Diabetes mellitus is characterised by chronic hyperglycaemia and is one of the most common chronic diseases. The prevalence of detected diabetes is around 3–4% in the general population and set to double worldwide by 2030, largely as a result of an ageing population and the epidemic of obesity. The most common types of diabetes are types 1 and 2. Type 1 diabetes represents around 10–15% of all cases of diabetes and is associated with absolute insulin deficiency. Type 2 diabetes accounts for 85–90% of all cases of diabetes and is associated with relative insulin deficiency. The increased prevalence of diabetes in schizophrenia is partly attributed to antipsychotic treatment, in particular second-generation antipsychotics, but the evidence has not been systematically reviewed.

**Aims**
Systematic review and meta-analysis comparing diabetes risk for different antipsychotics in people with schizophrenia.

**Method**
We searched MEDLINE, PsycINFO, EMBASE, International Pharmaceutical Abstracts, CINAHL and Web of Knowledge until September 2006. Studies were eligible for inclusion if the design was cross-sectional, case–control, cohort or a controlled trial in individuals with schizophrenia or related psychotic disorders, where second-generation antipsychotics (defined as clozapine, olanzapine, risperidone and quetiapine) were compared with first-generation antipsychotics and diabetes was an outcome. Data were pooled using random effects inverse variance weighted meta-analysis.

**Results**
Of the studies that met the inclusion criteria (n=14), 11 had sufficient data to include in the meta-analysis. Four of these were retrospective cohort studies. The relative risk of diabetes in patients with schizophrenia prescribed one of the second-generation v. first-generation antipsychotics was 1.32 (95% CI 1.15–1.51). There were insufficient data to include aripiprazole, ziprasidone and amisulpride in this analysis.

**Conclusions**
There is tentative evidence that the second-generation antipsychotics included in this study are associated with a small increased risk for diabetes compared with first-generation antipsychotics in people with schizophrenia. Methodological limitations were found in most studies, leading to heterogeneity and difficulty interpreting data. Regardless of type of antipsychotic, screening for diabetes in all people with schizophrenia should be routine.

**Declaration of interest**
R.P. has received fees for speaking and consulting from makers of antipsychotics, including Eli Lilly and Company, Bristol Myers Squibb, Sanofi, Pfizer, Janssen and Astra Zeneca. R.H. has received educational grants and fees for lecturing and consultancy work from Eli Lilly and Company, Bristol Myers Squibb and GlaxoSmithKline.
The proceedings of conferences during 2000–2005 on diabetes (American Diabetes Association, Diabetes UK, European Association for the Study of Diabetes, International Diabetes Federation) and psychiatry (American Psychiatric Association, Schizophrenia Research) were hand and electronically searched in the relevant sections.

The reference lists of included studies and reviews were searched for any additional studies. Although clozapine was first introduced in 1956 and withdrawn shortly after because of severe side-effects, there was a small risk of not detecting pre-1966 studies (when MEDLINE began), which was addressed by checking reference lists.

Corresponding authors and experts in the field were contacted for additional information on published and unpublished studies.

**Data extraction**

The abstracts of studies identified by electronic searches were examined by M.S. If unclear, the original article was retrieved, reviewed and discussed with co-investigators.

Data were extracted from papers selected for further review. Foreign papers were translated by doctors who were native speakers in that language.

Using a standardised data extraction sheet, we recorded and coded the following information (if available) from studies: country of origin; study design; setting; total sample size (and total number taking second-generation and first-generation antipsychotics); classification and method of assessment of schizophrenia; ascertainment of antipsychotic exposures; assessment and classification of outcome (diabetes); follow-up period; age; type of confounders adjusted; and source of funding. An attempt to retrieve missing data in the published article was made by contacting the author for correspondence on at least two occasions by email or letter.

**Quality assessment**

There is no consensus standardised method for the quality assessment of observational studies. We adapted the Meta-analysis of Observational Studies in Epidemiology (MOOSE)14 and Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE)15 guidelines to assess and code the quality of the studies.

