HHS Public Access

Author manuscript

Diabetes Metab Res Rev. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Diabetes Metab Res Rev. 2013 May ; 29(4): 273–284. doi:10.1002/dmrr.2393.

Antidepressant use and new-onset diabetes: a systematic review and meta-analysis

Sandipan Bhattacharjee[1,*], **Rituparna Bhattacharya**[1], **George A. Kelley**[2], and **Usha Sambamoorthi**[1]

[1]Department of Pharmaceutical Systems and Policy, School of Pharmacy, West Virginia University, Morgantown, WV, USA

[2]Meta-Analytic Research Group, Department of Biostatistics, West Virginia University, Morgantown, WV, USA

Summary

Antidepressant use has been linked to new-onset diabetes. However, the existing literature on this relationship has yielded inconsistent findings. The primary objective of this study was to systematically synthesize the literature on the relationship between antidepressant use and new-onset diabetes using meta-analysis.

A systematic literature search was conducted to identify relevant studies in seven electronic databases. Two independent reviewers identified the final list of studies to be included in the meta-analysis using *a priori* selection criteria. Results for the primary outcome of interest, that is, odds and hazards of developing new-onset diabetes, were pooled using a random-effects model. Egger's regression test and the Trim and Fill method were utilized to detect the presence of any potential publication bias. Sensitivity analysis was conducted using the leave-one-out method as well as individual categories of antidepressant drugs.

Eight studies met the inclusion criteria. Random effects models revealed that adults with any use of antidepressants were more likely to develop new-onset diabetes compared with those without any use of antidepressants [odd ratios = 1.50, 95% confidence interval (CI), 1.08–2.10; hazards ratio = 1.19, 95% CI, 1.08–1.32]. Sensitivity analyses revealed fair robustness; selective serotonin reuptake inhibitors and tricyclic antidepressants were more likely to be associated with the development of new-onset diabetes. Results from the Egger's regression test and Trim and Fill method revealed no evidence of publication bias.

Among adults, antidepressant use was associated with higher chances of new-onset diabetes. However, because a cause-and-effect relationship cannot be established by observational studies, future randomized controlled studies are needed to confirm this association.

[*]Correspondence to: Sandipan Bhattacharjee, Department of Pharmaceutical Systems and Policy, West Virginia University School of Pharmacy, Robert C. Byrd Health Sciences Centre (North), Morgantown, WV, USA. ; Email: sbhattacharjee@hsc.wvu.edu

Supporting information

Supporting information may be found in the online version of this article.

Conflict of interest

The authors declare no conflict of interests with this manuscript.

Keywords

antidepressants; new-onset; diabetes; systematic review; meta-analysis

Introduction

The association between antidepressant use and new-onset diabetes is an emerging research area. Association of antidepressant use with new-onset diabetes was first suggested from the results of a three-armed (intensive lifestyle, metformin and placebo) randomized controlled trial designed for the prevention of diabetes [Diabetes Prevention Programme (DPP)] [1]. Using secondary analysis of data from the DPP, it was found that the hazards of new-onset diabetes among participants in the placebo arm using antidepressants were 2.25 times as high as for those without antidepressant use. Individuals in the intensive lifestyle-arm were three times as likely as those without antidepressant use to develop diabetes [1]. However, to date, published studies using observational data have been inconsistent in finding an association between antidepressant use and new-onset diabetes. For example, some studies did not find a statistically significant association between antidepressant use and new-onset diabetes [2–4], whereas others reported statistically significant associations between antidepressant use and new-onset diabetes [5–9]. Preventing diabetes has become a top-priority area because diabetes is associated with poor quality of life due to serious complications such as neuropathy, nephropathy, retinopathy and cardiovascular adverse events [10], and its management is associated with extremely high healthcare expenditures [11]. Moreover, the rates of antidepressant use among all ages has increased by nearly five times from 1994 to 2008 [12] and in 2008, antidepressants were one of the most commonly prescribed drugs, with 164 million prescriptions at a cost of US$ 9.6bn [13].

