



# Real-World Data on the Adverse Metabolic Effects of Second-Generation Antipsychotics and Their Potential Determinants in Adult Patients: A Systematic Review of Population-Based Studies

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## ABSTRACT

**Introduction:** To assess the risk of occurrence and potential determinants of metabolic disorders in adult patients treated with second-generation antipsychotics (SGAs) under real-world practice conditions.

**Methods:** MEDLINE, EMBASE, and PsycInfo were searched in July 2019 from database inception. We included population-based, longitudinal, comparative studies that report the results of the outcomes of interest for adult

participants, including diabetes, ketoacidosis, hyperosmolar hyperglycemic state, weight gain/obesity, dyslipidemia, hypertension, and metabolic syndrome. Two reviewers independently extracted data on the study design, study quality, and study outcomes.

**Results:** We included 40 studies. Most studies showed that clozapine and olanzapine were associated with an increased likelihood of developing diabetes, while the results for risperidone and quetiapine were mixed. Although less well studied, ziprasidone and aripiprazole appeared to not be associated with the occurrence of diabetes. Information on antipsychotic-induced weight gain/obesity is extremely scarce. Regarding dyslipidemia, aripiprazole was not associated with an increased likelihood of developing dyslipidemia, clozapine was associated with an increased likelihood of developing dyslipidemia, and risperidone, olanzapine, quetiapine, and ziprasidone showed mixed results. Two studies suggested an association between ziprasidone and the occurrence of hypertension. Several studies found that the occurrence of a metabolic disorder acted as a risk factor for the development of other metabolic disorders. We did not find information on brexpiprazole, cariprazine, or lurasidone, and data on any long-acting SGA were lacking.

**Conclusion:** Although there are relevant differences among SGAs concerning the risk of metabolic disorders, it appears that none of the

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SGAs included in our review are fully devoid of these disturbances.

## PLAIN LANGUAGE SUMMARY

Patients with severe mental disorders often present metabolic disorders such as obesity, increased blood pressure, high blood sugar, and abnormal cholesterol or triglyceride levels. Treatment with antipsychotics may contribute to the occurrence of these disorders. Using a systematic review, we have evaluated the risk of occurrence of these metabolic disorders associated with the most frequently used antipsychotics—the so-called second-generation antipsychotics (SGAs)—and which factors increase the patient chances of presenting a metabolic disorder when they are treated with these drugs under routine clinical practice. After reviewing 40 studies, we found that, although there are relevant differences among SGAs concerning the risk of metabolic disorders, it appears that none of the drugs included in our review are fully free of these disturbances. Among the factors that increase the chances of these disturbances, we highlight that the presence of a particular metabolic disorder (e.g., increased blood pressure) acts as a risk factor for the occurrence of other metabolic disorders (e.g., high blood sugar), and that the duration of treatment could be a relevant factor for the occurrence of these disorders. Finally, we also found important gaps in our knowledge about this matter, mainly the limited information on the SGAs apparently associated with lower risk of metabolic disorders in experimental studies (that is, few studies evaluating ziprasidone and aripiprazole, and none evaluating brexpiprazole, cariprazine, or lurasidone) and the lack of information on long-acting injectable (that is, antipsychotics that are usually given every 2–4 weeks) SGAs.

**Keywords:** Antipsychotic; Diabetes; Dyslipidemia; Hyperosmolar hyperglycemic state; Hypertension; Ketoacidosis; Metabolic syndrome; Obesity; Weight gain

## Key Summary Points

### Why carry out this study?

Information on antipsychotic-associated metabolic disorders is derived from short-term (i.e., 6 weeks) randomized clinical trials—or systematic reviews of these trials—conducted in selected populations devoid of relevant medical or psychiatric comorbidities that received limited concomitant medications

Information from patients treated under real-world conditions for longer time would be useful for better delineating the risk of antipsychotic-associated metabolic disorders and their potential determinants

This systematic review of population-based case-control and cohort studies aimed to assess the risk of occurrence and potential determinants of metabolic disorders in adult patients treated with second-generation antipsychotics (SGAs) under real-world practice conditions

### What was learned from the study?

Although there are relevant differences among SGAs concerning the risk of metabolic disorders, it appears that none of the SGAs included in our review are fully devoid of these disturbances and there are important gaps in the literature, mainly the limited information on the SGAs apparently associated with better metabolic profile (i.e., few studies evaluating ziprasidone and aripiprazole, and none evaluating brexpiprazole, cariprazine, or lurasidone) and the lack of population-based studies on long-acting injectable SGAs

Among potential determinants of these disturbances, we highlight because of their clinical implications that the presence of a particular metabolic disorder acts as a risk factor for the occurrence of other metabolic disorders, and the length of antipsychotic exposure could be a relevant factor for the occurrence of these disorders

## DIGITAL FEATURES

This article is published with digital features, including a summary slide and plain language summary, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14113586>.

## INTRODUCTION

Metabolic disorders, frequently grouped as the so-called metabolic syndrome (i.e., the co-occurrence of abdominal obesity, hyperglycemia, hypertension, and hyperlipidemia), are common in patients with severe mental disorders [1–5] and play a determinant role in the increased risk of premature mortality, predominantly due to cardiovascular diseases, in psychiatric patients [6].

Treatment with antipsychotics may contribute to the occurrence of metabolic syndrome, and thus, clinical practice guidelines recommend initial physical and laboratory assessments and periodic follow-up after initiating antipsychotic treatment for the prevention, early recognition, and treatment of these metabolic disturbances [7]. Results from randomized clinical trials (RCTs) show that there are marked differences among antipsychotics in regard to their risks of inducing metabolic disorders [8]. However, this information is derived from short-term (i.e., 6 weeks) studies conducted in selected populations devoid of relevant medical or psychiatric comorbidities that received limited concomitant medications. Therefore, information from patients treated under real-world conditions for longer time would be useful for better delineating the risk of antipsychotic-associated metabolic disorders.

A systematic review on this topic has been published [9]. However, this otherwise interesting review is limited by the exclusion of studies conducted in subpopulations, such as studies conducted in patients with schizophrenia, patients with bipolar disorder, or hospital-based studies, and did not include information on the potential moderators of the risk of metabolic disorders. The review included

studies published only until July 2015, a time frame that limits information on most recently marketed antipsychotics (e.g., antipsychotics with apparently good metabolic profiles according to pivotal trials, such as brexpiprazole, cariprazine, and lurasidone [8], which obtained US Food and Drug Administration approval in 2015 or later). Antipsychotic treatment selection should be individualized and based on effectiveness and tolerability in addition to patients' preferences. Increasing knowledge of the tolerability profile of well-established antipsychotics as well as recently introduced antipsychotics will help achieve individualized antipsychotic treatment selection [10].

The objectives of this systematic review were to assess the risk of occurrence and potential determinants of diabetes or acute diabetes-related complications, weight gain/obesity, hyperlipidemia, hypertension, or metabolic syndrome in adult patients treated with second-generation antipsychotics (SGAs) under real-world practice conditions.

## METHODS

### Eligibility Criteria

#### *Type of Studies*

We focused on real-world population-based studies. We included longitudinal comparative studies (i.e., cohort or case-control studies) since cross-sectional studies do not allow for the establishment of a causal relationship.

#### *Types of Participants*

The studies needed to include or separately report the results of the outcomes of interest for adult participants aged 18 years and older. We did not focus on any specific diagnosis; however, to be included, studies had to be conducted in patients with a psychiatric diagnosis, or the psychiatric diagnosis had been included in the multivariate statistical model. The reason for this criterion is that the psychiatric diagnosis may have an independent impact on the risk of metabolic disorders [11].

### ***Types of Interventions***

Our interventions of interest were the following SGAs: amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, and zotepine. We included studies reporting data for individual drugs or for grouped SGAs. Information on first-generation antipsychotics (FGAs) was only sought as a comparator to the SGAs. We had no limitations regarding comparators.

### ***Types of Outcome Measures***

The outcomes of interest of the studies were diabetes, ketoacidosis, hyperosmolar hyperglycemic state, weight gain/overweight/obesity, dyslipidemia (hyperlipidemia) or the specific entities hypercholesterolemia or hypertriglyceridemia, hypertension, and metabolic syndrome. We accepted and recorded any definition of these clinical entities, including diagnoses based on any code system (e.g., ICD-10) and on exposure to specific treatments (e.g., antihypertensives). We excluded studies conducted on pregnant women.

