studies utilised DSM-IV criteria for schizophrenia. Furthermore, one study (Chen et al., 2013) featured the diagnosis of First-Episode Psychosis in its inclusion criteria, and another (Pelayo-Teran, 2011) allowed both Schizoaffective Disorder and Related Psychoses in its inclusion criteria.

The study on first-episode psychosis patients (Chen et al., 2013) specified less than two weeks of antipsychotic use as part of its inclusion criteria. This contrasts other studies in the analysis (Chen et al., 2014) that specified more than two years of antipsychotic use in its inclusion criteria, with the aim of matching the potential longer-term effects of antipsychotic use on metabolic profile. None of the studies included a 'non-medication' group, potentially a reflection of ethical practice. Whilst several studies stated antipsychotic use in their inclusion criteria, these studies did not state a specified length of time of antipsychotic use.

3.7 Statistical Analysis

All studies controlled for the presence of antipsychotic medication in their analyses. Age and gender was controlled for in all included studies. Race was controlled for in the analysis in two studies (Takayanagi et al., 2012, Dickinson et al., 2008). The presence of another metabolic disease features in the exclusion criteria in two studies (Takayanagi et al., 2012, Chen et al., 2013). The effect of smoking was controlled for in the analyses for all but three of the studies (Pelayo-Teran, 2011, Chen et al., 2014, Sicras-Mainar et al., 2015). Two studies controlled for BMI (Saatcioglu et al., 2016, Sicras-Mainar et al., 2015).

3.8 Study Findings

3.8.1. Symptom Severity

Two studies (Saatcioglu et al., 2016, Sicras-Mainar et al., 2015) found that a diagnosis of metabolic syndrome was significantly associated with increased symptom severity. One (Saatcioglu et al., 2016) found that those with metabolic syndrome had significantly higher SANS and CDSS scores than those without (t=2.23 & t=3.60, p<0.001 respectively). The second (Sicras-Mainar et al., 2015) found a diagnosis of metabolic syndrome to be associated with negative symptoms (p=0.002) and that metabolic syndrome increased the odds of the presence of negative symptoms (OR 1.6, 95% CI 1.3-2.0), though whilst the authors reported statistical significance in this case, a p-value was not described.

Another study (Pelayo-Teran, 2011) returned positive results in this regard, finding an association between glycaemic severity and poor self-care (r=0.390 p=0.006), lower social activity (r=0.332 p=0.024), disturbing behaviours (r=0.468 p=0.001) and total personal and social performance (r=0.332 p=0.020). One other study (Wysokinski, 2013) returned mixed results, finding total PANSS scores related to severity of glycaemia (OR=1.03 (no SD provided) p=0.002), particularly positive symptoms (OR=1.14 (no SD provided) p=0.01) and also found that CGI scores were negatively associated with glucose abnormalities (OR=0.61 (no SD provided) p=0.04) but that negative symptoms were negatively associated with MS (OR=0.92 (no SD provided) p=0.01). Three studies, (Ogawa et al., 2011) (p=0.60), (Chen et al., 2013) (p>0.05) and (Chen et al., 2014) (t=0.11 p=0.12) found no significant correlation between glycaemia and symptom severity.

3.8.2 Cognition

All four studies that included cognition in their analyses supported a negative correlation between glycaemia and cognitive function.

One study (Takayanagi et al., 2012) found a negative correlation between glycaemic severity and overall cognitive function (β=-0.08 p=0.002), and then most significantly in speed (β=-0.08 p=0.002) and reasoning (β=-0.06 p=0.03). Another study (de Nijs et al., 2016) similarly found glycaemia related to lower IQ (F=7.26 p=0.013), worse immediate (F=8.30 p=0.003) and delayed (F=5.88 p=0.004) recall, and slower reaction time (F=9.86 p=0.01) in patients with schizophrenia.

Another study (Dickinson et al., 2008) reported a negative correlation between HbA1c and cognition in patients with concurrent schizophrenia and diabetes (δ=0.26 p=0.01) and an included conference abstract (Gonzalez, 2015) found that FPG was significantly related to cognitive impairment in their preliminary study (no statistical data provided in abstract).

