Antidepressant Use and Diabetes Mellitus Risk: A Meta-Analysis

Original Article

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Background: Epidemiologic studies have reported inconsistent findings regarding the association between the use of antidepressants and type 2 diabetes mellitus (DM) risk. We performed a meta-analysis to systematically assess the association between antidepressants and type 2 DM risk.

Methods: We searched MEDLINE (PubMed), EMBASE, and the Cochrane Library (through Dec 31, 2011), including references of qualifying articles. Studies concerning the use of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), or other antidepressants and the associated risk of diabetes mellitus were included.

Results: Out of 2,934 screened articles, 3 case-control studies, 9 cohort studies, and no clinical trials were included in the final analyses. When all studies were pooled, use of antidepressants was significantly associated with an increased risk of DM in a random effect model (relative risk [RR], 1.49; 95% confidence interval [CI], 1.29 to 1.71). In subgroup analyses, the risk of DM increased among both SSRI users (RR, 1.35; 95% CI, 1.15 to 1.58) and TCA users (RR, 1.57; 95% CI, 1.26 to 1.96). The subgroup analyses were consistent with overall results regardless of study type, information source, country, duration of medication, or study quality. The subgroup results considering body weight, depression severity, and physical activity also showed a positive association (RR, 1.14; 95% CI, 1.01 to 1.28). A publication bias was observed in the selected studies (Egger's test, P for bias = 0.09).

Conclusion: Our results suggest that the use of antidepressants is associated with an increased risk of DM.

Keywords: Meta-Analysis; Antidepressive Agents; Serotonin Uptake Inhibitors; Tricyclic Antidepressive Agents; Diabetes Mellitus

INTRODUCTION

Antidepressants are now one of the most frequently prescribed medications in outpatient medicine.[1] They are used widely not only for treating depression but also for controlling fibromyalgia[2] and postmenopausal problems.[3] As use of antidepressants increases, so does interest in their potential side effects. It has been reported that tricyclic antidepressants can cause weight-gain[4] and cardio-toxic effects when taken in overdose.[5] Recently, it has been suggested that the use of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) may increase the risk of mortality, and SSRIs the risk of hemorrhagic and fatal stroke.[6]

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Furthermore, recent reports suggest that antidepressants may be associated with an increased risk of diabetes mellitus (DM).[7]

There is controversy regarding the relationship between the use of antidepressants and the risk of DM. Some studies have found an increased risk of DM among antidepressant drug users,[8,9] while others found no firm evidence.[10,11] There is also disagreement regarding the reason for the association between the use of antidepressants and DM risk. Some studies propose that antidepressants may bio-pharmacologically affect glucose homeostasis and insulin sensitivity.[12,13] On the other hand, it has been hypothesized that our understanding of the relationship between antidepressants and DM is confounded by depression, which has long been recognized to increase the incidence of DM.[14] Therefore, in the present study, we aimed to investigate the association between the use of antidepressants and the risk of DM via a meta-analysis of cohort studies, case-control studies and randomized clinical trials (RCT).

METHODS

1. Data Sources and Searches

Our review followed the Meta-analysis of Observational Studies in Epidemiology guidelines and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15] We performed our search in MEDLINE (PubMed) (inception to Dec 31, 2011), EMBASE (inception to Dec 31, 2011), and the Cochrane Library (inception to Dec 31, 2011) by using selected common key words regarding antidepressants and diabetes mellitus in case-control studies, cohort studies, and RCTs.

In addition, we searched the bibliographies of relevant articles in order to identify additional studies of interest. As the keywords for the literature search, we used 'antidepressants' OR 'antidepressive agents' OR 'antidepressive drugs' OR 'antidepressive medications' OR 'selective serotonin reuptake inhibitors' OR 'SSRIs' OR 'tricyclic antidepressants' OR 'TCAs' for the exposure factors and 'diabetes' OR 'iabetes mellitus' OR 'DM' for the outcome factors.