To be included in this review, articles needed to report the results of at least one of the outcomes of interest.

### **Search Methods for Study Identification**

The following databases were searched in July 2019 from inception by a medical information specialist (IS-A, see the Acknowledgments): MEDLINE, EMBASE, and PsycInfo. The search strategy is presented in Supplementary Table 1.

### **Study Selection**

A reviewer with a background in research methodology (FR-V) determined the eligibility of studies by reading the title/abstract of each study identified by the search. The reviewer discarded studies that clearly did not satisfy the inclusion criteria, and complete copies of the remaining studies were obtained. The reviewer assessed all the initially selected complete articles and selected the papers that met the

previously described eligibility criteria; doubts regarding whether an article met the criteria were solved by consensus with a second reviewer (RR). If no agreement could be reached, then a third reviewer (MB) was involved in the assessment.

We did not anonymize the studies prior to the assessment.

### **Data Extraction and Management**

Two reviewers (FR-V and RR) independently extracted data from half of the studies, each using a standard Microsoft Excel form. Both reviewers cross-checked the data extracted by the other reviewer with the source article. In cases of discrepancies, both reviewers discussed the specific difference to reach an agreement prior to entering data into the final tables. If no agreement could be reached, then a third reviewer (MB) was involved in the assessment.

As characteristics of the studies, we recorded information on the first author, year of publication, journal, study design, country, database, time frame, age as a selection criterion or as the mean/median, diagnosis and the tool used to make the diagnosis, type of exposure and its definition, type of control, outcomes evaluated and definition, multivariate model used in statistical analysis and the covariates included in the model, whether the study used propensity scores either for matching and/or adjusting for, and funding source.

After extracting the results of the studies, we recorded information on the size of the source population, length of treatment, duration of the follow-up, outcome evaluated, type of exposure, sample size of exposed/nonexposed or case/controls, summary statistic (e.g., percentage, incidence rate), type effect measure (i.e., odds ratio [OR], relative risk [RR], or hazard ratio [HR]), point estimate and 95% confidence interval (CI) of the effect measure, *p* value, and point estimates and 95% CI of the effect measures of the other potential determinants of the occurrence of metabolic disorders in a table.

## Assessment of Study Quality

The quality of the studies was evaluated by two reviewers (FR-V and RR) using the Newcastle–Ottawa scale, a widely used tool for evaluating the quality of nonrandomized studies in systematic reviews [12]. The Newcastle–Ottawa scale considers three dimensions in the evaluation by using a “star system”: the selection of study groups (maximum 4 stars); the comparability of the groups (maximum 2 stars); and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively (maximum 3 stars). To evaluate comparability, we decided to allocate one star if the study used propensity scores for matching and/or adjusting in the statistical analyses; a second star was allocated if the study explicitly reported controlling for age and gender, either by matching or adjusting in the multivariate model.

Following the same criteria used by other authors [13], a “poor” quality score was reflected as 0 or 1 star(s) in selection, 0 stars in comparability, or 0 or 1 star(s) in outcomes.

## Data Synthesis

Because substantial heterogeneity was expected, no quantitative synthesis was expected to be carried out. The results of individual studies are presented using forest plots for descriptive purposes. Since they require a different interpretation, forest plots are presented separately for odds ratios/relative risks (for binary outcomes) and hazard ratios (for time-to-event outcomes). When reported in the same forest plot, odds ratios and relative risks are clearly identified.

## Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## RESULTS

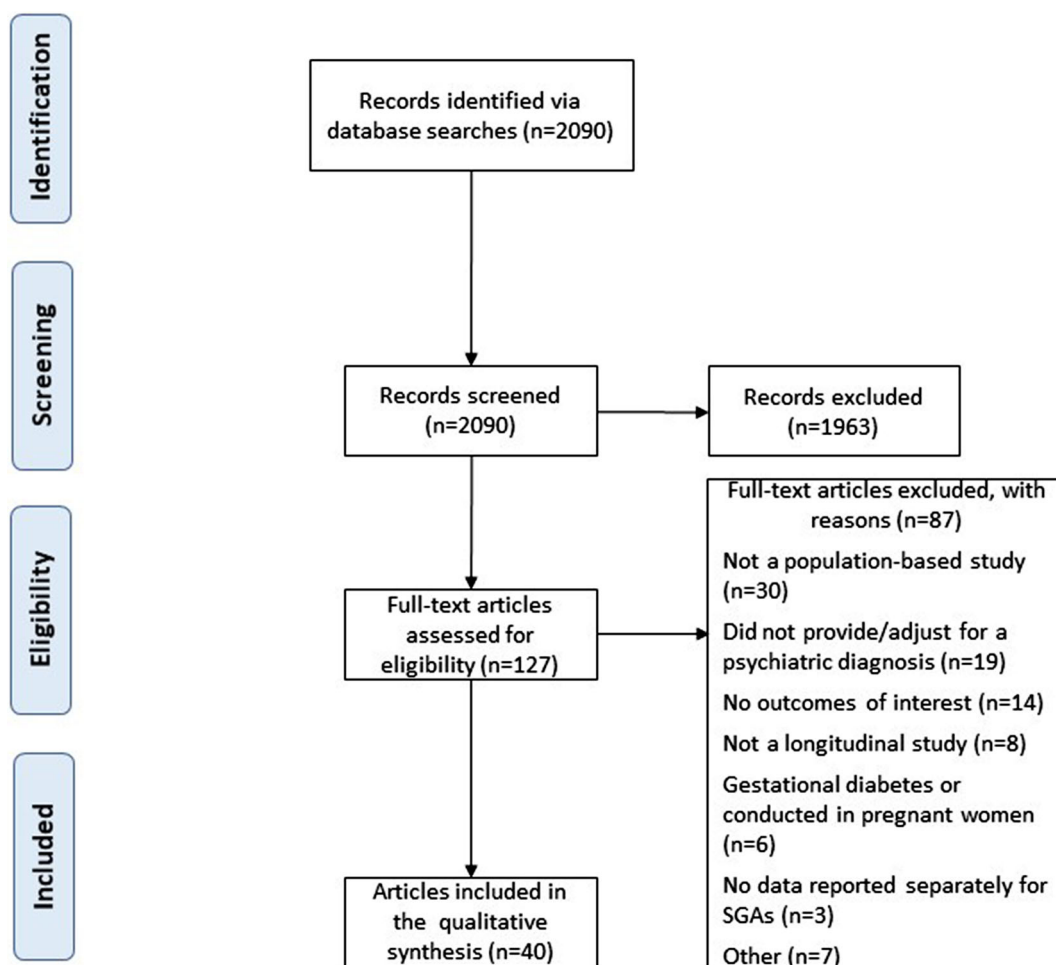
### Study Selection

Finally, 40 studies published between 2001 and 2019 were included in this review. The flow chart of the study selection process is presented in Fig. 1.

### Study Characteristics

A description of the main characteristics of the studies included in this review is presented in Supplementary Table 2. Twenty-six (65.0%) of the studies had a retrospective cohort design and 14 (35.0%) were case–control studies. Five (12.5%) studies employed a propensity score methodology, three using matching and two using propensity scores for adjustment in the statistical analysis. Most of the studies were conducted in North America, 24 in the USA and 5 in Canada; 5 studies were conducted in Taiwan; 5 studies were in Europe; and 1 study used databases from the UK and Canada. Nineteen of the studies were partially or fully supported by a pharmaceutical company (12 studies were supported by the comarketer of aripiprazole), 14 received noncommercial support, 6 did not report the funding source, and 1 did not receive any support.