4. Discussion

In recent years there has been a surge in the literature describing the metabolic risk associated with psychiatric disorders including depression, bipolar affective disorder and, as postulated in this review, schizophrenia, where we have attempted to analyse any association between schizophrenia severity and glycaemic control.

4.1 Main findings

The large heterogeneity between studies prevented the adoption of a meta-analytic approach to the interpretation of our findings. Nevertheless, the use of a narrative analysis permits the interpretation and combined synthesis of broad terms such as "schizophrenia severity" and any potential cross-over between what is defined as negative symptomology and as cognitive dysfunction.

Our first definition of schizophrenia severity, symptomatology, produced mixed results. Four studies (Saatcioglu et al., 2016, Sicras-Mainar et al., 2015, Wysokinski, 2013, Pelayo-Teran, 2011) analysing this definition yielded results that show an association between dysglycaemia and schizophrenia symptom severity. Conversely, three studies reported no association between symptom severity and glycaemia, and whilst two of these were of relatively small sample size (Chen et al., 2013, Ogawa et al., 2011), the other featured a relatively larger sample size (Chen et al., 2014).

Whilst all other studies controlled for the presence of antipsychotic medication at the post-hoc analysis stage, one study (Chen et al., 2013) removed this potential confounder by only including antipsychotic-naïve patients, rendering this study perhaps the most reliable. This study produced results that would partly support an association between schizophrenia severity and dysglycaemia. Its negative finding (a negative association between PANSS+ and glycaemia) was unexpected; however other studies in our analysis have found mainly negative symptoms to be related to glycaemia (Pelayo-Teran, 2011, Sicras-Mainar et al.,

2015, Saatcioglu et al., 2016) thus our findings may point to a stronger association between negative symptomatology and glycaemia.

The finding that glycaemia may be related to negative symptomatology may be further supported by the findings concerning cognition and glycaemia. One might argue that tests of negative symptomatology may share a cross-over with tests showing impairment in cognition, and out of the four included studies that measured the association between cognition and dysglycaemia (Takayanagi et al., 2012, de Nijs et al., 2016, Dickinson et al., 2008, Gonzalez, 2015), all four found an association which remained after controlling for the presence of antipsychotic medication, reporting that severity of glycaemia is related to worse cognitive function. Of note, two of these studies featured the largest sample sizes (Takayanagi et al., 2012, Dickinson et al., 2008) of all the included studies in our analyses, and both presented mean HbA1c values which were not statistically significantly different. However, it is known that the illnesses of diabetes and schizophrenia themselves can impact upon cognition (Kuperberg and Heckers, 2000, Awad et al., 2004). It is therefore interesting that the Dickinson et al (2008) (Dickinson et al., 2008) study found that comorbid schizophrenia and diabetes is associated with a compounded more-than-additive effect on cognition, in their comparison with different control groups of participants with diabetes-only, and participants with schizophrenia-only.

4.2 Strengths and Limitations

Overall, ten out of eleven studies included in our analysis report an association between dysglycaemia and increased schizophrenia severity, examined either by symptomatology or cognition. Only one study demonstrated no significant association.

To the authors' knowledge, this is the first systematic review to examine the possibility that schizophrenia and diabetes may share illness synchrony. If present, this may be based upon accumulating evidence to suggest both conditions have important shared inflammatory components with shared inflammatory genetic factors. Our results show dysglycaemia to be related to negative symptomatology and worse cognitive function in schizophrenia. Some might also argue that there is some cross-over between a finding of cognitive impairment and negative symptomatology, thus this may warrant further attention in future research. Our

work and the comparisons within may also help to light the way for more specifically designed, longitudinal studies in this area.