2. Study Selection and Data Extraction

We searched case-control studies, cohort studies and RCTs reporting an association between antidepressive drugs and diabetes mellitus risk. Included studies had to contain both of the following: a risk estimate (odds ratio, relative risk, or hazard ratio) and its 95% confidence interval (CI). We only selected articles written in English and excluded those studies with no available data for outcome measures.

All studies retrieved from databases and bibliographies were independently reviewed by two authors, and disagreements were resolved by authors' consensus. Of the articles found in the three databases, duplicate articles and those that did not meet the selection criteria were excluded. We extracted the following data from the remaining studies: study name (first author), year of publication, country and design, study period, population characteristics, and type of antidepressants. Adjustment variables were also collected during data extraction. We obtained adjusted estimates with priority rather than those unadjusted.

3. Quality Assessment

We assessed the methodological quality of included studies using the Newcastle-Ottawa Scale (NOS) for quality of case control and cohort studies in meta-analyses.[16] The NOS is quite comprehensive and has been partially validated for assessing the quality of non-randomized studies in meta-analysis. The NOS is judged on three broad subscales: the selection of the study groups (4 items), the comparability of the groups (1 item), and the ascertainment of the exposure or outcome of interest for case-control or cohort studies, respectively (3 items). A 'star system' (range, 0 to 9) has been developed for assessment. In the current study, we considered a study awarded 8 or more stars as a high-quality study, as standard criteria have not been established.

4. Statistical Analysis

The outcome of the meta-analysis was the risk for diabetes mellitus. We also conducted subgroup analysis by type of study design (case-controls studies, cohort studies), type of antidepressants (SSRIs, tricyclic antidepressants [TCAs]), duration of antidepressant use (within 12 months, greater than 12 months), source of drug information (self-report, database), country (USA, Europe), adjustment of dependent variables (body mass index [BMI], physical activity, depression symptoms) and study quality (high, low). We also performed subgroup analyses about a specific antidepressant if results of the individual antidepressant were reported by two or more studies

(e.g., citalopram, paroxetine, trazodone).

We pooled the estimates with a 95% CI based on both fixed-effects and random-effects models. Heterogeneity was assessed by using Higgins I^2 value, which measures the percentage of total variance across studies that is attributable to heterogeneity rather than chance.[17] Negative I^2 values are set at zero so that I^2 falls between 0% (no observed heterogeneity) and 100% (maximal heterogeneity). We considered an I^2 value greater than 50% to represent substantial heterogeneity and calculated based on the random-effects model.

We used the Woolf method (inverse variance method) for a fixed-effect analysis[18] and the DerSimonian and Laird method for a random-effect analysis.[19] Begg's funnel plot and Egger's test were used to identify publication bias. For studies with publication bias, the funnel plot was asymmetrical or the P-value was found to be less than 0.05 using Egger's test. We used Stata SE ver. 12.1 (Stata Co., College Station, TX, USA) for all statistical analysis.

RESULTS

1. Identification of Relevant Studies

Figure 1 shows a flow diagram of the study selection. A total of 2,934 articles were identified by searching the three databases and relevant bibliographies. Through review of titles and abstracts, we excluded 293 duplicate articles and 2,615 articles that did not satisfy the selection criteria. After the full text for the remaining 26 articles was reviewed, 14 articles were excluded, 8 demonstrated insufficient data,[20-27] 3 were reviews or correspondences,[28-30] and 3 were included totally or partially in another article.[31-33] As a result, we included 12 observational studies (3 case-control studies, 9 cohort studies, no RCTs), which ultimately met our inclusion criteria.

2. Study Characteristics and Quality

Table 1 shows the main characteristics of the 12 reviewed studies. All studies were published in the 2000s. The countries in which the studies had been conducted were as follows: the United States (n = 6),[7,8,14,33-35] Netherlands (n = 1),[11] the UK (n = 1),[36] Finland (n = 1),[9] Norway (n = 1),[10] Australia (n = 1),[37] and

