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Title Page

The association between first-episode psychosis and abnormal glycaemic control: Systematic review and meta-analysis of clinical studies

1) Dr. Benjamin Ian Perry. MBBS
[a]Academic Clinical Fellow, Coventry and Warwickshire Partnership NHS Trust, UK.
[b] Honorary Research Fellow, University of Warwick, Coventry, UK

2) Dr. Gemma McIntosh. MBBS
[a]Clinical Fellow, University Hospitals Birmingham, UK

3) Professor Scott Weich. MD
[a]Professor of Psychiatry(full), University of Warwick

4) Professor Swaran Singh. MD
[a]Professor of Psychiatry(full) and Head of Division, Mental Health and Wellbeing, University of Warwick
[b]Honorary Consultant Psychiatrist, Birmingham and Solihull Foundation Mental Health Trust

5) Dr Karen Rees. PhD
[a]Principal Research Fellow. Warwick Medical School, Division of Health Sciences, Statistics and Epidemiology Unit, University of Warwick

Abstract

Background.

Research suggests that schizophrenia, which is linked to a range of physical health conditions, may share intrinsic inflammatory disease pathways with type-two diabetes mellitus. However, psychotropic medication, which can adversely affect metabolic indices, has presented a major confounder in examining this association. First-episode psychosis patients present an interesting cohort to study this potential association, being generally younger with therefore less comorbidity to confound associations, and having had limited exposure to antipsychotic medication.

Aims

We aimed to assess whether first-episode psychosis, which could be described as 'developing schizophrenia', is associated with prediabetic markers, or 'developing diabetes', to determine whether intrinsic disease links could cause the conditions to develop in unison.

Methods

A systematic literature search was conducted using PRISMA criteria, searching Embase, Medline, PsychInfo, Web of Science and Google Scholar to 6th January 2016. We assessed case-control studies with biochemical assessment of prediabetic states in first episode psychosis patients alongside matched controls.

Results

Twelve studies were included in final analysis, including 1,137 participants. Several measurements were used to test for prediabetes, including fasting plasma glucose, impaired glucose tolerance and insulin resistance (measured by the homeostatic model assessment). Pooled analysis found first-episode psychosis to be related to impaired glucose tolerance (mean difference 1·31 [0·37, 2·25]), insulin resistance (mean difference 0·30 [0·18,0·42]) and the number of patients with impaired glucose tolerance (odds ratio 5·44 [2·63-11·27]).

Conclusion

Our findings are suggestive of a potential link between prediabetic markers, in particular impaired glucose tolerance and insulin resistance, and first episode psychosis. However, we cannot establish causality, and the studies contributing to this review were at some risk of bias. Nevertheless, the findings may help to explain the increased prevalence of T2DM in patients with schizophrenia and could have implications for the management of schizophrenia patients.

Introduction

Patients with schizophrenia have shortened life expectancy, with mortality rates twice that of the general population[1]. Causes for this extend beyond suicide, accidents and risk-taking behaviour[2]. Epidemiological evidence indicates that physical illnesses, including cardiovascular disease and type 2 diabetes mellitus[2] (T2DM) account for a majority of the increased mortality risk. The prevalence of T2DM in schizophrenia is increased by around one-third compared with the general population[3]. Many psychotropic medications affect metabolic parameters including glycaemic control[4]. However, recent research suggests intrinsic pathophysiological processes beyond the effects of medication, lifestyle and access to healthcare[5].

Diabetes was thought to be associated with mental disorders long before the discovery of Chlorpromazine in the 1950's[6]. This older body of work was largely overlooked by studies in early schizophrenia psychopharmacology, which focused instead on the metabolic effects of medications. There is renewed interest in this area, with consideration of the role of inflammation[7-9].

Poor glycaemic control in T2DM correlates with levels of inflammatory cytokines including C-reactive protein (CRP), Tumour Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6) and -1β (IL-1β) in the circulation[10-12],. Mouse gene knock-out studies implicate a specific neuroinflammatory component to T2DM and peripheral insulin resistance and impaired glucose tolerance can be induced by hypothalamic inflammation mediated by TNF-α and IL-6[13]. Several studies have also shown the benefit of anti-inflammatory medication in T2DM[14,15].