Despite these findings, there are several limitations that necessitate caution in the interpretation of our findings. Firstly, all studies are observational in a nature, thus we are only able to demonstrate correlation rather than causation. Moreover, the majority of included studies are cross-sectional in nature, therefore at an inherent risk of bias. The other studies, which were a combination of cohort and case-control, were analysed in a cross-sectional fashion. This is most pertinent because most studies featured participants on antipsychotic medication, and many studies did not specify which antipsychotic medications were taken by participants, the dosages or the lengths of prescription. Certain antipsychotics can themselves cause deranged metabolic indices, and therefore we cannot discount that our positive findings may be related to reverse-causality, in that participants being more acutely unwell with schizophrenia may be treated with higher doses of potentially diabetogenic antipsychotic medication, or antipsychotics with poorer metabolic profiles such as clozapine, thus the impact upon glycaemic indices may be greater. However, one included study (Chen et al., 2013) featured only participants with first-episode psychosis and stipulated <2 weeks use of antipsychotic medication, and all other studies controlled for the antipsychotic medication in their analyses, thus the effect of this significant confounder may be reduced. Despite this, future work may seek to focus on first-episode patients to remove the confounder of antipsychotic medication, as they are typically younger and the likelihood of potential confounding variables, such as antipsychotic medication and physical comorbidity, will be reduced.

The STROBE scores for the included studies ranged from 10 to 20 (with the maximum available score being 21), with many points lost in the reporting of the methods section for the lower scoring studies. Therefore, all studies were at some risk of bias, which may necessitate caution in interpreting our findings.

Additionally, any studies examined other aspects of metabolic syndrome, which is not the focus of this review, but may in part explain the variation in methodology across the studies. Whilst we have focused on dysglycaemia in this review, there may be evidence to suggest other elements of the metabolic syndrome may also be intrinsically associated with schizophrenia also. Dyslipidaemia has been shown to be associated with first-episode psychosis (Perry et al., 2016, Misiak et al., 2017b), and an abnormal inflammatory response

in patients with first-episode psychosis (Russell et al., 2015, Miller et al., 2013). It is therefore possible that our hypothesis may extend to other elements of the metabolic syndrome, and this may warrant future research.

There is also a wide distribution in age-range amongst the included studies. The relatively older age of study participants might reflect the chronicity of illness amongst the patients, and therefore may confer a greater number of potential confounding variables, including length of treatment and comorbid physical illness that may disrupt the results. However, many included studies did feature exclusion criteria for potential participants with chronic physical illnesses. Furthermore, the use of different biochemical tests for glycaemia, with FPG relating to present glycaemic status and Hb1Ac providing an overall summary of glycaemic control over the preceding three months make comparisons difficult. HbA1C is known as a relatively less-sensitive measure of dysglycaemia (Olson et al., 2010), and future research may seek to examine more sensitive measures of dysglycaemia such as insulin resistance or impaired glucose tolerance. Many studies also did not provide mean data; therefore, the comparisons we were able to generate between studies were significantly limited.

The diagnostic criteria used to define schizophrenia differed amongst studies. Whilst both the DSM-IV & ICD-10 criteria show reasonable congruence rates in the diagnosis of schizophrenia (Cheniaux et al., 2009), there are some notable differences, for example duration of symptomatology and presence of decreased functionality that may act as possible confounders to the comparison of findings.

Furthermore, we are unable to completely rule out publication bias from our results. We did however include several conference abstracts within our analysis, and our analysis does include some negative results.

There is the also the important possibility that schizophrenia symptom severity is aberrantly able to cause poor glycaemic control, with many precipitants such as increased impulsivity in diet, social withdrawal (thus withdrawal from healthcare appointments,) and non-compliance with physical medication to name but a few. However, a recent systematic review (Misiak et al., 2017a) has found raised inflammatory markers to be associated with cognitive impairment in schizophrenia, which may add confidence in our own findings.

Finally, since none of the included studies featured participant groups with other mental disorders, we are unable to discount that our findings aren't a result of mental distress, which is likely a factor in those who are acutely unwell with schizophrenia. The acutely stressed state can cause release of adrenaline, growth hormone and cortisol (Hori et al., 2010), all of which are able to raise blood sugar levels. This may be due to central neuronal activity rather than systemic and neuroinflammation.

5. Conclusion

Despite the potential limitations in our work, our comprehensive systematic review and narrative synthesis does present evidence that dysglycaemia is associated with increased negative symptomatology and poorer cognition in schizophrenia. Any association between glycaemic status and positive symptoms appears less clear.

Our review also reveals a gap in the literature that may be relevant, particularly regarding longitudinal or experimental studies. If diabetes mellitus and schizophrenia are prognostically linked via neuroinflammatory processes, then the knowledge that many antipsychotic medications available are diabetogenic, may raise questions (and provide some possible answers) on their efficacy, at least in a subset of patients.

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