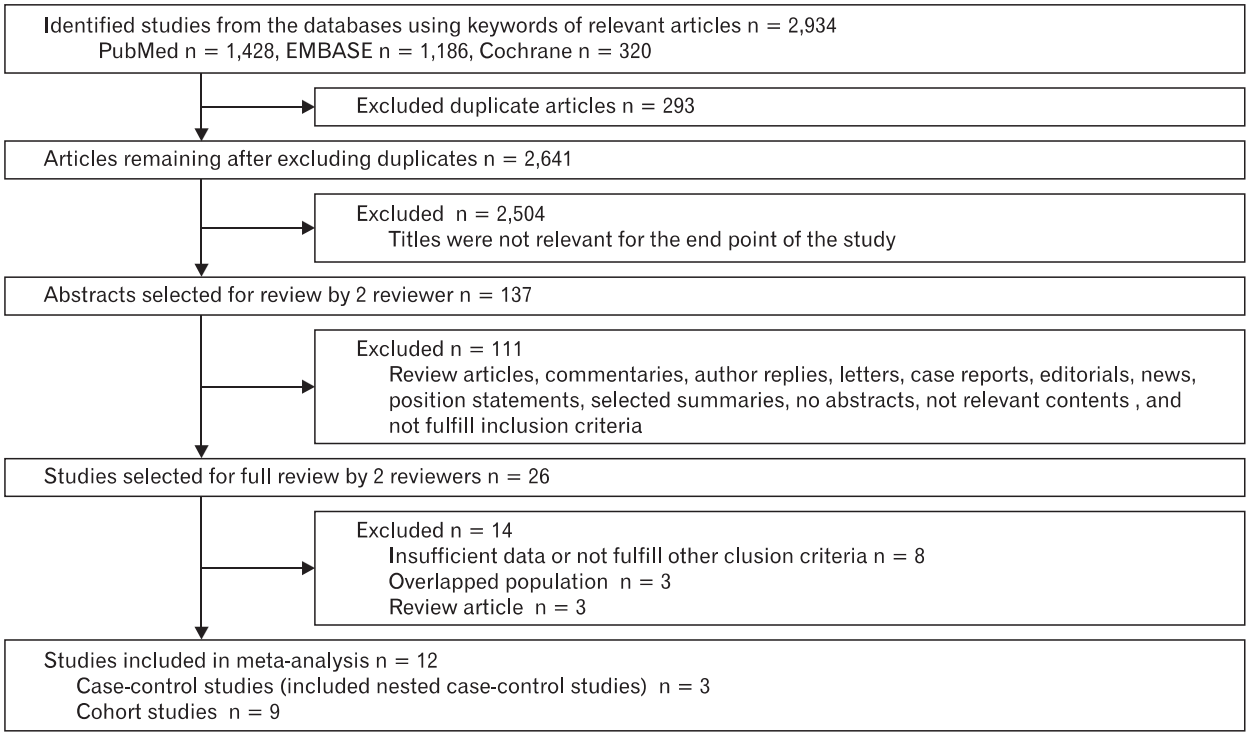

Figure 1. Flow diagram of selecting studies for inclusion in meta-analysis.

Table 1. Characteristics of studies included in the final analysis of antidepressants and risk of diabetes mellitus

	Country	Type of study	Study period	Type of agent	Source of drug information	Adjustment variables	No. of events	No. of patients	Age	NOS
Pan et al.[33] (2012)-HPFS	USA	RCS	1990–2006	SSRIs: fluoxetine, sertraline, paroxetine, citalopram TCAs: amitriptyline, imipramine, nortriptyline Others: no description	Self-report	Common variables: age, ethnicity, marital status, smoking status, alcohol intake, multivitamin and aspirin use, physical activity, metabolic equivalent, FHx of DM, BMI NHS I, II: mental health index NHS II only: menopausal status, hormone use, oral contraceptive	1,287	29,776	43-80	8
NHS I			1996–2008				3,514	61,791	50-79	6
NHS II			1993–2007				1,840	76,858	29-46	6
Khoza et al.[35] (2012)	USA	RCS	2002–2009	SSRI: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline TCA: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine SNRI: desvenlafaxine, duloxetine, venlafaxine Others: bupropion, isocarboxazid, maprotiline, mirtazapine, nefazodone, phenelzine, selegiline, tranylcypromine, trazodone	Database	Age, gender, race/ethnicity, no. of diabetogenic medications, chronic disease score	2,937	44,715	18-64	9
Ma et al.[7] (2011)	USA	PCS	NA	No description	Database	Age, race/ethnicity, education, smoking status at baseline, BMI, hours of recreational activity for week, alcohol intake, total daily energy intake, FHx of DM, hormone therapy use	152,550	NA	Postmenopausal	8