Similarly, evidence for an inflammatory component in mental disorders is accumulating, as in depression[16], bipolar affective disorder[17] and schizophrenia; Increased serum levels of IL-1β, CRP and TNF-α in those with schizophrenia have been found[18,19], and raised CRP and IL-6 levels in childhood may predict psychotic illness in later life[20]. Additionally, antipsychotics are known for their immunomodulatory and anti-inflammatory effects, and studies involving anti-inflammatory agents as treatment adjuncts have shown promise[21]. Raised levels of IL1, IL6 and TNFα have also been found in schizophrenia patients with metabolic syndrome[22], compared with normo-glycaemic schizophrenia patients and healthy

controls, suggesting that there may be a common association between inflammation, dysglycaemia and schizophrenia.

There has also evidence of genetic susceptibility to both conditions. Mutations in genes encoding for inflammatory markers such as TNF-α, IL-6, phospholipase A2, and the HLA complex, are found in both T2DM and schizophrenia[23]. Although there are clear differences between systemic and neuro-inflammation due to the blood brain barrier, evidence suggests that there may be a common pathway. Cytokines are thought to cross the blood brain barrier[24], and its permeability may be increased in hyperglycaemic states, as shown in both animal[25] and human[26] models.

First-Episode Psychosis (FEP), though a standalone diagnosis, may progress to schizophrenia, and therefore the study of FEP may advance our knowledge of the pathophysiology of schizophrenia. The study of FEP patients, who are generally younger with less physical comorbidity, also avoids the potential confounding by antipsychotic medication on glycaemic control.

A previous systematic review[27] assessed the prevalence of metabolic syndrome in FEP with or without antipsychotic medication, concluding that T2DM, as well as other elements of the metabolic syndrome, were uncommon in un-medicated FEP. However, this study only considered established cases of T2DM, and not those with markers of less severe glucose dysregulation such as impaired glucose tolerance or insulin resistance. As postulated by Fernandez-Egea et al (2013)[28], glucose intolerance exists on a continuum, and subclinical dysglycaemia may only be identifiable after a glucose challenge. This less severe degree of impairment, termed ‘prediabetes’, was reported in many of the studies of glucose regulation in schizophrenia patients that antedated modern antipsychotics[29].

Given this evidence and the potential implications for the understanding and management of both conditions, we conducted a systematic review of clinical evidence, proposing that due to shared inflammatory pathways, FEP and prediabetic states may be linked. We attempted to ascertain the possibility of a link between prediabetes and FEP, on the grounds that these may represent ‘developing’ states of T2DM and schizophrenia, respectively. We have been unable to locate a systematic review examining this research question.

Methods

A systematic literature search was conducted. The hypothesis stated that biochemical measures of prediabetic states would be more commonly found in antipsychotic naïve patients experiencing their first episode of schizophrenia spectrum psychosis than in healthy matched controls.

OvidSP was used to search EMBASE (1947-present), MEDLINE (1946-present) and PsychInfo (1806-present) to 6th January 2016**.** Web of Science was searched from inception to 6th January 2016. We also searched the first twenty pages of Google Scholar (as recommended in a recent review[30]), alongside searching references of included studies. The search strategy, appearing in full in Appendix 1, was developed in association with an Information Specialist. MeSH headings or their equivalent, and text word terms were used. Inclusion and exclusion criteria are shown in tables 1 and 2 respectively.

We applied the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines[35] for assessing search results.

Titles and abstracts were screened independently by two authors (BP and GM). Full texts were screened by two reviewers independently (BP and GM). Discrepancies were resolved in consultation with a third author (KR).

Data were extracted by two reviewers from studies that met the inclusion criteria (BP and GM). Quality appraisal was conducted using the Newcastle Ottawa Scale[36] for case-control studies. Disagreements between the review authors over the risk of bias were resolved through discussion, with involvement of a third author (KR) if necessary. Publication bias was examined using funnel plots to test for asymmetry.

The searches were re-run immediately prior to the final analyses, and further studies retrieved for inclusion using the processes outlined above.

For continuous variables, the mean and standard deviations for each outcome and number in each group were entered into a meta-analysis programme (RevMan 5.3), with mean

differences and 95% confidence intervals between cases and controls calculated and displayed in forest plots. The inverse variance method was used where the weight given to each study was the inverse of the variance of the effect estimate. For dichotomous outcomes, the number of events and number in each group were entered into RevMan 5.3 and the Mantel-Haenszel method used to pool studies. Fixed effects models were used to pool data unless there was substantial heterogeneity (I^2>50%) when a random effects model was used.

Role of the Funding Source

The authors received no funding for the completion of this work.