Six (15.0%) studies included subjects aged 65 or older. Fourteen (35.0%) studies included patients with schizophrenia, three (7.5%) patients with bipolar disorder, and two (5.0%) patients with depression, and the remaining studies included patients with a variety of diagnoses. The antipsychotics most commonly studied were olanzapine ( $n = 26$ , 65.0%), risperidone ( $n = 21$ , 52.5%), quetiapine ( $n = 20$ , 50.0%), and clozapine ( $n = 15$ , 37.5%), while the less commonly studied antipsychotics were ziprasidone ( $n = 7$ , 17.5%) and aripiprazole ( $n = 5$ , 12.5%). We did not find any studies that evaluated any other SGAs under study (namely, amisulpride, asenapine, brexpiprazole, cariprazine, iloperidone, lurasidone, paliperidone, sertindole, or zotepine) or data on any long-acting SGA. The most common comparators were FGA ( $n = 17$ , 42.5%) and patients not



**Fig. 1** Flow diagram study selection

receiving antipsychotics ( $n = 13$ , 32.5%). Three studies provided a comparison of the various SGAs. Two studies were conducted with antipsychotic-naïve patients as a comparator, and another study used the general population. Regarding outcomes, diabetes ( $n = 32$ , 80%) was the most commonly studied, followed by dyslipidemia ( $n = 9$ , 22.3%), hypertension ( $n = 7$ , 17.5%), hyperglycemia/ketoacidosis ( $n = 4$ , 10.0%), and weight gain/obesity ( $n = 3$ , 7.5%); we did not find any study reporting the risk of occurrence of metabolic syndrome as a whole.

### Risk of Bias Within Studies

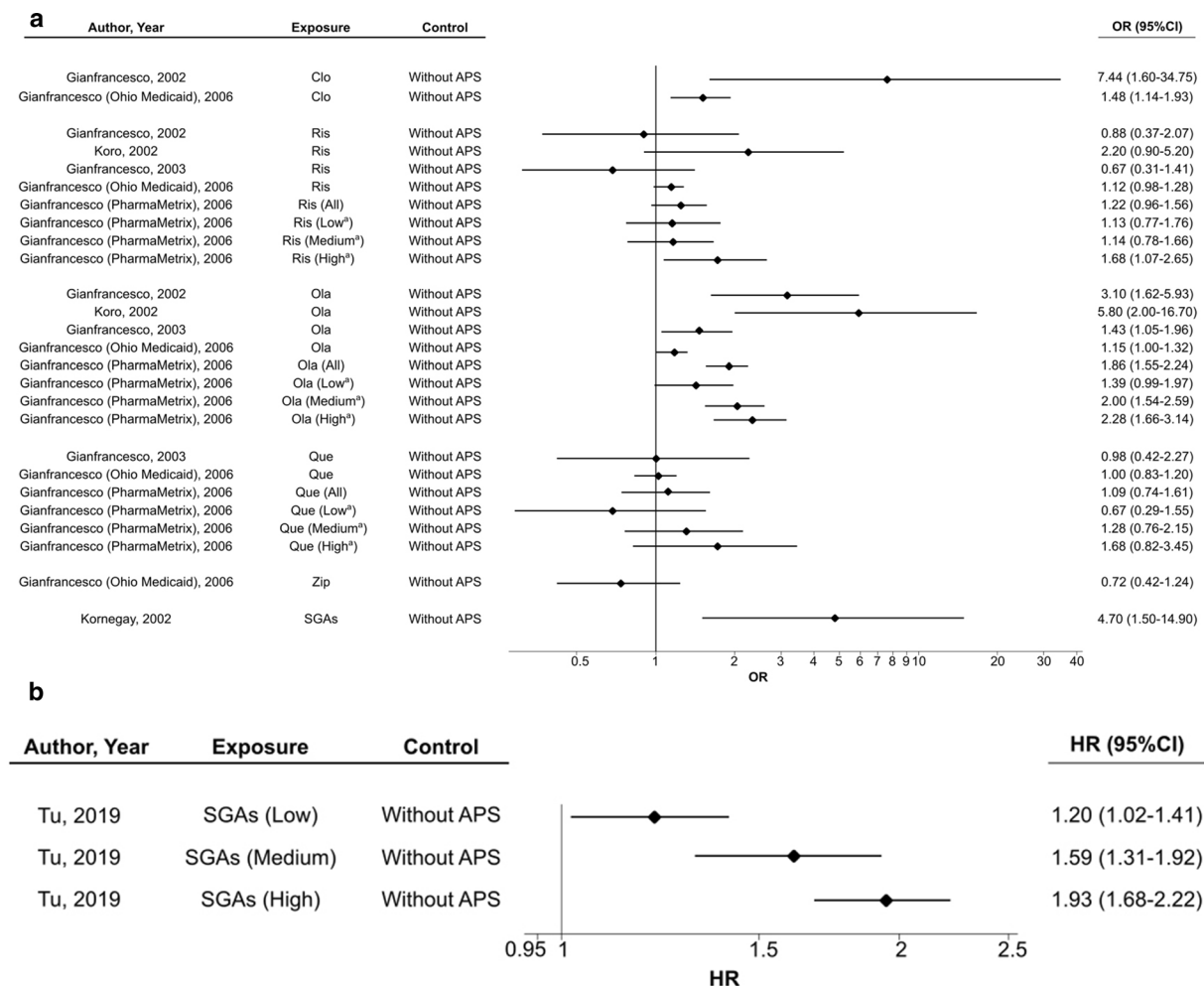
The evaluation of the quality of the studies using the Newcastle–Ottawa scale is presented

in Supplementary Table 3 for the cohort studies and in Supplementary Table 4 for the case–control studies. Six (23.1%) of the 26 cohort studies and 1 (7.1%) case–control study had at least one dimension categorized as poor quality.

### Results of Individual Studies

#### *Studies Conducted in Adults*

**Diabetes** The results of the studies comparing the risk of occurrence of diabetes with individual antipsychotics compared to subjects who did not receive antipsychotics are presented in Fig. 2a. Two studies showed that clozapine is associated with an increased likelihood of occurrence of diabetes, with heterogeneous



**Fig. 2 a** Risk of diabetes in adults who received second-generation antipsychotics compared to subjects who did not receive antipsychotics (binary outcome). <sup>a</sup>In Gianfrancesco et al. [16] low, medium, and high dose corresponded to the bottom, middle, and top third of the daily dose range for each patient subgroup within each antipsychotic category. **b** Risk of diabetes in adults who received second-generation antipsychotics compared to subjects who did not receive antipsychotics (time-to-event outcome). Results are reported for young adults (i.e.,

18–29 years) with low exposure (30–179 cumulative defined daily dose [cDDDs]), medium exposure (180–364 cDDDs), and high exposure (at least 365 cDDDs) compared to subjects who did not receive antipsychotics (exposure less than 30 cDDDs). *APS* antipsychotic, *CI* confidence interval, *Clo* clozapine, *HR* hazard ratio, *Ola* olanzapine, *OR* odds ratio, *Que* quetiapine, *Ris* risperidone, *SGAs* second-generation antipsychotics, *Zip* ziprasidone

results [14, 15]. Five studies evaluated the risk of diabetes in patients treated with risperidone or olanzapine compared to subjects who did not receive antipsychotics [14–18]. Risperidone was not associated with the occurrence of diabetes [14–18], except in one study that showed that a high dose (i.e., a dose within the top third of the daily dose range for the specific subgroup) was

associated with the occurrence of diabetes (OR 1.68, 95% CI 1.07–2.65) [16]. With heterogeneous results regarding the strength of the association, olanzapine was consistently associated with an increased likelihood of diabetes [14–18]; in one study, the higher the dose, the greater the likelihood of developing diabetes with olanzapine [16]. Compared with subjects

who did not receive antipsychotics, quetiapine was not associated with the occurrence of diabetes [15–17], regardless of the dose [16]. A single study evaluating ziprasidone did not find an association with the occurrence of diabetes. Compared to subjects who did not receive an antipsychotic, SGAs as a whole were associated with an increased likelihood of diabetes [19] (Fig. 2a), and the likelihood increased as exposure increased [20] (Fig. 2b).