A study method was considered as high-quality if the following criteria were present:

(a) the design was prospective, including randomised controlled trials (RCTs)
(b) case definition for participants with schizophrenia was based on the past three editions of the ICD or the DSM
(c) the study included only patients who did not have diabetes at recruitment (baseline) of the sample
(d) recruitment of the sample was consecutive or random
(e) ascertainment of antipsychotic medication exposure used an objective technique, such as screening of electronic prescription databases
(f) ascertainment of diabetes mellitus as an outcome was based on accepted diagnostic criteria, such as the American Diabetes Association (ADA)16 and the World Health Organization (WHO)17
(g) temporality of an association between antipsychotic and diabetes was assessed with at least 1 year of follow-up reported

The data were controlled for the six main independent risk factors for diabetes (body mass index, family history of diabetes (first-degree relatives), ethnicity, age, physical activity and socio-economic status).

All other descriptions, or lack of any description, were coded as low-quality.

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**Fig. 1 Flow chart of systematic review.**
Setting and funding status of the studies were recorded but not coded for quality as it was difficult to assess with confidence how this could have introduced a bias.

We did not summarise the quality of studies with a score as this approach has been criticised as allocating equal weight to different aspects of methodology.18

Statistical analysis
Quantitative data from studies of high quality were pooled using random effects inverse variance weighted meta-analysis19 in Stata, version 9 for Windows. Where available, approximate relative risks (odds ratios or hazard ratios) and corresponding 95% confidence intervals (CIs) for diabetes, which compared second-generation antipsychotics with first-generation antipsychotics, were used from each study. Where results were given after different adjustments for confounding factors, the result for the largest confounding set was used. If only numbers with diabetes by drug type were available, these were first used to compute unadjusted odds ratios and corresponding 95% CIs for that study. Where no diabetes events occurred in any drug group, the study was excluded from the meta-analysis. Some studies gave separate results for different second-generation drugs but no overall result. In these cases, meta-analysis was used to create a pooled result, over all second-generation drugs, for that study only. This result was carried forward to the overall meta-analysis. The percentage of heterogeneity between studies not attributable to random noise was estimated using Higgins’ $I^2$-squared statistic.19

Results
The search strategy identified 1974 abstracts from which 73 full texts were selected for further extraction. Data extraction from full texts identified 14 studies that met the criteria for inclusion in the systematic review. A total of 11 studies had sufficient information to be included in the meta-analysis. The number of studies that were excluded from the review and meta-analysis are shown in Fig. 1. The studies included in the systematic review are described in the online Table DS1.

Of the 14 studies, 10 were based in a hospital setting, 1 was based in primary care and 3 comprised a mixed hospital and primary care setting. Seven studies used a health administration database,5,20–25 Only 1 study used a database designed for conducting research.26
The majority of study designs were either cross-sectional ($n=4$), retrospective cohort ($n=4$) or case–control ($n=2$) with only a handful using prospective selection ($n=3$). The majority used consecutive or convenience sample selection, with two studies using random selection (Table DS1).

Nine (64.3%) studies used a classification system for schizophrenia (ICD, DSM–IV) but the majority were based on a clinical assessment with only one study using a research diagnostic interview, namely the Structured Clinical Interview for DSM–III–R27 (Table DS1). The average age was 45.0 years (s.d.=7.7) ($n=12$ studies with age data).

Second-generation antipsychotics included in these studies were clozapine, olanzapine, risperidone and quetiapine, with clozapine studied on its own in four of the studies.5,23,28,29 Although sulpiride is classified as a second-generation antipsychotic in one paper,30 it is classified as a first-generation in the BNF and therefore was excluded from our list of second-generation antipsychotics.

The diagnosis of diabetes mellitus was according to WHO guidelines in 3 (21.4%) studies,2,20,21,23,25 ICD–9 diagnosis in 5 (35.7%) studies,2,20,21,23,25 and ADA guidelines in 3 (21.4%) studies.29,32,33 Most of the studies ensured that there was no evidence of diabetes prior to antipsychotic use but certain studies did not clearly differentiate between new and existing cases of diabetes.8,29,30 In addition, some studies used prescription of diabetes medication for diagnosis of diabetes.20,21,23–26

Excluding cross-sectional studies, follow-up periods ranged from 2 to 62 months and the median duration of follow-up from the start of the study was 12 months (interquartile range 2.6–16.8 months).

Most studies did not adjust for confounders in the methods or analysis. Studies also did not adjust for all risk factors for diabetes (Table DS1).