Table 1. Continued

	Country	Type of study	Study period	Type of agent	Source of drug information	Adjustment variables	No. of events	No. of patients	Age	NOS
Wilkins et al.[14] (2011)	USA	RCS	2004–2007	No description	Database	Age, gender, race/ethnicity, marital status, socioeconomic status, physical health, self-reported mental health, hypertension, BMI, smoking status, exercise	359	26,990	>21	8
Kivimaki et al.[9] (2010)	Finland	NCC	1995–2005	SSRI: fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram TCA: clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin Others: venlafaxine, moclobemide, mianserin, trazodone, mirtazapine, milnacipran, reboxetine	Database	Hypertension, coronary heart disease, cerebrovascular disease, cancer	781	4,861	Working-aged men and women	9
Atlantis et al.[37] (2010)	Australian	PCS	1994–2004	No description	Self-report	Demographic variables, lifestyle, functional health, prevalent chronic disease predictors	155	826	>65	8
Jerrell et al.[8] (2010)	USA	RCS	1996–2005	Amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxapram, doxepin, duloxetine, escitalopram, fluoxetine HCl, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, venlafaxine	Database	Age, gender, ethnicity	448	12,015	0–17	8

Table 1. Continued

	Country	Type of study	Study period	Type of agent	Source of drug information	Adjustment variables	No. of events	No. of patients	Age	NOS
Andersohn et al.[36] (2009)	UK	NCC	1990–2005	SSRI: fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram TCA: amitriptyline, amoxapine, clomipramine, dothiepin, doxepin, lofepramine, imipramine, iprindole, nortriptyline, protriptyline, trimipramine, maprotiline, mianserin MAOI: isocarboxazid, moclobemide, phenelzine, tranycypromine Others: bupropion, reboxetine, venlafaxine, nefazodone, mirtazapine, trazodone	Database	BMI, smoking, hypertension, hyperlipidemia, history of medication	2,243	11,206	>30	9
Derijks et al.[13] (2008)	Global	NCC	1969–2005	Cluster 1: sertraline, fluvoxamine, paroxetine, venlafaxine, fluoxetine, citalopram, clomipramine Cluster 2: amitriptyline, doxepin, imipramine Cluster 3: maprotiline, nortriptyline, mianserin, mirtazapine Cluster 4: trazodone	Database	Age, gender, reporting year, hypo-or hyperglycemia-inducing medication	1,953	190,339	>18	9
Rubin et al.[34] (2008)-PLB* Rubin et al.[34] (2008)-ILS†	USA	PCS	1997–2001	No description	Self-report	Age, sex, race/ethnicity, education, FBS, weight, and weight change	270 130	1,082 1,079	>25	8

Table 1. Continued

	Country	Type of study	Study period	Type of agent	Source of drug information	Adjustment variables	No. of events	No. of patients	Age	NOS
Knol et al.[11] (2007)	Netherland	RCS	1996–2003	Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram, clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin, venlafaxine, moclobemide, mianserin, trazodone, mirtazapine, milnacipran, reboxetine	Database	Age, sex, Chronic Disease Score (heart disease, respiratory illness, cancer, ulcer, high cholesterol)	499	41,927	NA	7
Raeder et al.[10] (2006)	Norway	RCS	1997–1999	SSRI: paroxetine, citalopram, sertraline, fluoxetine, fluvoxamine	Self-report	Age, gender, smoking, coffee, alcohol, physical exercise, educational level, anxiety, depression, and use of cholesterol-lowering medication	452	24,847	40–49, 70–74	7