The results of the comparisons of SGAs with FGAs are presented in Fig. 3a for binary outcomes and Fig. 3b for time-to-event outcomes. Seven studies reported binary outcomes [11, 18, 21–25], showing a lack of association with the occurrence of diabetes for risperidone and quetiapine compared to FGA and mixed results for clozapine and olanzapine (Fig. 3a). A study showed no apparent dose–response association between exposure to low, medium, and high doses of clozapine, risperidone, and quetiapine [24]; low doses of olanzapine were not associated with an increased likelihood of developing diabetes (OR 1.10, 95% CI 0.90–1.50), while medium (OR 1.60, 95% CI 1.30–1.90) and high doses (OR 1.50, 95% CI 1.20–1.80) were associated with an increased likelihood of developing diabetes [24]. Comparisons with FGAs using time-to-event outcomes (Fig. 3b) [26–31] showed mixed results for clozapine, risperidone, and quetiapine, while the results for ziprasidone from three studies showed no significantly increased likelihood of developing diabetes; of the six studies, five showed an association between exposure to olanzapine and the likelihood of developing diabetes with heterogeneous results regarding the strength of the association (the HR varied from 1.15 to 3.66).

Three studies provided head-to-head comparisons among SGAs and two of them using time-to-event outcomes showed no difference among them for the risk of developing diabetes (Supplementary Fig. 1a) [32, 33], while a study using a binary outcome showed a 20% increased likelihood of the occurrence of diabetes in olanzapine-treated patients compared to those treated with risperidone (OR 1.20, 95% CI 1.00–1.43) [34] (Supplementary Fig. 1b). Studies of the risk of developing diabetes in those who

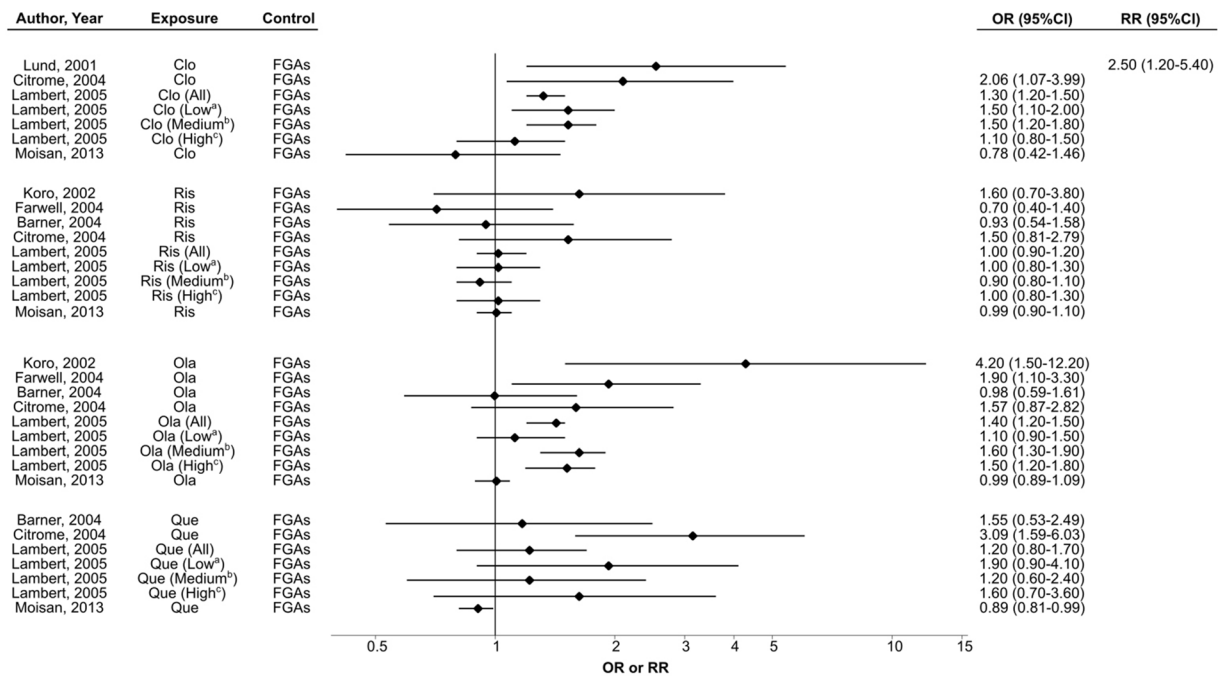
**Fig. 3 a** Risk of diabetes in adults who received second-generation antipsychotics compared to those who received first-generation antipsychotics (binary outcome). Lambert et al. [24] defined <sup>a</sup>low dose as < 7.5 mg for olanzapine, < 3 mg for risperidone, < 300 mg for clozapine, and < 250 for quetiapine; <sup>b</sup>medium dose as 7.5–12.5 mg for olanzapine, 3–6 mg for risperidone; 300–600 mg for clozapine; and 250–500 mg for quetiapine; and <sup>c</sup>high dose as < 12.5 mg for olanzapine, > 6 mg for risperidone, > 600 mg for clozapine, and > 500 mg for quetiapine. **b** Risk of diabetes in adults who received second-generation antipsychotics compared to those who received first-generation antipsychotics (time-to-event outcomes). *Ari* aripiprazole, *CI* confidence interval, *Clo* clozapine, *FGAs* first-generation antipsychotics, *HR* hazard ratio, *Ola* olanzapine, *OR* odds ratio, *Que* quetiapine, *Ris* risperidone, *RR* relative risk, *Zip* ziprasidone

received SGAs using comparators other than not receiving antipsychotics, FGAs, or head-to-head comparisons are presented in Supplementary Fig. 2 for binary outcomes and Supplementary Fig. 3 for time-to-event outcomes [35–40]. Among these latter studies, Rajkumar et al. [39], in young adults with schizophrenia, showed that the three individual antipsychotics analyzed, namely, clozapine, olanzapine, and aripiprazole, were associated with a significantly increased likelihood of developing diabetes compared with antipsychotic-naïve patients. Nielsen et al. [38] also used antipsychotic-naïve patients as comparators and reported an increased likelihood of developing diabetes for clozapine and olanzapine but a reduced likelihood of developing diabetes for aripiprazole; they reported no association for risperidone, quetiapine, and ziprasidone.

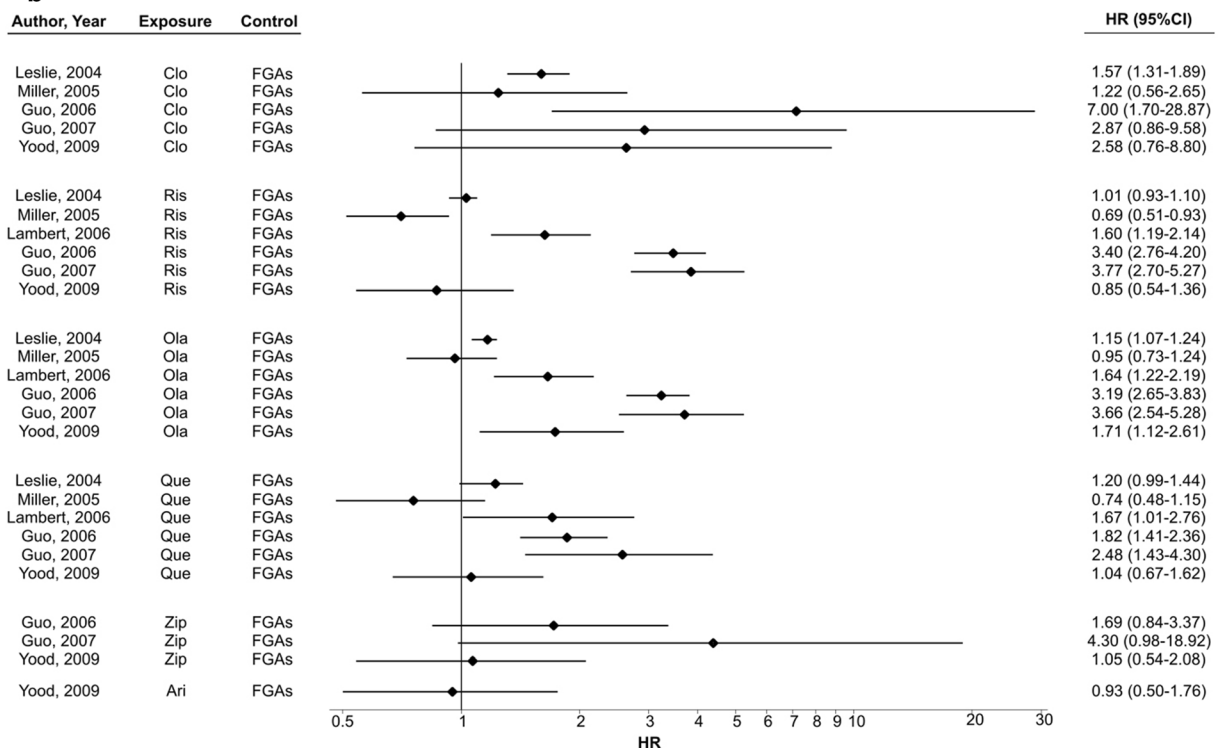
**Diabetes-Related Complications** Two studies evaluated the risk of developing diabetes-related complications, such as hyperglycemia crisis, ketoacidosis, and a hyperosmolar hyperglycemic state [29, 41]. One of the studies excluded patients with a previous diagnosis of diabetes [29]. The other study did not exclude patients with diabetes, but most patients did not have a diagnosis of diabetes [41]. These studies showed an increased likelihood of these complications with clozapine (HR 3.75, 95% CI



**a**



**b**



1.39–10.09) and olanzapine (HR 1.77, 95% CI 1.05–2.98) compared to FGAs and no difference between olanzapine and risperidone or between quetiapine and risperidone in this regard (Fig. 4).