Results

Electronic searches identified 1,436 studies (Fig 1); 1,015 after removal of duplicates. 989 excluded at this stage. Twenty-six were shortlisted for full text retrieval, with twelve meeting the inclusion criteria[37-48].

Eleven[47-51] of twelve were case-control studies. One was a randomised controlled trial[48], though data were available at baseline for FEP patients and healthy matched controls, and so this study was treated as a case control study in the analyses. Table 3 outlines study characteristics.

Sample size ranged from 52[41]to 149[43], with 1,137 participants included in total. The majority of studies recruited an equal number of cases and controls. Average age across studies was 28·8. Age and gender was well matched between cases and controls in all studies. Across all studies, there was male predominance (overall 64% male).

Included studies featured a varied definition of ‘antipsychotic naïve’. Several stipulated no prior exposure to antipsychotic medication[37,39,40,42,46,48], whereas others[38,43,47] stipulated a maximum antipsychotic prescription length of one week, with nil taken in the last thirty days.

All studies used DSM-IV criteria. Most used clinical diagnosis (from patient records) only, though five[39,42,43,45,47] used the Structured Clinical Interview for DSM-IV (SCID) to clarify the diagnosis. However, studies differed in the definition of FEP. Whilst several[37,38,42,45] included patients with a first hospital presentation of schizophrenia spectrum disorder, two[40,46] specified a first presentation meeting diagnostic criteria for schizophrenia only. Two studies[43,537] subdivided their participants into 'deficit' and 'non-deficit' schizophrenia.

Recruitment methods for control group selection were similar. Eleven studies screened for the absence of physical and mental ill health. One[48] screened only for matched demographics. Recruitment was achieved in a variety of ways, from advertising in universities[37,41,42,45], to local advertising[38,39,47], to advertising in the hospital[40,44,46]. One study[48] did not report their recruitment strategy, though stated they included 'matched healthy controls'.

Table 4 outlines which biomarkers of prediabetes were used in each study.

All twelve studies measured FPG. Pooling this data showed that there was no significant difference in FPG between those with FEP and controls. (mean difference 0·03 mmol/L, 95% CI -0·04,0·09 p=0·43), (fig 2).

Nine studies measured the HOMA (fig 3). The pooled data showed that insulin resistance was significantly higher in those with FEP than controls (mean difference 0·30 units, 95% CI 0·18,0·42 p=<0·0001). We were unable to pool data from one study[37], which were presented as medians and ranges. In this study the effect size was; cases (effect size 1·84, 95%CI 0·43,2·67), controls (effect size 0·92 (0·27-16·64)(p=<0·01).

Seven studies used the OGTT to measure IGT (fig 4). Pooling the data suggested increased IGT in FEP patients (mean difference 1·31mmol/L, 95% CI 0·37,2·25 p=<0·0001). There was a high level of heterogeneity in this analysis led by one outlier, so a random effects model was used.

Seven studies compared the number of patients meeting criteria for IGT between cases and controls (fig 5.) Pooled data show a greater number of FEP participants met the criteria for IGT than controls (OR 1·31, 95% CI 2·63,11·27 p=<0·0001).

We also performed an analysis of the 7 studies with both measures of FPG and IGT, and the findings are still non-significant for fasting glucose. There was no consistent pattern in the 7 studies. (effect estimate 0·07, 95% CI -0·03, 0·16).

Many studies measured a battery of other metabolic indices to assess for the metabolic syndrome as a whole. To test that our glycaemic findings aren't related to wider metabolic abnormalities in the included studies, we performed analyses on the other aspects of the metabolic syndrome tested (appendix 2). These analyses show no significant difference between cases and controls in LDL, triglycerides, BMI and waist circumference. Both total and HDL cholesterol were significantly greater in controls than cases.

Studies were appraised using the Newcastle Ottawa Scale[36] (NOS) for case-control studies. Studies scored between 4 and 8, out of a possible 9. Appendix 3 presents the NOS assessment for each study. There was variability between studies for each of the quality assessment domains; selection, comparability and exposure. Only 4 of 12 studies scored maximum points for selection and 7 of 12 for comparability.

Only one study[48] returned results of the OGTT that were not in favour of the hypothesis. This study also scored the minimum of four in the NOS. This RCT was also the only study that did not report the recruitment strategy for control subjects. Removing this study in a sensitivity analysis reduced heterogeneity to 0% and increased the effect size (mean difference 1.61, 95% CI 1.3, 1.92). In addition, both studies with the highest recorded score of eight[37,47] found results wholly in support of the hypothesis.