NOS: Newcastle-Ottawa Quality Assessment Scale, HPFS: Health Professionals Follow-up Study, RCS: Retrospective Cohort Study, SSRIs: selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants, FHx: family history, DM: diabetes mellitus, BMI: body mass index, NHS: Nurses' Health Study, SNRI: serotonin and norepinephrine reuptake inhibitor, PCS: Prospective Cohort Study, NCC: Nested Case-Control study, MAOI: monoamine oxidase inhibitor, PLB: protective lifestyle behavior, ILS: intensive lifestyle intervention, FBS: fasting blood glucose, NA: not available.
*Standard lifestyle group. †Intensive lifestyle group.

Table 2. Overall and subgroup analyses for use of antidepressants and risk of diabetes mellitus

Factor	No. of studies	Pooled RR (95% CI)		I^2 (%)
		Fixed effect model	Random effect model	
Overall studies		1.31 (1.26–1.37)	1.49 (1.29–1.71)	85.8
Type of antidepressants				
SSRI	8	1.29 (1.20–1.38)	1.35 (1.15–1.58)	75.5
TCA	6	1.44 (1.29–1.59)	1.57 (1.26–1.96)	72.3
Specific antidepressant				
Paroxetine	2	1.40 (1.09–1.80)	1.52 (0.95–2.45)	35.7
Citalopram	2	1.13 (0.85–1.49)	1.13 (0.85–1.49)	0.0
Trazodone	2	1.48 (0.81–2.71)	1.49 (0.75–2.96)	22.5
Country				
USA	9	1.30 (1.24–1.37)	1.50 (1.25–1.80)	90.3
Non-USA	6	1.36 (1.22–1.53)	1.48 (1.18–1.85)	66.6
Type of study				
Case control study	3	1.65 (1.41–1.92)	1.65 (1.41–1.92)	0.0
Cohort study	12	1.29 (1.23–1.35)	1.44 (1.23–1.70)	87.6
Source of drug information				
Self-report	7	1.20 (1.12–1.28)	1.45 (1.18–1.77)	76.2
Database	8	1.40 (1.32–1.48)	1.49 (1.22–1.82)	88.7
Duration of medication (y)				
<1	2	1.26 (1.01–1.57)	1.26 (1.01–1.57)	0.0
≥1	4	1.46 (1.31–1.63)	1.61 (1.30–1.99)	59.6
Adjustment for specific risk factor*				
Body mass index	9	1.21 (1.14–1.28)	1.37 (1.18–1.59)	76.6
Physical activity	7	1.17 (1.11–1.24)	1.18 (1.09–1.27)	21.7
Depression severity	8	1.20 (1.12–1.29)	1.45 (1.17–1.79)	78.0
All above†	4	1.14 (1.05–1.22)	1.14 (1.01–1.28)	38.4
Quality of study				
High (≥8)	11	1.47 (1.39–1.56)	1.67 (1.39–2.01)	84.0
Low (<8)	4	1.13 (1.05–1.21)	1.13 (1.05–1.21)	5.8
Adult or child/adolescence				
Adult	14	1.28 (1.22–1.34)	1.39 (1.23–1.57)	79.1
Child/adolescence	1	2.74 (2.15–3.50)	2.74 (2.15–3.50)	-

RR: relative risk, CI: confidence interval, SSRI: selective serotonin reuptake inhibitor, TCA: tricyclic antidepressant.
*Subgroup of studies including following risk factor as adjustment variable. †Subgroup of studies including depression severity, body mass index, and physical activity as adjustment variable.

multiple countries (n = 1).[13] We identified 15 eligible estimates from 3 nested case control articles,[9,13,36] 6 retrospective cohort studies,[8,10,11,14,33,35] and 3 prospective cohort studies.[7,34,37] Ten studies included both SSRIs and TCAs as antidepressants. Only one study was performed in the young.[8] The mean value for the methodological quality of the included 12 studies using the NOS was 7.9 stars.