**Obesity and Weight Gain** We found a single study that evaluated the risk of occurrence of obesity with SGAs, reporting that, compared to FGAs, risperidone, quetiapine, ziprasidone, and aripiprazole were not associated with the occurrence of obesity (the effect sizes were not reported), while olanzapine was associated with a reduced likelihood of occurrence of obesity (OR 0.60, 95% CI 0.36–1.00) [42].

Two studies reported the risk of weight gain with olanzapine and risperidone compared to the risk with FGAs [23] (Supplementary Fig. 4) and the risk with olanzapine and quetiapine compared to lithium [35] (Supplementary Fig. 5). All three SGAs were associated with an increased likelihood of weight gain compared with the controls.

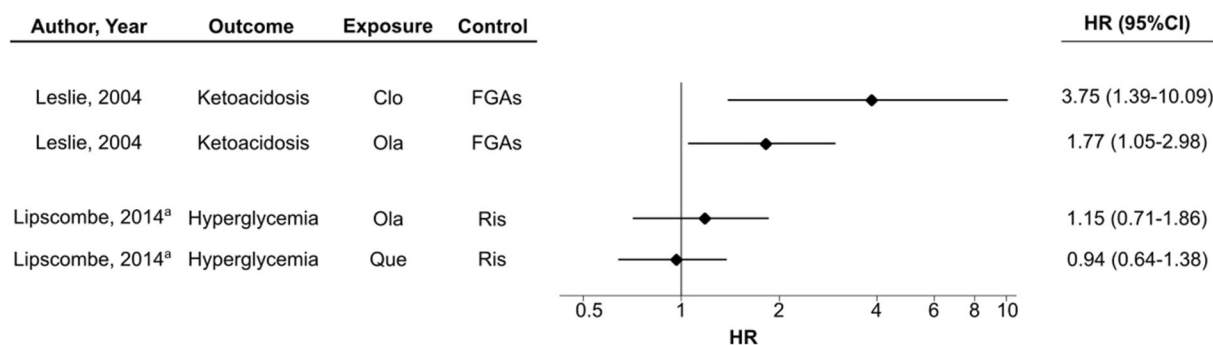
**Dyslipidemia** Seven studies reported the risk of developing dyslipidemia with SGAs in adults (Fig. 5a, b) [11, 36, 40, 43–46]. The results of two studies indicated that aripiprazole was not associated with an increased likelihood of developing dyslipidemia, while clozapine was consistently associated with the occurrence of dyslipidemia in three studies. Risperidone,

olanzapine, quetiapine, and ziprasidone showed mixed results. Overall, SGAs were associated with an increased risk of developing dyslipidemia compared to patients without schizophrenia [36] and the general population [43] but not compared to FGAs [43, 46].

**Hypertension** The results of the six studies that evaluated the potential association between treatment with SGAs and the risk of hypertension [11, 35, 36, 42, 46, 47] are presented in Fig. 6a, b. Two studies conducted by the same research group reported an increased risk of occurrence of hypertension with ziprasidone compared to FGAs; in those studies, the authors reported no association with hypertension for risperidone, olanzapine, quetiapine, and aripiprazole [42, 46]. In another study, compared with lithium, olanzapine was associated with a higher likelihood of developing hypertension, but quetiapine was not [35].

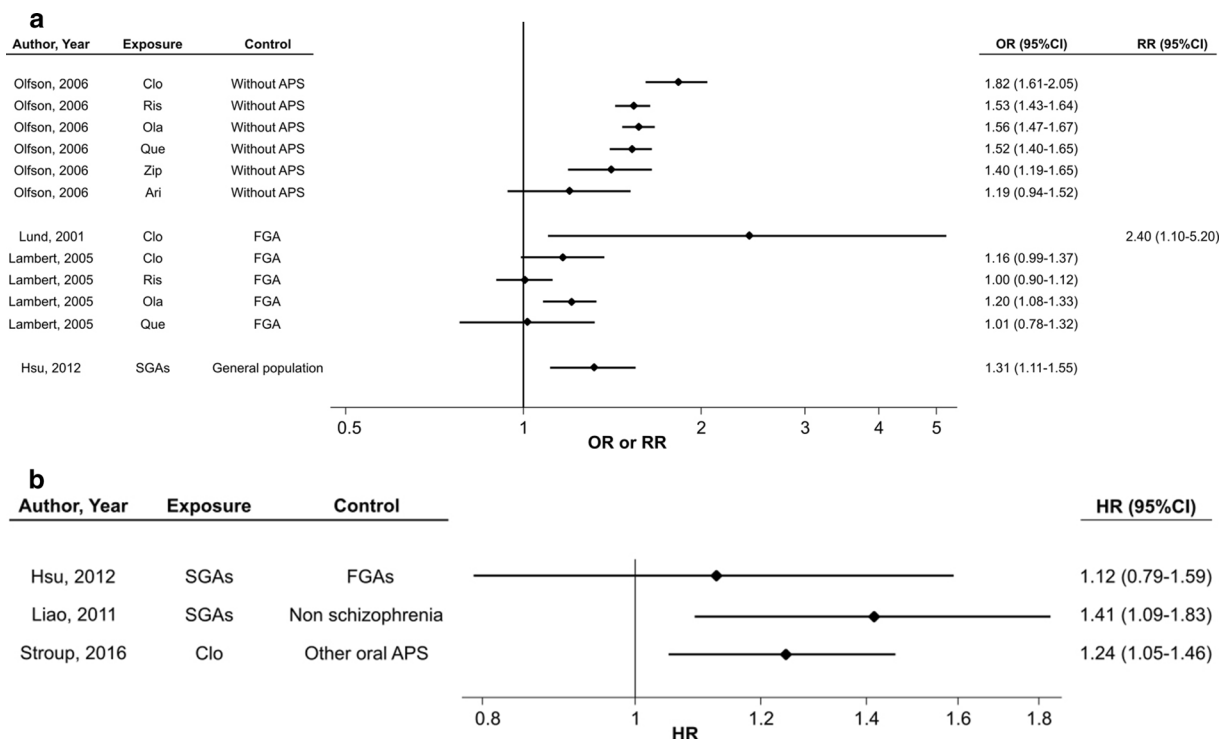
#### Studies Conducted in Patients Aged 65 Years or Older

In this review, six studies were conducted specifically in patients aged 65 years or older [25, 48–52], and one study reported separate results for patients within this age stratum [41]. The results regarding the risk of occurrence of diabetes are mixed but consistently show that SGAs as a whole are associated with an



**Fig. 4** Risk of hyperglycemia-related complications in individuals who received second-generation antipsychotics (time-to-event outcomes). *CI* confidence interval, *Clo* clozapine, *FGAs* first-generation antipsychotics, *HR* hazard ratio, *Ola* olanzapine, *Que* quetiapine, *Ris* risperidone.