We explored publication bias using a funnel plot for FPG, which was the only outcome with sufficient studies to do so (n=12) (Appendix 4). There was no obvious asymmetry, but the number of studies with which to explore this formally was limited.

Discussion

We aimed to examine whether an association exists between FEP and prediabetes, possibly due to shared inflammatory processes. To our knowledge, this is the first systematic review and meta-analysis addressing this question.

In line with other published work[27], patients with FEP did not have significantly impaired FPG compared with matched controls (fig 2). However, our findings show an association between FEP and prediabetic states measured by IGT and HOMA.

A number of studies[37,38,39,41,43,45,48] expressed IGT as simply the number of cases and controls who met WHO/ADA criteria for IGT (using OGTT), demonstrating higher levels of IGT in cases. However, the binary of with/without IGT may not adequately describe the spectrum of IGT, and may therefore be less sensitive.

Another frequently measured parameter of prediabetes by studies was the HOMA. The relationship between glucose and insulin levels depends upon the balance between hepatic glucose production and pancreatic insulin secretion. The original model[49] ($HOMA_1$) provides a simple mathematical equation to estimate insulin resistance. An improved, computerised model ($HOMA_2$) was later developed and is preferable to $HOMA_1$[33]. Our pooled analysis for the HOMA method shows that insulin resistance is more common in patients with FEP than in matched controls, with a low degree of heterogeneity. Seven studies use the $HOMA_1$ equation, with one[38] using the more precise $HOMA_2$ model. One[37] did not state which model was used. Our findings also show that the effect sizes between FEP and IGT are greater than with insulin resistance. This may be explained by the use of the less sensitive $HOMA_1$ equation in many studies, though the possibility of difference in disease process is possible.

Analyses of other elements of the metabolic syndrome returned two significant results, with HDL (albeit with relatively high heterogeneity) and total cholesterol higher in controls. The higher total cholesterol may be a by-product of a higher 'cardio-protective'[52] HDL component in controls. It may however raise questions around the selection of 'healthy' controls, and relate to the relatively high prevalence of undiagnosed familial hypercholesteraemia in the general population[53]. It is likely that many non-

anthropomorphically matched potential controls had been screened out of inclusion, thus reducing the potential generalizability of our results. However, one might argue that matching in this manner is preferable, to help control for the confounding effect of poor diet and general health on glycaemic parameters. Contrarily, lower cholesterol may feature as part of the metabolic abnormality seen in FEP. It would be insensible to speculate further here, though this finding may warrant further attention in future. Finally, since a lower number of studies measured the other metabolic indices, there is a higher likelihood of confounding.

Strengths and Limitations

We present findings to suggest that the glycaemic abnormalities associated with FEP may be intrinsic, and extend beyond the known effects of medication, lifestyle and access to healthcare. It is possible that these findings could represent a similar association in schizophrenia. Some might term FEP a 'developing' schizophrenia, and others might term prediabetes a 'developing' diabetes, hence the results might suggest that the two conditions do indeed develop in unison. The results may suggest further research is warranted into a possible intrinsic link between diabetes and schizophrenia. As previously noted, examination into the metabolic effects of psychiatric disease is better conducted on participants that have not yet been exposed to potentially confounding medication, which renders FEP patients, who are also generally younger (with less comorbid medical conditions), a valid cohort to study.

However, there are several limitations that must be considered. Firstly, case-control studies are intrinsically susceptible to selection bias arising from a number of sources, as demonstrated in the NOS scores for the majority of studies. Whilst recall bias should be minimised due to screening participants and controls equally, and observer bias minimised due to the objectivity of biochemical assessment, the nature of recruitment of the control group was not always fully reported in included studies.

Publication bias is another limitation to be considered. Whilst we did not exclude unpublished results, theses or conference abstracts in our search, only published studies met inclusion criteria. However, visual inspection of the funnel plots revealed no obvious asymmetry. Furthermore, glycaemic status was but one outcome measure in studies equally examining other aspects of the metabolic syndrome.

None of the studies report how many potential participants were initially screened from taking part in the respective studies. This may be pertinent in light of the non-significant findings of certain other elements of the metabolic syndrome (i.e. BMI, lipid metabolism, waist circumference), which may be associated with physical illness and the need to take physical medication. This may have resulted in being screened from inclusion, potentially causing sampling bias.