Meta-analysis is a quantitative approach for combining results from different studies on the same topic. Some of the strengths of meta-analysis include (1) greater statistical power for outcomes of interests (primary endpoints), (2) arriving at a consensus from varying study results and (3) increasing estimates of treatment effectiveness [14]. To date, only one published report [6] has pooled data from different studies in order to assess the risk of new-onset diabetes with antidepressant use. However, this study was not a true meta-analysis because it was limited to three of the investigative team's own research versus an exhaustive search for all previous studies on the topic. As a result, this previous investigation, from a meta-analytic perspective, suffers from what is known as selection bias. Given the advantages of meta-analysis and inconsistent findings from the existing literature regarding antidepressant use and risk of new-onset diabetes, the purpose of this study was to conduct an aggregate data meta-analysis of observational studies to determine the association between antidepressant use and new-onset diabetes among adults 18 years of age or older.

Methods

Data sources and search strategies

A systematic literature search was conducted to identify relevant studies in seven different electronic databases (PubMed, CINAHL, The Cochrane Library, Dissertation Abstracts

International/Proquest, Web of Science, Scopus and PsycINFO). Cross-referencing from the obtained studies was also performed. A West Virginia University Health Sciences Information Scientist was consulted to plan search strategies for the different databases in order to obtain a comprehensive list of available studies. Different search strategies for different electronic databases were utilized for the purpose of this study because of the fact that these different databases require such. A detailed description of the search strategies used is shown in Appendix I.

Study selection

The *a priori* inclusion criteria for the current study were as follows: (1) observational studies assessing the risk of new-onset diabetes among antidepressant users compared with non-users, (2) adults ≥ 18 years of age, (3) use of any antidepressants [antidepressant drugs belonging to any of the following categories tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, selective norepinephrine reuptake inhibitor, selective serotonin reuptake inhibitors (SSRIs) and others (maprotiline, bupropion, mirtazapine, nefazodone, trazodone)], (4) published and unpublished (dissertations and master's theses) studies, (5) studies published in English language only, (6) studies published from the inception of the respective databases to 26 November 2012 and (7) minimum follow-up of 12 months from the start of antidepressant use. Studies not meeting all of the aforementioned criteria were excluded from this systematic review. Study selection was conducted by the first two authors with consultation from the last author on discrepant issues. The corresponding authors of two studies [4,7] were contacted to obtain necessary point estimates to be included in the final analysis. In addition, estimates to conduct sensitivity analysis on different categories of antidepressant medications were requested and provided by the corresponding author of one study [7], whereas data from another study [5] was retrieved from their online appendix (supplemental data).

Data abstraction

Data from individual studies were abstracted and coded into a Microsoft Excel (2007) codebook that was developed by the first two authors (S.B. and R.B.). Data were coded into the following three broad categories: (1) study characteristics, (2) subject characteristics and (3) outcomes. Data coded included, but were not limited to, the following: funding sources of the original studies, country, methods used and length of follow-up, participant numbers in the intervention group (antidepressant users) and control group (non-users), outcomes (new-onset diabetes) and factors controlled for. The first two authors (S.B. and R.B.) independently coded all studies. Each coded item was then assessed and reviewed for accuracy. Disagreements were resolved by consensus. When consensus could not be reached, the fourth author (U.S.) acted as an arbitrator.

Study quality assessment

The quality of the included studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies [15]. The STROBE statement, which provides guidelines for reporting observational studies, is a 22-item checklist that assesses the risk of potential bias in the title and abstract, introduction, methods, results and discussion sections of articles. There were two levels for assessing each

of these domains – low or high risk of bias. A description of the decision rules for assessing the risk of bias is shown in Table 1. The risk of bias assessment was restricted to the primary outcome (new-onset diabetes only). All risk of bias assessments were conducted by the first two authors (S.B. and R.B.), independent of each other. Disagreements were resolved by consensus.