There were 7 studies funded by the pharmaceutical industry.20–22,24–26,33 One study was translated into English.32

Our meta-analysis found an overall relative risk of a diagnosis of diabetes in people with schizophrenia prescribed a second-generation antipsychotic of 1.32 (95% CI 1.15–1.51) compared with being prescribed a first-generation antipsychotic (Fig. 2).

The percentage of variability across studies that is attributable to heterogeneity rather than chance was 80% (95% CI 66–89) and the test for heterogeneity was highly significant (P<0.001). Both these results suggest that there is considerable variation between the studies.

To explain this heterogeneity, sensitivity analyses were carried out. Relative risks for separate second-generation drugs were as follows: risperidone 1.16 (95% CI 0.99–1.35; $n=6$ studies), quetiapine 1.28 (95% CI 1.14–1.45; $n=3$ studies), olanzapine 1.28 (95% CI 1.12–1.45; $n=8$ studies) and clozapine 1.39 (95% CI 1.24–1.55; $n=7$ studies).

Discussion
The study criteria for this systematic review identified 14 papers comparing the risk of having or developing diabetes while on second generation antipsychotics with first-generation antipsychotics in people with schizophrenia or related disorders. Eleven of these studies had sufficient data to pool. Meta-analysis found that second-generation antipsychotics were associated with a small increased relative risk for diabetes compared with first-generation antipsychotics.34 Methodological limitations in nearly all the studies were evidenced by significant heterogeneity and this raises some difficulties in interpreting and comparing the studies.

Strengths and limitations
The strengths of our review are that the study is based on principles derived from the Cochrane Collaboration methods, such as an a priori protocol. In addition, established Cochrane Collaboration search strategies were adapted as well as hand searching of references of relevant papers, including non-English ones. Experts in the field were contacted for missing data and further information. We also conducted separate analyses comparing individual second-generation antipsychotics with first-generation antipsychotics to take account of the unequal distribution and potentially different diabetogenic potential of individual drugs.

A possible limitation of our review is that we used a narrow search strategy which may have excluded well-designed studies that focused on related outcomes other than diabetes, such as weight gain or insulin levels. Although cardiovascular risk factors other than diabetes mellitus such as abnormal lipid metabolism, blood pressure and obesity may also have a significant effect on the physical health of patients with schizophrenia, we chose to focus on diabetes and exclude metabolic syndrome. Although the diagnosis of diabetes is relatively uniform, no such consensus
Relative risk of diabetes in people with schizophrenia exists for metabolic syndrome. We also chose to exclude homoeostasis model assessment as an outcome as it is a research tool and its validity for predicting diabetes remains unclear. We excluded patients taking antipsychotics when the clinical indication was not clear. We excluded studies of mixed psychiatric populations where subgroups of patients with schizophrenia who developed diabetes could not be distinguished. This led to some studies that included people with schizophrenia being excluded. The rationale for including only schizophrenia and related illnesses, and excluding all other psychiatric illnesses or studies which did not state diagnosis, was the importance of considering schizophrenia as an independent risk factor for diabetes. Studies that did not compare a second-generation antipsychotic with a first-generation antipsychotic, but instead to another second-generation antipsychotic or placebo were excluded. We included all second-generation antipsychotics but there were no studies that met our eligibility criteria for the more recent drugs such as ziprasidone, amisulpride and aripiprazole, which have been suggested to be less diabetogenic in some case reports. Future studies comparing their diabetogenic profiles are awaited.

Quality of studies

We found that the average duration of studies was around 12 months with three studies having a follow up of only 3 months or less. It could be that these studies did not follow up their patients for long enough, perhaps several years, to capture the long-term risk for diabetes and this may have led to an underestimation of our findings. However, there is also some evidence that the diabetogenic effects are rapid in onset – within the first few months. It is possible that there may be several glucose-metabolism-altering mechanisms, a short- and a long-term process, and studies with repeated measurements over several years could help to elucidate the diabetogenic patterns.

Most studies included in this review were retrospective or pharmacoepidemiological using large databases. Limitations in analysing data from such studies, mainly due to the quality of clinical data recorded, exist. Database studies do not rely on a standardised method of diagnosing diabetes mellitus. Random blood glucose measures were often used, highlighting the difficulty of obtaining fasting blood samples from this patient group. Furthermore, utilisation of established diagnostic guidelines for diabetes such as those provided by the WHO or ADA was inconsistent. Prescription of hypoglycaemic medication as a method of diagnosis may exclude patients receiving non-pharmacological treatment for diabetes such as those on diet alone. It may also include some people receiving metformin for other indications such as polycystic ovarian syndrome. Little evidence existed that the diagnosis of diabetes in databases was reliable or valid. The date of the first listed claim may not represent the actual date of onset of diabetes as the diagnosis may have been previously made but recorded elsewhere.