Problems with confounding may also reduce confidence in the results. All included studies were either observational or included with data used in the manner of an observational study, and are thus prone to confounding. We cannot establish causality with data from case control studies, rather an association between FEP and pre-diabetic markers. Meta-analyses of observational studies are known to be less reliable than with randomised controlled trials[50] and the results should therefore be interpreted with caution.

Inclusion criteria also differed. Whilst one study[40] followed its 'case' group for six months after data collection to ensure diagnostic stability of first-episode schizophrenia , others were less strict, accepting all patients with first episode schizophrenia spectrum disorder. Confidence in diagnosis might therefore be lower in these studies.

Studies also varied in their definition of 'antipsychotic naïve'. Whilst the majority specified cases to have no prior exposure to antipsychotic medication, three[38,43,47] stipulated that cases may have taken antipsychotics for a maximum of one week, with none in the thirty days prior to the study. Results from these studies[38,43,47] were broadly in line with the results from studies with stricter definitions of 'antipsychotic naïve'. Although reasonable attempts were made to minimise exposure to antipsychotic medication prior to assessment, any exposure could lead to confounding. However, the sole RCT[48] measured FPG following an OGTT at six and fourteen weeks after included participants were prescribed one of four commonly used antipsychotics, and found no significant elevation in either FPG or two-hour glucose at six weeks. These findings help to support the assertion that minimal past exposure to antipsychotic medication as described here may be unlikely to confound the results of this review.

Furthermore, severity of symptoms is not widely addressed. Most studies recruited FEP

patients from a hospitalised population, from which one may deduce that participants were experiencing relatively severe symptoms. However, all participants were required to provide written informed consent to take part in their respective studies, which may have excluded patients with the most severe forms of illness causing impaired capacity to enter the study. Research suggests that even within the spectrum of schizophrenia disorders there may be differences in glycaemic control. This was proposed by Kirkpatrick et al (2009)[47], in which those patients with 'nondeficit' drug-naive schizophrenia had a significantly higher two-hour glucose level than those with 'deficit' schizophrenia. It could be argued then, that if such differences in pre-treatment glycaemic control exist as part of the spectrum of schizophrenic illness, the inclusion of a quantitative assessment of symptoms would be beneficial. Relevance of illness severity may be appropriate in light of a previous systematic review by Perry et al (in submission)[51], which found that although all studies were observational in nature, poor glycaemic control was consistently related to greater schizophrenia severity, as measured by symptom score or cognitive function. This finding was based on cross-sectional analyses, and was therefore prone to confounding and reverse causality, as well as selection bias.

Inclusion criteria for controls may also predispose to confounding. Whilst recruitment was mostly homogenous across studies, one did not report their method of recruitment. As the comparator across studies was healthy matched controls, rather than subjects with other types of mental illness, there is the possibility that any association derived from the results may not specifically be due to first episode psychosis, rather mental distress.

There is also the possibility that our results have occurred by chance. A potential contributing factor on glucose regulation in an acutely stressed state is cortisol. Though we did not examine cortisol as an outcome measure in our pooled analyses, this was discussed by a number of the studies. Five measured early morning cortisol and included it as part of their covariate analyses[37-39,41,47]. Of these, two reported significantly raised cortisol[39,41] whereas three studies reported no significant difference[37,38,47]. The finding that insulin resistance in FEP patients is abnormal compared with healthy matched controls even when cortisol and fasting glucose levels are accounted for provides strong evidence that hypercortisolaemia cannot fully account for the findings in this review, though further research in this area would be beneficial.

Finally, whilst we have presented that FEP may constitute a 'developing schizophrenia', this may be inaccurate. FEP and schizophrenia remain separate diagnostic entities, and not all sufferers of FEP will progress to schizophrenia. Nevertheless, the pathophysiology of psychosis may be shared between the two diagnoses, and secondly, the study of FEP as schizophrenia may be the only ethical way to study un-medicated patients, since antipsychotic medication can inherently affect glycaemic indices.

Conclusions

Our findings may suggest an association between markers of prediabetes, which might be termed a 'developing' diabetes, and FEP, which might be termed a 'developing' schizophrenia.

The FEP participants across all studies were relatively young, physically healthy, and had not been treated with antipsychotic medication for a period before the study (though this varied between studies), meaning the potential confounding variables were reduced. Our findings cannot therefore rule out the possibility that schizophrenia and diabetes share intrinsic disease links, which may be inflammatory in nature. This may warrant further work in future.