<sup>a</sup>Hyperglycemia was defined as the first hospital admission in the 365 days following drug initiation that was associated with a preadmission diagnosis of hyperglycemia, diabetic ketoacidosis, or a hyperglycemic hyperosmolar state based on ICD-9 and ICD-10 diagnostic codes



**Fig. 5 a** Risk of dyslipidemia in individuals who received second-generation antipsychotics (binary outcomes). Note: a study conducted by Jerrell et al. [46] reported that risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole were not associated with an increased likelihood of dyslipidemia, but the authors did not report the specific results for these SGAs. **b** Risk of dyslipidemia in

individuals who received second-generation antipsychotics (time-to-event outcomes). *APS* antipsychotic, *Ari* aripiprazole, *CI* confidence interval, *Clo* clozapine, *FGAs* first-generation antipsychotics, *HR* hazard ratio, *Ola* olanzapine, *OR* odds ratio, *Que* quetiapine, *Ris* risperidone, *RR* relative risk, *SGAs* second-generation antipsychotics, *Zip* ziprasidone

increased likelihood of occurrence of diabetes-related complications (Fig. 7). One study evaluated the head-to-head risk of metabolic disorders in this population [41], showing that quetiapine was associated with a lower likelihood of developing diabetes-related complications than risperidone (HR 0.69, 95% CI 0.53–0.90), and olanzapine and risperidone did not differ in terms of the risk of developing diabetes-related complications (HR 1.13, 95% CI 0.87–1.48) (Fig. 8).

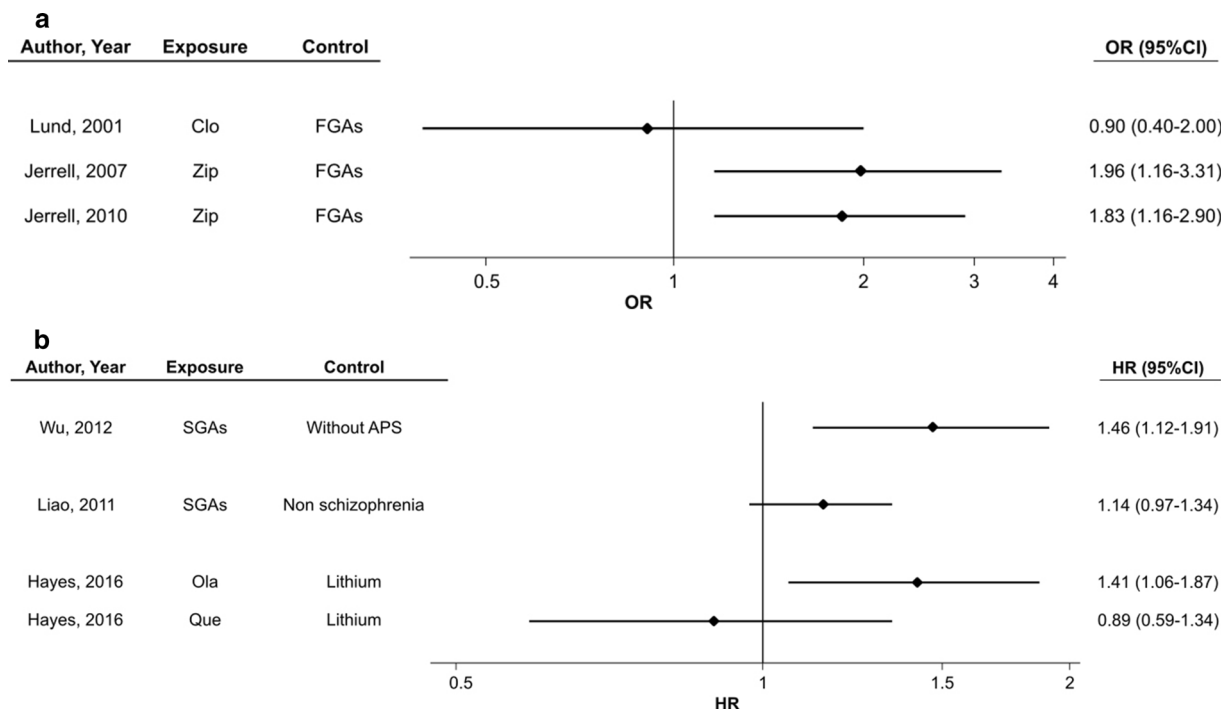
**Polypharmacy with Antipsychotics**

Nine studies explicitly stated that they took into consideration the use of a combination of antipsychotics and five of them reported specific results for that subgroup (Supplementary Table 1). Citrome et al. found that, compared to

FGAs, the use of two or more SGAs was associated with an increased likelihood of occurrence of diabetes among psychiatric inpatients (OR 2.86, 95% CI 1.57–5.2) [22], and Lambert et al. found that any combination of SGAs and FGAs was associated with an increased likelihood of occurrence of diabetes in patients with schizophrenia (OR 1.6, 95% CI 1.3–1.9) [24]. However, three additional studies did not find an association between antipsychotic polytherapy and the occurrence of diabetes compared to untreated patients [14, 17] or patients receiving FGAs [25].

**Potential Determinants of Occurrence of Metabolic Disorders**

Twenty studies reported the results of potential determinants other than the specific

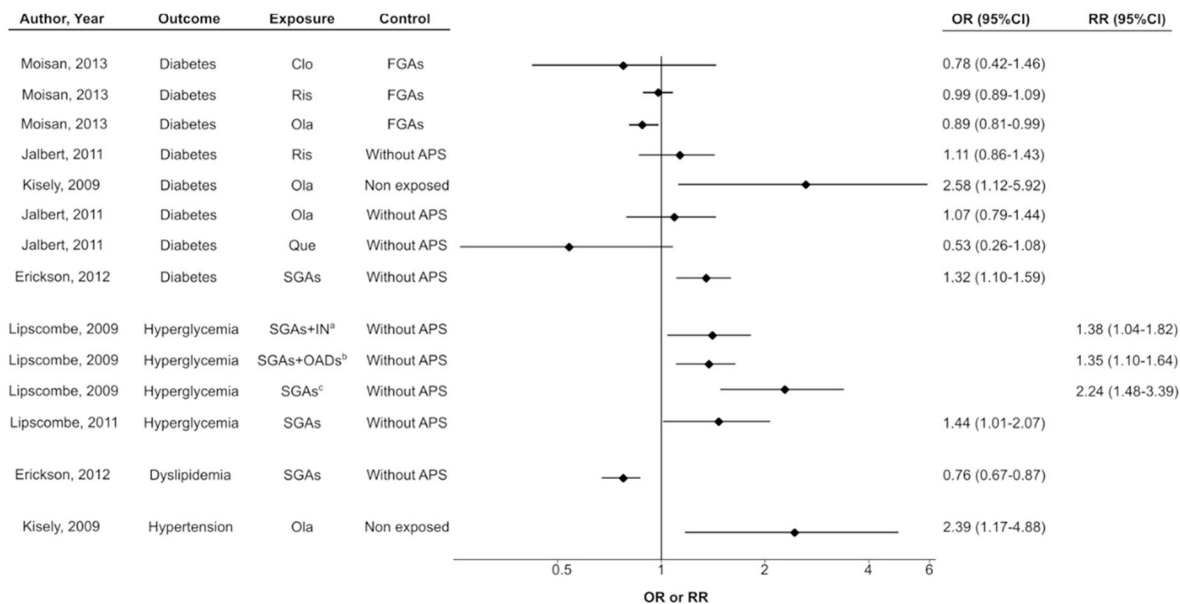


**Fig. 6 a** Risk of hypertension in individuals who received second-generation antipsychotics (binary outcomes). Jerrell and McIntyre [46] reported that risperidone, olanzapine, quetiapine, and aripiprazole were not associated with an increased likelihood of hypertension, but they did not report the specific results for these SGAs. **b** Risk of

hypertension in individuals who received second-generation antipsychotics (time-to-event outcomes). *APS* antipsychotic, *CI* confidence interval, *Clo* clozapine, *FGAs* first-generation antipsychotics, *HR* hazard ratio, *Ola* olanzapine, *OR* odds ratio, *Que* quetiapine, *SGAs* second-generation antipsychotics, *Zip* ziprasidone