Statistical analysis

The primary outcome of interest was the odds or hazards of new-onset diabetes from each study. New-onset diabetes was measured among individuals with no prior history of diabetes. Presence of diabetes was assessed by any of the following: self-report, physician diagnosis, 'International Classification of Diseases, 9th Revision, Clinical Modification' code of 250.xx, fasting glucose >126 mg/dL, casual plasma glucose ≥200 mg/dL, 2-h plasma glucose ≥200 mg/dL during oral glucose tolerance test measures, HbA1C value ≥7%, new prescription of oral anti-diabetic medications or insulin use [11,16]. Random effects models, which incorporate heterogeneity between studies were used to estimate the pooled effect of antidepressant use on new-onset diabetes. As studies reported either odd ratios (OR) or hazards ratios (HR), separate random effects models were used. Statistically significant results were considered as those in which the 95% confidence interval (CI) did not include one. Because one study included multiple groups according to dosing [5], data are reported separately as well as with all groups collapsed so that only one estimate represented each study.

The OR and HR from each study were weighted by the inverse of the variance. In addition, Q and I^2 statistics were used to assess heterogeneity. The alpha value for a statistically significant Q statistic was set at ≤0.10. The I^2 statistic was categorized as either small (from 25% to <50%), medium (from 50% to <75%) or large (≥75%) [17]. Results were reported using the pooled OR and HR along with their 95% CI. Non-overlapping CIs were considered statistically significant. Egger's regression test and the Trim and Fill method were used to examine for the presence of potential publication bias [18,19]. For Egger's regression test, the alpha value for statistical significance was set at ≤0.05. In addition, funnel plots were used to detect potential publication bias. Sensitivity analysis was conducted using the leave-one-out method (influence analysis). Sensitivity analysis was also conducted to assess the effects of individual antidepressant categories (SSRIs, TCAs and others) associated with the risk of new-onset diabetes. All statistical analyses were performed using STATA, version 11.0. (STATA, College Station, TX, USA).

Results

Study characteristics

A total of 409 citations were initially identified. After removal of all duplicates, 320 citations were screened on the basis of the title and abstract. Of these, eight met the criteria for inclusion [2–9]. A flow diagram depicting the search process is shown in Figure 1. A list of excluded studies is available upon request from the first author.

The overall characteristics of the eight studies that met the criteria for inclusion are shown in Table 2. Of these, one was added by a manual search [6]. Over 500 000 patients (n = 504 836) were included. With the exception of one study [4], all reported receiving funding from government agencies, pharmaceutical companies or both. Three studies were conducted in the USA [4,6,9], one in Australia [3], one in the Netherlands [2], one in Finland [5] and two in England [7,8]. Two studies used a prospective cohort design [3,5], one used a nested case–control study design [7], three used a longitudinal design [4,8,9], one used a historical cohort design [2] and one pooled data from three prospective cohort studies [6].

Risk of bias assessment

The risk of bias assessment is shown in Figure 2. On the basis of the decision rules for assessing the risk of bias, it was found that overall, the Results, Discussion, and Other Information sections had a low risk for bias. Of the eight observational studies assessed, only one did not provide information regarding funding [4]. Another study did not mention how they handled missing data or whether sensitivity analysis was conducted [2], whereas another did not mention the generalizability of findings when interpreting the results [3]. Four [2–5] of the eight studies did not provide adequate methods information for one or more of the following: sensitivity analysis, potential sources of bias and handling of missing data. Two studies did not adequately describe the design of the study in the title and/or abstract [2,8], whereas two others [6,9] were considered to be at a high risk of bias because adequate scientific background was not provided in the introduction section of the report.