Moreover, our findings may suggest that if patients are at an increased risk of developing glycaemic regulation abnormalities even prior to the administration of antipsychotics, heightened vigilance and stricter control of the metabolic indices of patients is essential to help reduce the physical health burden associated with the disease.

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Authorship Statement

The hypothesis and background were designed by BP. The literature search was designed by BP, with assistance from KR. The search was carried out by BP and GM, with assistance by KR when needed. Forest plots and statistical analyses were completed by KR. Other figures and tables were designed by BP and GM. Interpretation of findings was by BP, GM, SW and SS. The paper was written by BP and GM, with amendments suggested by SW, KR and SS.

Conflicts of Interest

The authors declare no conflicts of interest.

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Original clinical studies examining the co-existence of a first-episode psychosis with prediabetes.
Patients over the age of sixteen (to ensure diagnostic accuracy in the face of rarer occurrence below this age) having presented to services with a diagnosis matching a first presentation of psychosis, as per study criteria; based upon a specific diagnostic classification (DSM/ICD) for first-episode psychosis.
Patients defined as being 'antipsychotic naïve' or 'antipsychotic free' at the time of assessment, as per study criteria.
As a primary measure, quantitative assessment of prediabetes defined as per specific diagnostic criteria by World Health Organisation (WHO)[31] / American Diabetic Association (ADA)[32] o Impaired Fasting Glucose (IFG) – Defined as a fasting plasma glucose (FPG) of 5.6-6.9mmol/L o Impaired Glucose Tolerance (IGT) – Defined as a plasma glucose two-hours following administration of 75g glucose as part of an Oral Glucose Tolerance Test (OGTT) of 7.8-11.0mmol/L
In addition to WHO/ADA criteria which focus on common clinical measures for prediabetes, studies were included that used the Homeostatic Model Assessment (HOMA), a sensitive mathematical means of estimating insulin resistance from FPG and insulin levels, commonly used in observational and interventional research relating to glycaemic control[33,34].
HbA1c, which is included in WHO criteria[31], was not measured as an outcome, due to reported poor sensitivity[32] in comparison to other measures.

Table 1: Inclusion Criteria

Studies that did not have a matched control group for comparison of glycaemic parameters.
Studies including participants under the age of sixteen either in the patient or control group as the epidemiology of FEP rates are rare below this age, hence diagnostic accuracy in these patients might be reduced.

Table 2: Exclusion Criteria

	FPG	HOMA-IR	75g OGTT	HbA1C	Fasting Insulin
Petrikis et al, (2015)[42]	x	x		x	
Fernandez-Egea et al, (2009)[43]	x	x	x	x	
Spelman et al, (2007)[44]	x	x	x	x	
Arranz et al, (2004)[45]	x	x			
Ryan et al, (2003)[46]	x	x	x		
Wu et al, (2013)[47]	x	x			
Kirkpatrick et al, (2012)[48]	x		x		
Dasgupta et al, (2010)[49]	x	x			
Sengupta et al, (2008)[50]	x	x	x		
Enez-Darcin et al, (2015)[51]	x	x			x
Kirkpatrick et al, (2009)[52]	x		x	x	x
Wani et al, (2015)[53]	x		x		