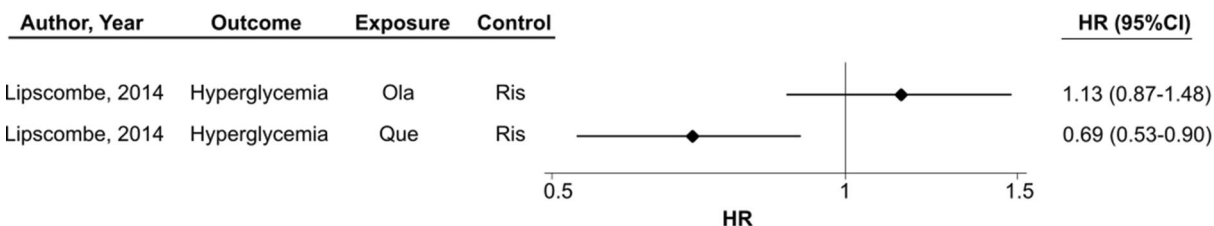
antipsychotic of the occurrence of diabetes (Supplementary Table 5) [14–17, 19–28, 30, 31, 33, 36–38]. The factors most frequently reported as being associated with the occurrence of diabetes were age [14–16, 21, 36–38], nonwhite race [15, 21, 24], length of exposure [16, 17, 25, 33], obesity/body mass index (BMI) [15, 16, 19, 20, 23, 26, 27, 31], hypertension [19, 20, 26, 27, 36], dyslipidemia [20, 21, 26, 36, 37], and treatment with concomitant medications, such as beta-blockers [15–17, 24, 31]; thiazides [15, 16, 24, 31]; angiotensin-converting enzyme inhibitors [24]; antihypertensives [38]; lipid-lowering drugs [38]; specific lipid-lowering drugs, including fibrates [31] and statins [15, 31]; and selective serotonin reuptake inhibitors (SSRIs) [15, 24]. Regarding the type of psychiatric diagnosis, some studies found an increased risk of occurrence of diabetes for those with schizophrenia

[16, 30, 31], bipolar disorder [30], and post-traumatic stress disorder [30], while others found that major affective disorders were associated with a reduced risk of occurrence of diabetes [17]; finally, some studies did not find that the type of diagnosis was a factor associated with the occurrence of diabetes [14, 20, 23]. When psychiatric diagnosis was evaluated as a comorbidity, an increased risk of diabetes was reported for impulse control disorders [26] and substance use disorders [15, 27], while the presence of a comorbid bipolar disorder was associated with a reduced risk of diabetes in one study [33]. We did not find information on the potential determinants of hyperglycemia complications; however, in a bivariate analysis, the incidence of these complications was higher in patients aged 66 years or older than in those aged 18–65 years, overall and for any antipsychotic [41]. Regarding weight gain, Farwell et al.



**Fig. 7** Risk of metabolic disorders in patients aged 65 years or older who received second-generation antipsychotics (binary outcomes). Lipscombe et al. [51] reported results separately for patients treated with insulin (a), patients who received oral antidiabetic agents (b), and

patients who did not receive antidiabetics (c). APS antipsychotic, CI confidence interval, IN insulin, OADs oral antidiabetic drugs, Ola olanzapine, OR odds ratio, Que quetiapine, Ris risperidone, RR relative risk, SGAs second-generation antipsychotics



**Fig. 8** Risk of metabolic disorders in patients aged 65 years or older who received second-generation antipsychotics (time-to-event outcomes). CI confidence interval,

Clo clozapine, HR hazard ratio, Ola olanzapine, OR odds ratio, Que quetiapine, Ris risperidone

[23] reported that baseline weight was associated with a reduced risk of weight gain of at least 7% (OR 0.99, 95% CI 0.96–0.99).

The potential determinants of the occurrence of dyslipidemia were reported in three studies (Supplementary Table 6) [36, 43, 44]. Age [36, 43], the presence of diabetes [36, 43, 44], and the presence of hypertension [36, 43] were reported to be associated with an increased likelihood of developing dyslipidemia.

Studies reporting the potential determinants of the occurrence of hypertension are shown in

Supplementary Table 7. Regarding the potential determinants of the occurrence of hypertension, two studies reported that it increased as age increased [36, 47], and the results regarding sex were conflicting, with one study reporting an increased likelihood of developing hypertension in women (OR 1.38, 95% CI 1.09–1.74) [42] and another study reporting an increased likelihood in men (HR 1.24, 95% CI 1.01–1.53) [47]. One study reported that the presence of diabetes or dyslipidemia was associated with an increased likelihood of hypertension [36].

## DISCUSSION

Randomized controlled trials provide robust evidence of the efficacy of antipsychotics and important information on their tolerability and safety. However, they require selected samples for isolating the drug effects [53]. In addition, these explanatory trials, usually performed for registrational purposes, are focused on the efficacy of drugs and with short-term duration. Therefore, they are not the best option for evaluating infrequent outcomes (e.g., diabetic ketoacidosis) or those that require longer latency periods such it is the case of most metabolic side effects. Therefore, this information should be complemented with the results of long-term—preferably pragmatic—trials or observational studies that better resemble clinical practice.

According to our review, diabetes is the most frequently studied metabolic disorder under real-world conditions using a population-based design; this is consistent with the long-standing interest in the relationship between cardiometabolic disorders, especially diabetes, and psychosis [54]. The results of this review consistently indicate that clozapine and olanzapine are associated with an increased likelihood of developing diabetes in clinical practice. The results for risperidone and quetiapine are mixed, although most studies analyzing time-to-event data indicate that both of these SGAs are associated with an increased likelihood of developing diabetes compared to FGA. Information on ziprasidone and aripiprazole is scant. Ziprasidone was consistently reported to not be associated with an increased likelihood of occurrence of diabetes in the four studies analyzing this outcome compared to patients who did not receive antipsychotics [15] and patients who received FGAs [26, 27, 31]. Only three studies reported data on the risk of diabetes with aripiprazole, showing no increased likelihood of developing diabetes compared to FGA in one study [31]; compared to antipsychotic-naïve patients, a study showed a reduced likelihood of developing diabetes with aripiprazole using a binary outcome [38], while another study showed an increased likelihood using a

time-to-event outcome [39]. Head-to-head comparisons among the SGAs are limited to three studies [32–34], which indicated no difference in two of the paired comparisons [32, 33], including comparisons of aripiprazole with risperidone, olanzapine, quetiapine, and ziprasidone in a study using propensity scores [32]; however, a third comparison showed a slightly increased risk of occurrence of diabetes with olanzapine compared to risperidone [34].

We are not aware of any prior systematic reviews of RCTs evaluating the risk of diabetes with SGAs; however, our findings are fairly consistent with the results of systematic reviews evaluating changes in glucose levels. A recent network meta-analysis compared the effects of 18 antipsychotics on several metabolic parameters from 100 RCTs with a median treatment duration of 6 weeks [8]. The 37 studies that evaluated changes in fasting glucose indicated that clozapine and olanzapine were associated with greater increases in serum glucose concentration, while ziprasidone was associated with the lowest increase [8]. The authors did not find strong evidence of changes in serum glucose concentration with risperidone, quetiapine, ziprasidone, or aripiprazole [8]. In a previous network meta-analysis evaluating changes in glucose levels from baseline that included 47 randomized trials, the authors found that among the antipsychotics included in our review, only olanzapine was associated with a significant increase in glucose compared to placebo and only ziprasidone and risperidone were associated with significantly better results than olanzapine; when ranked using the surface under the cumulative ranking values, ziprasidone was ranked as the best and clozapine and olanzapine as the worst antipsychotics regarding their impact on serum glucose levels [55]. Yu et al. [56], in a meta-analysis of 14 studies in Chinese patients, found a higher likelihood of insulin resistance with olanzapine than with risperidone, ziprasidone, or aripiprazole. Another meta-analysis of studies conducted in healthy volunteers suggested that the occurrence of insulin resistance depends on treatment length [57], reinforcing the need for long-term studies on antipsychotic-induced metabolic disorders.