Synthesis of results

Figure 3 shows the pooled OR results with different dosing levels reported separately for the Kivimaki *et al.* (2010) study [5]. As can be seen, the odds of developing new-onset diabetes were statistically significant, with antidepressant users 59% more likely than non-antidepressant users to develop new-onset diabetes. A large amount of heterogeneity was observed. When different dosing levels from the Kivimaki *et al.* (2010) [5] study were collapsed into one OR, results remained statistically significant with a large amount of heterogeneity (Figure 4). Visual inspection of the funnel plot shown in Figure 5 suggested no presence of publication bias. In addition, quantitative assessment using Egger's regression test found no statistically significant presence of publication bias (p = 0.69). Furthermore, no studies needed to be imputed using the Trim and Fill method, suggesting that no publication bias was present.

Figure 6 shows the pooled HR results with the three studies used by Pan *et al.* reported separately [6]. As can be seen, there was a 20% higher likelihood for antidepressant users to develop new-onset diabetes. Heterogeneity was small. Study level results collapsing the three studies used by Pan *et al.* [6] are shown in Figure 7. As can be seen, HR revealed that antidepressant users, when compared with non-antidepressant users, had a statistically significant 19% higher likelihood of developing new-onset diabetes (Figure 7). Heterogeneity was considered to be small. Visual inspection of the funnel plot shown in Figure 8 suggested no presence of publication bias. In addition, quantitative assessment using Egger's regression test found no statistically significant presence of publication bias (p

= 0.58). Furthermore, although the Trim and Fill method resulted in one imputation, results were similar to the original findings (HR = 1.18, 95% CI, 1.07–1.31).

Sensitivity analyses results using the leave-one-out method (influence analysis) is shown in Table 3. As can be seen, the 95% CI included the value of 1 when the Kivimaki *et al.* (2010) [5] and Andersohn *et al.* (2009) [7] studies were removed from the OR models. Similarly, the 95% CI included the value of 1 when the Pan *et al.* (2011) [6] study was excluded from the overall HR model. Furthermore, sensitivity analysis based on the individual antidepressant categories revealed that SSRIs (pooled OR = 1.34, 95%CI, 1.02–1.77) and TCAs (pooled OR = 1.30, 95%CI, 1.07–1.58) were 34% and 30%, respectively, more likely to be associated with new-onset diabetes. The 'other' antidepressant category was not significantly associated with new-onset diabetes (Table 4).

Discussion

The current study assessed the association between antidepressant use and new-onset diabetes. To the best of the authors' knowledge, this is the first aggregate data meta-analysis to evaluate new-onset diabetes among antidepressant users. On the basis of the pooled analysis of OR and HR, it was found that antidepressant use increased the likelihood of new-onset diabetes. This finding is consistent with a three-arm randomized controlled trial that also found a significant association between antidepressant use and risk of new-onset diabetes [1].

Several factors may help support the association between antidepressant use and the risk of new-onset diabetes. For example, because it is well-documented that serotonin regulates glucose homeostasis and that antidepressant use increases the transmission of serotonin, there may be an altering in the regulation of glucose and a subsequent increase in the risk for new-onset diabetes [20,21]. In addition, hyperglycemia induced by antidepressant utilisation has been observed in animal studies involving mice and rats [22–26]. The blocking of insulin signals may lead to cellular insulin resistance [24], which in turn may increase the risk for developing diabetes. It has also been proposed that the hypothalamo-pituitary-adrenal axes are associated with antidepressant-induced hyperglycemia [26]. Antidepressant use has been associated with hypercortisolemia, which may lead to insulin resistance and subsequent hyperglycemia [27]. Moreover, both short-term and long-term uses of some antidepressants have been associated with weight gain [28], and increases in weight are associated with an increase in the risk of diabetes [29,30]. Insulin resistance and insulin secretion are two important factors that explain diabetes development and different receptors are involved, which mediates these factors [31]. Antidepressants have a high affinity towards the H_1 and 5-HT_2C receptors known to influence insulin resistance and weight gain [32]; antidepressants also have an affinity towards M_3 muscarinic receptors that play a pivotal role in the regulation of insulin secretion [32].