Table 4: Biochemical measures of prediabetes

1 Figures

2

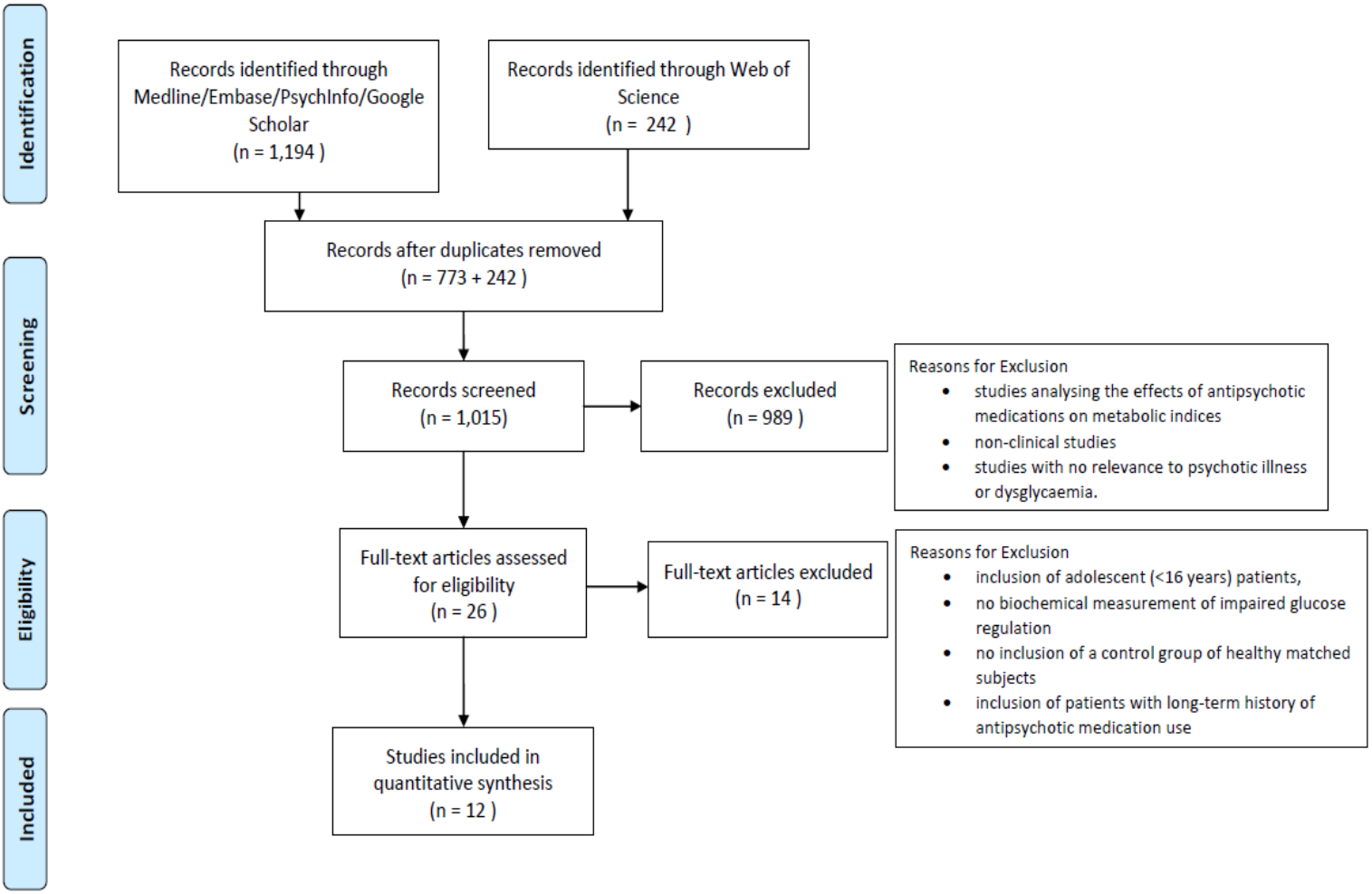

Fig 1. Search flow diagram

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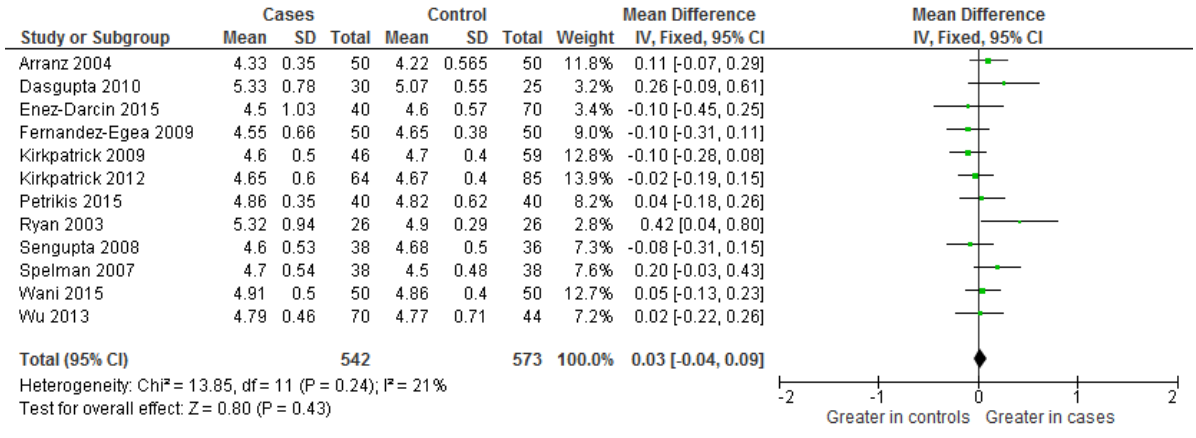