3. Overall Risk of DM by Using Antidepressants

As seen in Table 2, the use of antidepressants was significantly associated with an increased risk of DM in overall studies when using both a fixed-effect model (RR, 1.31; 95% CI, 1.26 to 1.37) and random-effect model (RR, 1.49; 95% CI, 1.29 to 1.71). And the overall heterogeneity of the studies was high (I^2 = 85.8%). Figure 2 shows the association between the use of antidepressants and DM risk using a random-effect model.

4. Subgroup Meta-Analyses

As shown in Table 2, SSRI use was associated with an increased risk of DM[8-10,33,35,36] (RR, 1.35; 95% CI, 1.15 to 1.58; n = 8; I^2 = 75.5%) and TCA use was also associated with an increased risk of DM[9,33,35,36] (RR, 1.57; 95% CI, 1.26 to 1.96; n = 6; I^2 = 72.3%) when using the random-effect model. There are only three types of antidepressants (paroxetine, citalopram, and trazodone) which were estimated individually. However, all of them failed to show statistical significance in the random-effect model.

In the included studies, the major country was the USA. But the elevated risk of DM in the USA[7,8,14,33-35] (RR, 1.50; 95% CI, 1.25 to 1.80) was similar to that in other countries[9,10,13,23,36,37] (RR, 1.48; 95% CI, 1.18 to 1.85). According to type of study, the pooled estimate of cohort studies was slightly lower than that of case-control studies. The subgroup analyses by source of drug information were consistent with overall results.

Regarding the duration of medication, the risk of DM in the subgroups over 1 year of use[7,9,13,36] (RR, 1.61; 95% CI, 1.30 to 1.99) was relatively higher than within 1 year of use[13,36] (RR, 1.26; 95% CI, 1.01 to 1.57).