Of the eight studies included in the meta-analysis, five (62.5%) reported a statistically significant association between antidepressant utilisation and new-onset diabetes [5–9], whereas the other three (37.5%) did not [2–4]. One possible explanation for the discrepant findings between studies may be related to the different methods used to determine new-

onset diabetes. For example, Knol and colleagues [2] identified diabetes with a prescription for any glucose lowering drug. This definition may have misclassified those individuals with diabetes and without any prescription for glucose lowering drugs as individuals without diabetes. Consequently, this study may have underestimated the number of antidepressant users with new-onset diabetes. The prospective study by Atlantis and colleagues [3] found that depressive symptoms rather than antidepressant use was associated with new-onset diabetes. Their findings could be partially explained by that fact that they measured antidepressant use at baseline but did not provide the duration and dose of antidepressant usage. Similarly, Wilkins and Sambamoorthi [4] did not only find an association between antidepressant use and new-onset diabetes but also lacked information on the duration and dose of antidepressant use. In addition, Wilkins and Sambamoorthi [4] used a short follow-up period (12 months). Duration and dosage may be important because studies that found a significant relationship between antidepressant use and new-onset diabetes all included either duration or dosage of antidepressant use.

The summary findings from the meta-analysis have significant implications for expanding antidepressant use and using antidepressants for persistent depression. For example, the workgroup on depressive disorders of Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) has been considering definitional changes to diagnosed depression. Specifically, using DSM-IV, depressive symptoms in individuals who were in bereavement were classified as normal. However, using DSM-5, these individuals can be classified as having a major depressive disorder [33]. This inclusive definition of depression has been a matter of great debate because it might result in increasing the number of individuals with depression, leading to an increase in the use of antidepressants. Because evidence from this meta-analysis suggests a significant association of antidepressant use with new-onset diabetes, increased antidepressant use by a large number of individuals who are otherwise healthy might increase the incidence of diabetes.

Some of the studies in our systematic review suggested a relationship between duration of antidepressant use and new-onset diabetes. Recent studies have suggested that depression tends to be persistent [34] and treatment of depression with antidepressants can fail in many individuals [35]. Findings from the first ever randomized trial of depression care in real world practice settings revealed that depression remains persistent in at least 25% of individuals [36] and the odds of overcoming depression was reduced as the number of failed treatments increased [37]. As the duration of antidepressant use increases, it is possible that the risk of developing diabetes may also increase.

Existing literature suggests that depression is an independent risk factor for diabetes over and above different potential confounding factors, including demographic characteristics such as sex, age, race/ethnicity, socioeconomic status, education, health services utilisation, psychiatric disorders and body weight [38,39]. A recent meta-analysis found that depression was associated with a 37% increased risk of new-onset diabetes [40]. In the current meta-analysis, only three studies controlled for depression or depressive symptoms [4,5,9], with two [5,9] of the three reporting a statistically significant association between antidepressant use and new-onset diabetes. The former notwithstanding, the significant association between antidepressant utilisation and new-onset diabetes could have been mediated by the presence

of depression in the other included studies [2,3,6–8]. This mediating relationship is important because the depression rather than antidepressant utilisation may have affected new-onset diabetes. If this is true, then the clinical focus should probably be on preventing depression rather than reducing antidepressant use.

The results of this meta-analysis may also be especially timely given the increasing use of antidepressants. For example, a recent study reported a 13% increase between 1996 and 2007 in the proportion of visits in which antidepressants were prescribed without any psychiatric diagnoses [41]. Even in patients with depression, the results from a meta-analysis of four different efficacy trials with antidepressants showed that antidepressants were only marginally efficacious as compared with placebo. The Sequenced Treatment Alternatives to Relieve Depression trial, the largest antidepressant effectiveness trial ever conducted, showed less than modest remission rates [42]. Thus, clinicians should be cautious in the prescription of antidepressants.