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Fig 2. FPG in included studies

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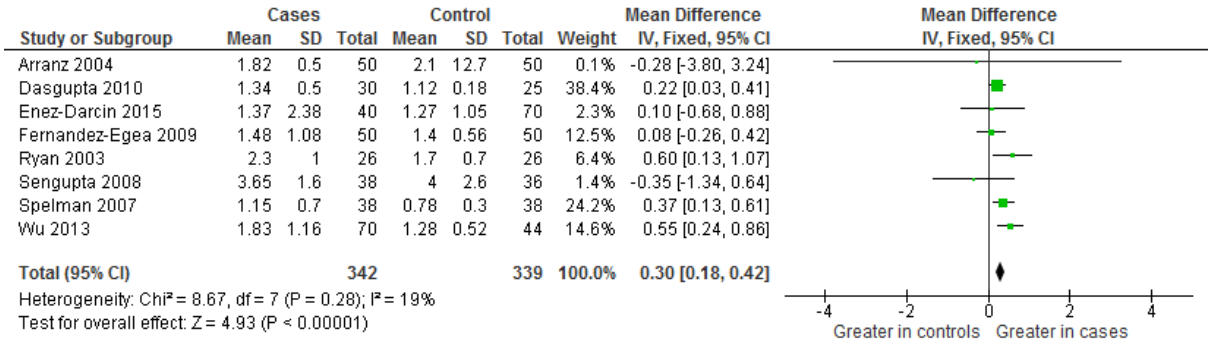

Fig 3.HOMA-IR in included studies

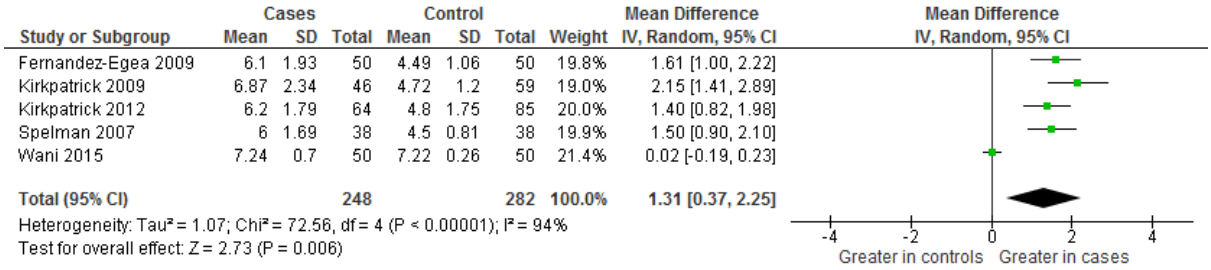

Fig 4.2hG in included studies

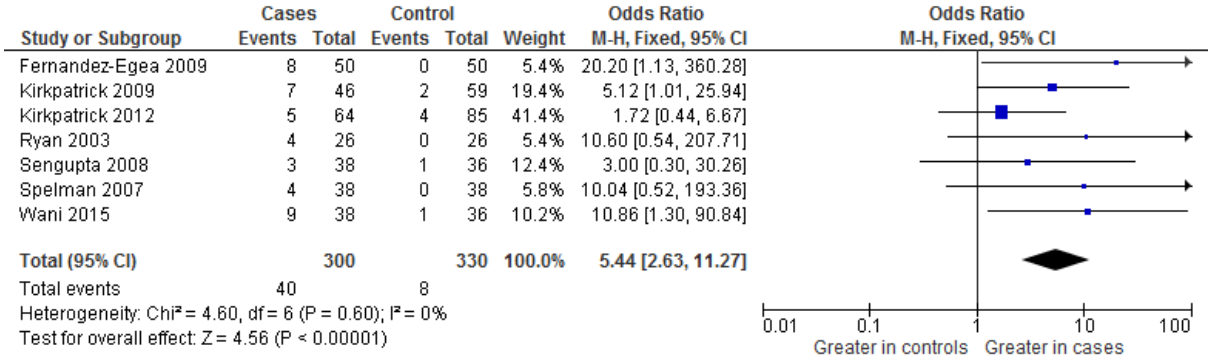

Fig 5. No. Participants with IGT