Although the information is very limited, two studies indicated that SGAs might have a differential effect on the risk of ketoacidosis, with clozapine and olanzapine associated with an increased risk compared to FGAs, and quetiapine and risperidone showing different effects depending on age (i.e., a longer time to the occurrence of hyperglycemic emergencies [i.e., hospitalizations because of hyperglycemia, diabetic ketoacidosis, or hyperglycemic hyperosmolar state] with quetiapine compared to risperidone in elderly patients but not in younger adults). Two studies suggested that SGAs are associated with an increased likelihood of occurrence of hyperglycemic emergencies in elderly patients [51, 52], regardless of whether they are treated with antidiabetics [51]. A systematic review evaluated case reports or case series of diabetic ketoacidosis with type 1 diabetes mellitus etiology, but the publication bias and uncontrolled design inherent in these reports do not allow us to assess the risk of this complication with SGAs [58]. However, it is important to stress the relevance of this potential complication associated with the use of SGAs since ketoacidosis has been associated with a high mortality rate, especially in patients with significant comorbidities and in elderly patients [59].

There is a large body of evidence based on RCTs concerning the risk of obesity or weight gain associated with SGAs [8, 57, 60]. Notably, we found only one study that evaluated obesity and two studies that evaluated weight gain. Although it is only speculative, we believe that this gap in information from population-based studies could be related to the lack of or poor information about this topic in administrative databases. Most recent meta-analyses of short-term RCTs show that there are important differences among various SGAs in regard to the degree of weight gain or the risk of clinically relevant weight gain [8, 60, 61]. Although more limited because of the small number of studies, the results from long-term RCTs support these differences [62].

The few studies evaluating antipsychotic-induced dyslipidemia included in our review suggest that aripiprazole is not associated with an increased risk of this metabolic effect, while

clozapine is, with the remaining antipsychotics showing mixed results. The results of a meta-analysis of short-term RCTs show that among the antipsychotics included in our review, risperidone, ziprasidone, and aripiprazole were not associated with deleterious effects on lipid parameters, while clozapine, olanzapine, and quetiapine were associated with increases in total cholesterol and triglycerides, and olanzapine and quetiapine were associated with increases in low density lipoprotein (LDL) cholesterol [8]. A recently published randomized short-term comparison of seven antipsychotics that included risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole showed that all of these antipsychotics were associated with significant increases in triglycerides and that risperidone, olanzapine, and quetiapine were also associated with significant increases in LDL cholesterol [63]. When evaluated as a change from baseline in the diagnosis of hyperlipidemia, ziprasidone remained unchanged, risperidone showed an increase in the proportion of patients with that diagnosis but was not statistically significant, and aripiprazole and, to a greater extent, olanzapine and quetiapine showed a statistically significant increase in the proportion of patients with hyperlipidemia at the end of the follow-up [63]. More long-term studies are needed on SGAs to further clarify their impact on lipid parameters.

Although six studies evaluated the potential association between SGAs and the occurrence of hypertension, no confirmatory evidence can be drawn from them. It appears that SGAs are associated with an increased likelihood of hypertension, and among the individual agents, in two studies, ziprasidone was associated with an almost two-fold increase in the likelihood of developing hypertension compared to FGA [42, 46]. However, these studies of ziprasidone were conducted by the same research group using the same database and therefore these findings require replication. The limited information from randomized comparisons is not consistent. The short-term randomized head-to-head comparison of seven antipsychotics mentioned above showed no significant changes in blood pressure with any of the antipsychotics studied [63]. However, a secondary analysis of

the 3-month results from the Clinical Antipsychotics Trials of Intervention Effectiveness (CATIE) found that in patients with baseline systolic blood pressure (SBP) above the median (122 mmHg), all of the antipsychotics studied showed a decrease in SBP, while in patients with SBP below the median, SBP among ziprasidone-treated patients increased to a greater extent than among those treated with perphenazine (+ 8.6 mmHg vs. + 4.2 mmHg,  $p = 0.005$ ) [64].

The potential determinants of the occurrence of diabetes found in our review included age, nonwhite race, obesity/BMI, hypertension, dyslipidemia, and treatment concomitant drugs such as antihypertensives, lipid-lowering drugs, and SSRIs; these factors are consistent with those reported in the literature for the general population [65–67]. However, it is important to stress that, probably because of the limitations of the information included in administrative databases, the studies included in this review did not evaluate many well-demonstrated nongenetic factors of type 2 diabetes mellitus, such as psychosocial, lifestyle, and dietary factors. Therefore, our picture of the risk factors for antipsychotic-induced diabetes is incomplete. Regarding antipsychotic treatment, several of the studies included in this review found that the risk of diabetes increases with the length of exposure. In our view, this finding is important, because among other implications, it reinforces the limitations of short-term pivotal studies on antipsychotics for establishing the metabolic profile of antipsychotics and the need for the continuous monitoring of metabolic parameters in patients who receive treatment with antipsychotics. Regarding the latter, despite the availability of recommendations for monitoring the physical health of patients with severe mental disorders, adherence to those recommendations is far from optimal [68]. Although the information on potential determinants of hyperlipidemia and hypertension is very limited, another important issue is that all of these metabolic disorders seem potential factors associated with the development of the other metabolic disorders.

In addition to the other limitations mentioned above, the literature on the metabolic adverse effects of second-generation

antipsychotics has some other important limitations. The most common comparator in the studies included in this review was FGAs as a group, and the risk of metabolic side effects differs from one FGA to another. We did not find any population-based study reporting data on metabolic adverse events of long-acting injectable SGAs. Long-acting antipsychotics are associated with an increased adherence compared to oral antipsychotics [69], and consequently to a greater exposure to these drugs that in turn could be associated with a greater risk of metabolic side effects. Supporting this hypothesis, it has been reported that, compared to oral SGAs, long-acting injectable SGAs are associated with a greater risk of some adverse events, such as extrapyramidal and prolactin-related symptoms [70, 71], and some metabolic disorders, such as changes in LDL cholesterol [72]. Despite the benefits of long-acting injectable SGAs [73], it is important to know the metabolic risk associated with these formulations to facilitate the rational use of these compounds.

On the basis of the results of a meta-analysis of RCTs, the SGAs associated with better metabolic profiles are, in alphabetical order, aripiprazole, brexpiprazole, cariprazine, lurasidone, and ziprasidone [8]. However, according to our results, the worst metabolically characterized SGAs are ziprasidone and aripiprazole, and we did not find any population-based studies evaluating brexpiprazole, cariprazine, or lurasidone.

Finally, although our evaluation of the quality of the studies using the Newcastle–Ottawa scale suggests that the overall quality of the studies is fairly good, it is important to stress that only five of the studies included in this review used an adequate methodology to try to control for confounding by indication (e.g., propensity scores). Confounding by indication is a significant threat to the internal validity of observational studies of interventions [74], including the study of antipsychotic-induced metabolic disorders [75], and its potential impact was recognized by several of the authors of the studies included in this review [11, 20, 22, 39].



## CONCLUSIONS

Our results indicated that although there are relevant differences among SGAs concerning the risk of metabolic disorders, with ziprasidone and aripiprazole at one extreme of the risk continuum and olanzapine and clozapine at the other, it appears that none of the SGAs included in our review are fully devoid of these disturbances. This is a relevant finding since recent data from 14 developed countries indicates that olanzapine is the second most frequently prescribed antipsychotic in adults [76], and clozapine is increasingly prescribed [77] in addition to being the only indicated and evidence-based treatment option for treatment-resistant schizophrenia [78]. Importantly, our results suggest that the presence of a particular metabolic disorder acts as a risk factor for the occurrence of other metabolic disorders. This finding reinforces the recommendation from psychiatric clinical practice guidelines that in any patient with a metabolic disorder, it is also important to assess other contributors to metabolic syndrome [7]. In addition, as recommended in the general guidelines for the management of individual metabolic conditions in the general population, the management of these complications of antipsychotic treatment requires an integrated approach since the presence of one disorder may affect the management of the other [79–81]. However, important gaps in the routine screening of metabolic disorders are found in clinical practice [82]. The barriers associated with these gaps include healthcare system-related factors such as the fragmentation of care and time and resources constraints, and patient-related factors such as disability resulting from mental health conditions, knowledge, and skills of the patients [83].

Despite almost 20 years of real-world research using population-based studies, many gaps in the understanding of the metabolic side effects of SGAs still exist. Future research should help to characterize the metabolic profile of the increasingly used long-acting injectable antipsychotics and of new oral SGAs identified in RCTs that have a better metabolic profile, such

as brexpiprazole, cariprazine, or lurasidone, and to ascertain to what extent and how antipsychotic-induced metabolic disorders contribute to the burden of disease.

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