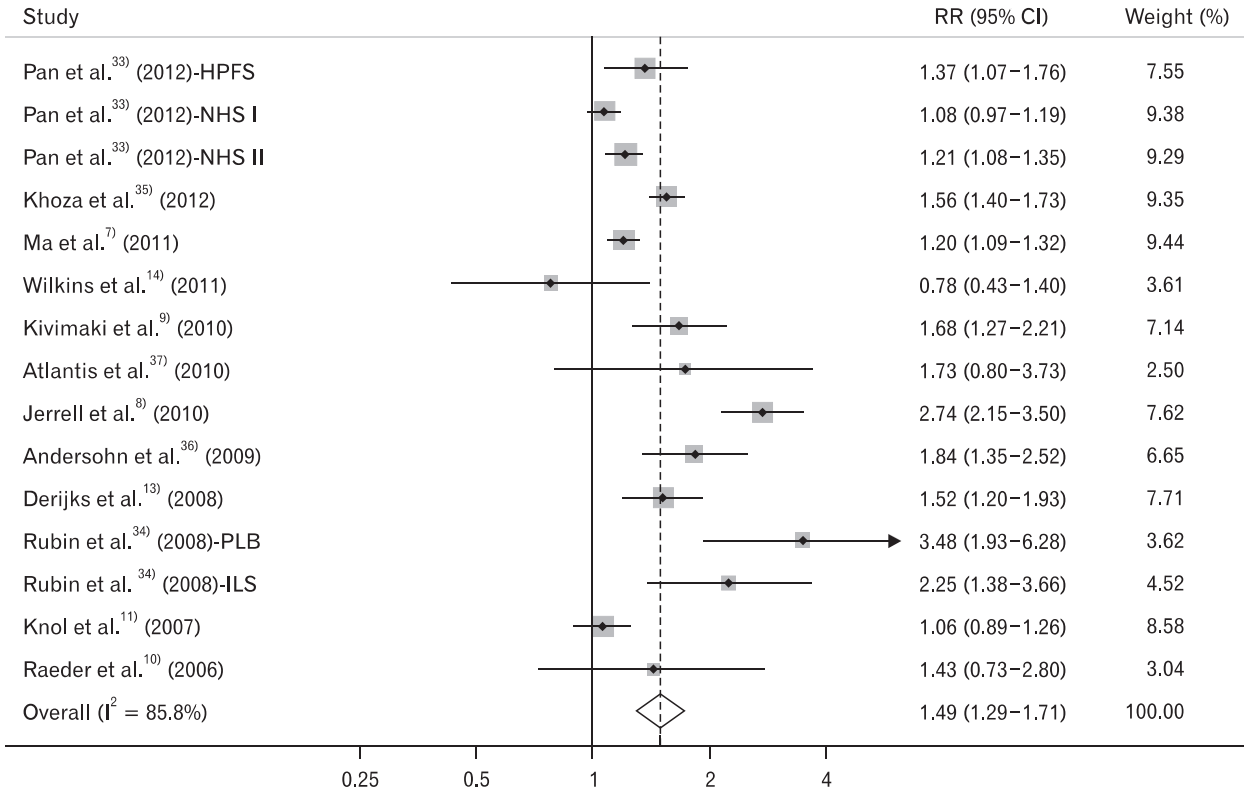

Figure 2. Meta-analyses and pooled relative risk (RR) of diabetes mellitus in antidepressant use comparing not in use. Weights are from random effects analysis. CI: confidence interval, HPFS: Health Professionals Follow-up Study, NHS: Nurses' Health Study, PLB: protective lifestyle behavior, ILS: intensive lifestyle intervention.

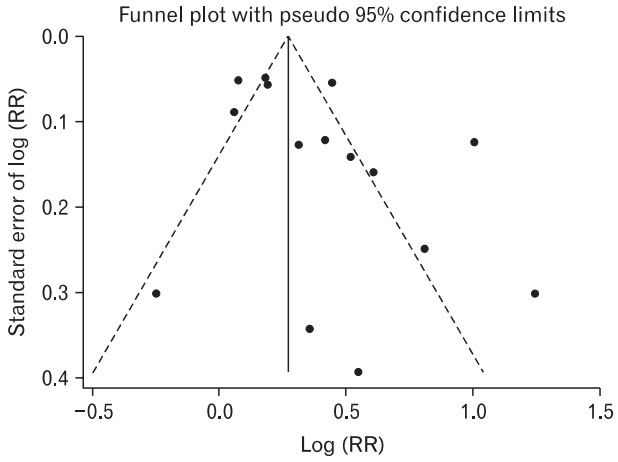

Figure 3. Funnel plots for publication bias. RR: relative risk.

In a subgroup analysis of studies controlling specific risk factors, the associations between antidepressant use and risk of DM were consistent with the overall results. However, a pooled estimate of studies controlling physical activity[7,10,14,33,37] (RR, 1.18; 95% CI, 1.09 to 1.27) was attenuated comparing the overall result in the random effect model.

When we grouped studies by quality, both subgroups showed significantly increased risk of DM associated with the use of antidepressants. The pooled risk ratio of high quality studies[7-9,13,14,33-37] was particularly higher than overall results (RR, 1.67; 95% CI, 1.39 to 2.01).

5. Publication Bias

A publication bias was observed in the selected studies (Egger's test, P for bias = 0.09) (Figure 3).

DISCUSSION

Our meta-analysis suggests that the use of antidepressants is associated with an increased risk of DM. This finding is consistently observed in subgroup analyses by type of antidepressants (TCA, SSRI), study design, country and source of drug information. Generally, TCAs are known to increase the risk of cardiovascular disease as an adverse effect.[5] Relatively, SSRIs were thought to have fewer side effects, less toxicity and be more safe to use.[38] Thus, treatment with SSRIs has been increased to exceed the use of TCAs.[39,40] Given the widespread use of anti-depressants, the implications of this increased risk are serious.

Several possible explanations exist for the association between the use of antidepressants and risk of DM. First, some anti-depressants may cause weight gain, and increased body weight may increase the risk of DM. Among antidepressants, TCA treatments are well known to be associated with weight gain[41,42] through antihistaminergic effects.[41,42] The association between SSRI treatment and weight change is complex. Some randomized controlled trials suggested that there were differences in weight increase caused by individual SSRIs.[43] Paroxetine users reported an increase in body weight.[43] From the results of subgroup analyses by individual antidepressants, we might explain these results as follows. Although there was no statistical significance, paroxetine showed a slightly higher risk ratio than citalopram, which was not reported to cause weight gain.[41] But increased body weight does not fully explain the association between antidepressants and risk of DM. Although there was no study adjusting for change in body weight, the relationship between antidepressants and risk of DM in subgroup analysis by studies controlling basal BMI was positive. These findings suggest that there are additional mechanisms beyond weight gain which explain the association between antidepressants and DM.