The statistically significant and positive association between antidepressant medication use and new-onset diabetes became non-significant on exclusion of two studies [5,7] in the OR model. The HR model also gave similar results on removal of the Pan *et al.* 2011 [6] study. It is noteworthy that each of these studies had the highest weights as estimated by the inverse weighting technique. The loss of statistical significance on removal of studies with the highest weights could be explained by the loss of precision resulting from the exclusion of these studies. Upon removal of the Kivimaki *et al.* (2010) [5] study, it was observed that the between-study heterogeneity increased slightly from 76.2% to 78% and the sample size was reduced by 5085 individuals. Similarly, removal of the Andersohn *et al.* (2009) [7] study increased between-study heterogeneity and lowered the sample size, thus resulting in higher standards errors and lower precision. Removal of the Pan *et al.* (2011) [6] study from the HR model also led to similar results. Thus, the large sample sizes of these studies as compared with other studies in the models might have led to lack of robustness in the estimates. In addition, sensitivity analysis using individual categories of antidepressant drugs revealed that SSRIs and TCAs are associated with higher risks of developing new-onset diabetes. This can be attributed to the fact that both short-term and long-term uses of some of the individual antidepressant drugs such as amitriptyline (TCA), paroxetine (SSRI) and fluvoxamine (SSRI) have been shown to be associated with weight gain, which in turn might increase the risk of developing diabetes [7].

Our study findings have implications for diabetes prevention efforts. The significant association between antidepressant use and diabetes suggests that prevention strategies may need to include a thorough assessment of the diabetes risk profile as part of screening efforts among individuals initiating antidepressant use as well as continued monitoring of antidepressant users for diabetes risk. For those who have already been exposed to antidepressant use, developing and testing new interventions to prevent diabetes may become part of the tool-kit in preventing diabetes.

There were a number of strengths of the current meta-analysis. For example, a large number of participants from each study were included. In addition, the relationship was studied with a wide-range of follow-up (1–18 years). Furthermore, analyses were based on studies from

several different countries. Thus, the risk of country bias may have been minimized. Although there were several strengths to this meta-analysis, the results also need to be viewed with respect to the following potential limitations. First, because only observational studies were included in the analysis, a cause-and-effect relationship could not be established. Second, there was a large amount of heterogeneity between studies. Third, influence analysis showed that the results were not robust when several of the studies were excluded from the overall models. Fourth, different studies have taken into account different sets of risk factors of diabetes and hence, the point estimates obtained by pooling the data might be slightly biassed as all the different risk factors were not adjusted together. The former notwithstanding, this is the first aggregate data meta-analysis to our knowledge that has evaluated the risk of new-onset diabetes with antidepressant use. Consequently, summary evidence from a quantitative systematic review is now available.

In conclusion, our overall results suggest that antidepressant use is associated with an increased risk for new-onset diabetes in adults. However, because a cause-and-effect relationship cannot be established with observational studies, future long-term randomized controlled studies are needed to confirm this association. Several different factors such as depressive symptoms, persistent depression, duration and dosage of antidepressant use, type of antidepressants, lifestyle risk factors (including pre-diabetes) and other potential mediating factors should be considered in those studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Mr. Bhattacharjee received research assistance and Dr. Sambamoorthi was partially supported for infrastructure from the West Virginia Collaborative Health Outcomes Research of Therapies and Services (WV CoHORTS) Centre. The authors would also like to thank Jean Siebert for her valuable help in developing the revised search strategies.