The techniques and methods used to diagnose schizophrenia cannot be inferred accurately from the databases. We observed that not all antipsychotics were included in the databases. This may be a reflection of the country where the study was undertaken and the availability of, and preference for, one type of antipsychotic over another. Many of the databases were of specific populations and mainly in the USA, which may limit their generalisability to other populations. In addition, a number of studies had only a few weeks or months of observation which may have captured those individuals who have rapid weight gain but which may be too short a time to identify later onset of diabetes.

Association between antipsychotics and diabetes

The first observation of an association between antipsychotics and diabetes occurred over 50 years ago, but renewed interest in this...
link has developed with second-generation antipsychotics in the past decade. Second-generation antipsychotics have been shown to reduce extrapyramidal side-effects and are beneficial to many patients. However, the concerns that second-generation antipsychotics may also increase the risk of metabolic dysregulation must also be carefully considered.

As the majority of studies were cross-sectional or retrospective cohort in design, it is not possible to determine the direction of the association between second-generation antipsychotics and diabetes. Our review highlights that most studies were limited in quality with none of the studies fulfilling all of the quality criteria; five studies had four or fewer quality criteria (Table DS1). Any association detected in this review is likely to be significantly biased. The possibility of residual confounding also cannot be dismissed. One residual confounder not reported in any of the studies was whether an increased amount of screening occurred in those on second-generation antipsychotics compared with first-generation antipsychotics, owing to greater clinical awareness. This is important because of the high prevalence of undiagnosed diabetes in people with schizophrenia, among whom as many as 75% of cases of diabetes may be missed.

Our review found that second-generation antipsychotics were associated with a 30% increased risk of diabetes compared with first-generation antipsychotics in people with schizophrenia – this is probably a biased observation with the true association probably being smaller. This review was unable to find sufficient evidence to differentiate the risk associated with individual antipsychotics, nor did the studies we identified help shed any light on causal mechanisms. Our review emphasises that, to date, the evidence is very poor and should not be used alone as a guideline for or switching antipsychotic medications or implementing diabetes screening and management protocols for schizophrenia until further evidence comes to light.

In epidemiological terms, a relative risk of less than 2 is considered low, whereas a relative risk of greater than 3 is considered high. This is an important clinical issue to consider when treating patients with antipsychotic medication. Importantly, clinicians should implement protocols for identifying physical illnesses, in particular diabetes, in people with schizophrenic illnesses, while also reviewing the rationale and dosage of prescribing antipsychotic medication both in terms of treatment of psychotic symptoms and risk of diabetes. Our review has identified the key confounders and methodological issues that need to be considered in evaluating the association between diabetes and antipsychotic medication in schizophrenia. There also remains an urgent need for continuing to identify and understand the biological pathways and increase the epidemiological evidence base for diabetes in schizophrenia. In particular, randomised controlled trials comparing first- and second-generation drugs should consider the implications of their study’s power to detect differences in onset of diabetes as an adverse event, bearing in mind these events are likely to be rare.

Acknowledgements

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Melkersson KI, Dahl ML. Relationship between levels of insulin or triglycerides and serum concentrations of the atypical antipsychotics clozapine and olanzapine in patients on treatment with therapeutic doses. Psychopharmacol 2003; 170: 57–66.