Second, depression may act as a confounding variable in the relationship between antidepressant and risk of DM. It has been widely known that depression and DM were related to each other and increased risk reciprocally.[44,45] Antidepressant users might have severe underlying depression that needs to be treated. Thus, the possible effect of depression on the relationship between antidepressant treatment and risk of DM should be considered. To examine this, some studies reported their results with adjustment of depressive symptom severity via variant depression scales. In subgroup analysis of these studies, our findings suggest that antidepressant drug treatment itself and not the depression increase the risk of DM.

Additionally, some explanations exist for the association between antidepressants and DM as the reflection of the depression working as a confounding factor. Antidepressant users might have underlying depression, and depressive patients might have an unfavorable lifestyle.[26] Their lifestyle factors might make depressive patients predisposed to DM.[46] A DM-predisposing lifestyle included low physical activity and a poor diet rich in carbohydrates and saturated fat. In the subgroup meta-analysis

with adjustment for physical activity, the elevated risk of DM was lower than overall results. Unfortunately, other lifestyle factors such as diet or behavior were not considered in previous studies. As a result, we assumed that physical activity level, at least, would have an influence on the risk of DM in antidepressant use.

The results, considering all of the above (body weight, depression severity, and physical activity), were still positive. Moreover, the subgroup analyses were consistently positive regardless of study type, information source, country, and study quality. Consequently, it is not easy to deny the hypothesis that antidepressants themselves affect the risk of DM. This hypothesis is consistent with the result that the risk ratio in the subgroup with longer duration, one year or more, was higher than the subgroup with shorter duration, less than one year. This may reflect a mechanism in which antidepressants increase DM risk by their own neuroendocrine traits. It is assumed that antidepressants affect the hypothalamic–pituitary–adrenal axis, which results in an increase of plasma cortisol level and insulin resistance.[22,47] Some SSRIs might work as inhibitors of insulin signaling and cellular insulin resistance by activation of insulin receptor substrate 1 kinases.[48] TCAs have binding properties for the 5-HT2c receptor, H1 receptor and norepinephrine (NE) reuptake transporter. Inhibition of the NE reuptake transporter increases synaptic NE disposal directly by promoting gluconeogenesis and glycogenolysis.[49] Some TCAs have high affinity for the M3-, α-1-adrenergic receptors. Blockage of M3 receptors in beta cells suppresses insulin secretion and induces hyperglycemia.[50]

Lastly, only one study in the young reported similar results. Therefore, it is necessary to consider the risk of DM in young depressive patients and to perform further studies in the young of age.

Our meta-analysis has several limitations. First, all studies included in our meta-analysis were observational studies, and there seems to be publication bias surrounding this issue. To reduce publication bias, we performed a subsequent search for all relevant studies without any language restrictions, however, none of them met the inclusion criteria. Therefore, the uncertainty about these issues still remains until well-designed RCTs are performed. Secondly, almost all the included studies were from the USA or Europe. The only study which was performed globally did not describe the results by race. Therefore Asian or other racial studies should be performed for generalization of the results. Finally, the included studies were heterogeneous methodologically, and did not contain enough information about medication dosage, health behaviors, or other interventions which might be associated with DM risk. To determine optimal dosage without increasing risk of DM, dosage information will be helpful.

Our results suggest that the use of antidepressants is associated with an increased risk of DM. Physicians who prescribe antidepressants should consider carefully possible adverse effects in their patients, especially those who are already at risk of DM. Further studies are needed specifically to test the effect of individual antidepressants including newly developed antidepressants such as SNRI or norepinephrine-dopamine reuptake inhibitor on DM risk.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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