<table>
<thead>
<tr>
<th>First author, year, country</th>
<th>Study design, sample selection, setting</th>
<th>Study size (second/first generation), classification and assessment of schizophrenia</th>
<th>Follow-up period (months)</th>
<th>Assessment of selection bias</th>
<th>Adjusted for confounders in the design or analysis</th>
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<tbody>
<tr>
<td>Hagg, 1998 Sweden</td>
<td>Cross-sectional Consecutive Hospital</td>
<td>58/58, ICD–9 and clinical interview</td>
<td>NS</td>
<td>Participation and withdrawals not accounted for</td>
<td>None</td>
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<td>Chae, 2001 Korea</td>
<td>Prospective cohort NS Hospital</td>
<td>17/10, NS</td>
<td>2</td>
<td>Withdrawals not accounted for</td>
<td>None</td>
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<tr>
<td>Lund, 2001 USA</td>
<td>Retrospective cohort Consecutive Hospital and primary care</td>
<td>552/2461, ICD–9 and clinical interview</td>
<td>25</td>
<td>No control for other diabetogenic medication</td>
<td>None</td>
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<tr>
<td>Kurt, 2002 Turkey</td>
<td>Prospective cohort Random Hospital</td>
<td>49/26, DSM–IV and SCID</td>
<td>2</td>
<td>Excluded losses to follow-up</td>
<td>None</td>
</tr>
<tr>
<td>Sernyak, 2002 USA</td>
<td>Cross-sectional Consecutive Hospital</td>
<td>22648/15984, ICD–9 and clinical interview</td>
<td>NS</td>
<td>No control for weight, other diabetogenic medication</td>
<td>Age, income, gender, ethnicity, disability, comorbid psychiatric illness, service use</td>
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<td>Koro, 2002 USA</td>
<td>Case–control Consecutive Primary care</td>
<td>3231/18443, clinical interview</td>
<td>62</td>
<td>No control for race, social class, weight gain, severity of schizophrenia</td>
<td>Age, gender, index year, duration follow-up, use of other diabetes-inducing medication</td>
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<tr>
<td>Lindenmeyer, 2003 USA</td>
<td>Randomised controlled trial Random Hospital</td>
<td>76/25, DSM–IV and clinical interview</td>
<td>3</td>
<td>Last observation carried forward</td>
<td>None</td>
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<td>Zhao, 2003 USA</td>
<td>Retrospective cohort Consecutive Hospital</td>
<td>462/353, ICD–9 and clinical interview</td>
<td>12</td>
<td>Risk factors (fasting hyperglycaemia, diabetes mellitus, ethnicity, obesity, lifestyle) not accounted for</td>
<td>Age, gender, region, enrollment status, treatment duration, comorbidity</td>
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<td>Dillerendorf, 2004 USA</td>
<td>Retrospective cohort Consecutive Hospital</td>
<td>1826/617, ICD–9 and clinical interview</td>
<td>14</td>
<td>Intention to treat, selection bias, no adjustment for body mass index, lipid levels, fasting hyperglycaemia, race, ethnicity</td>
<td>Age, gender, health plan type, region, number of diabetes screening tests</td>
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<td>Leslie, 2004 USA</td>
<td>Retrospective cohort Consecutive/ Hospital and primary care</td>
<td>Not known,^a^ clinical interview</td>
<td>12^b^</td>
<td>Prior medication unknown</td>
<td>Age, gender, race, income, comorbid psychiatric illness, service use, disability</td>
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<td>Miller, 2005 USA</td>
<td>Cross-sectional Consecutive Hospital</td>
<td>24/21, clinical interview</td>
<td>NS</td>
<td>More blood tests with clozapine</td>
<td>None</td>
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<tr>
<td>Lambert, 2005 USA</td>
<td>Case–control Consecutive Hospital and primary care</td>
<td>16/10/1993, ICD–9 and clinical interview</td>
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<td>Diagnosis not validated, no control for body mass index, fasting hyperglycaemia</td>
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<tr>
<td>Cohen, 2005 The Netherlands</td>
<td>Cross-sectional Consecutive Hospital</td>
<td>142/101,^c^ DSM–IV</td>
<td>NS</td>
<td>No control for lifestyle, diet</td>
<td>Age</td>
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<tr>
<td>Lambert, 2006 USA</td>
<td>Retrospective cohort Consecutive Hospital</td>
<td>12759/3008, ICD–9</td>
<td>12</td>
<td>No control for weight, family history of diabetes mellitus, physical activity, socio-economic status</td>
<td>Gender, age, ethnicity, marital status, exposure to other diabetogenic medication</td>
</tr>
</tbody>
</table>

NS, not stated.

^a^ Total study size=56,849.

^b^ Minimum follow-up was 12 months.

^c^ We classified sulpiride as a first-generation and not a second-generation antipsychotic in this review.
First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis
M. Smith, D. Hopkins, R. C. Peveler, R. I. G. Holt, M. Woodward and K. Ismail
Access the most recent version at DOI: 10.1192/bjp.bp.107.037184

Supplementary Material
Supplementary material can be found at:
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