References

1. Rubin RR, Ma Y, Marrero DG, et al. Diabetes prevention program research group. Elevated depression symptoms, antidepressant medicine use, and risk of developing diabetes during the diabetes prevention program. Diabetes Care. 2008; 31(3):420–6. [PubMed: 18071002]
2. Knol MJ, Geerlings MI, Egberts AC, Gorter KJ, Grobbee DE, Heerdink ER. No increased incidence of diabetes in antidepressant users. Int Clin Psychopharmacol. 2007; 22(6):382–6. [PubMed: 17917558]
3. Atlantis E, Browning C, Sims J, Kendig H. Diabetes incidence associated with depression and antidepressants in the Melbourne Longitudinal Studies on Healthy Ageing (MELSHA). Int J Geriatr Psychiatry. 2010; 25(7):688–96. [PubMed: 19806604]
4. Wilkins TL, Sambamoorthi U. Antidepressant use, depression, lifestyle factors, and new-onset diabetes. Int Clin Psychopharmacol. 2011; 26(3):159–68. [PubMed: 21471774]
5. Kivimäki M, Hamer M, Batty GD, et al. Antidepressant medication use, weight gain, and risk of type 2 diabetes: a population-based study. Diabetes Care. 2010; 33(12):2611–6. [PubMed: 20823343]
6. Pan A, Sun Q, Okereke OI, et al. Use of antidepressant medication and risk of type 2 diabetes: results from three cohorts of US adults. Diabetologia. 2012; 55(1):63–72. [PubMed: 21811871]

7. Andersohn F, Schade R, Suissa S, Garbe E. Long-term use of antidepressants for depressive disorders and the risk of diabetes mellitus. Am J Psychiatry. 2009; 166(5):591–8. [PubMed: 19339356]
8. Kivimäki M, Batty GD, Jokela M, et al. Antidepressant medication use and risk of hyperglycemia and diabetes mellitus: a noncausal association? Biol Psychiatry. 2011; 70(10):978–84. [PubMed: 21872216]
9. Ma Y, Balasubramanian R, Pagoto SL, et al. Elevated depressive symptoms, antidepressant use, and diabetes in a large multiethnic national sample of postmenopausal women. Diabetes Care. 2011; 34(11):2390–2. [PubMed: 21911776]
10. Vijan S, Hayward RA, American College of Physicians. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. Ann Intern Med. 2004; 140(8):650–8. [PubMed: 15096337]
11. American Diabetes Association. Standards of medical care in diabetes–2008. Diabetes Care. 2008; 31(Suppl 1):S12–54. [PubMed: 18165335]
12. National Center of Health Statistics. Health, United States, 2010: With Special Feature on Death and Dying. Hyattsville MD: 2011.
13. IMS Health. Top-line industry data. 2008 US sales and prescription information. 2008. Available at, http://www.imshealth.com., accessed February 16, 2012
14. Kelley GA, Kelley KS, Roberts S, Haskell W. Efficacy of aerobic exercise and a prudent diet for improving selected lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. BMC Med. 2011; 15(9):74. [PubMed: 21676220]
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Bull World Health Organ. 2007; 85(11): 867–72. [PubMed: 18038077]
16. Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. Diabetes Res Clin Pract. 2010; 89(2):189–95. [PubMed: 20363043]
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414):557–60. [PubMed: 12958120]
18. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000; 56(2):455–63. [PubMed: 10877304]
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109):629–34. [PubMed: 9310563]
20. Chaouloff F, Laude D, Baudrie V. Effects of the 5-HT1C/5-5-HT2 receptor agonists DOI and alpha-methyl-5-HT on plasma glucose and insulin levels in the rat. Eur J Pharmacol. 1990; 187(3): 435–43. [PubMed: 2127400]
21. Chaouloff F, Gunn SH, Young JB. Central 5-hydroxytryptamine2 receptors are involved in the adrenal catecholamine-releasing and hyperglycemic effects of the 5-hydroxytryptamine indirect agonist d-fenfluramine in the conscious rat. J Pharmacol Exp Ther. 1992; 260(3):1008–16. [PubMed: 1545373]
22. Sugimoto Y, Inoue K, Yamada J. Involvement of serotonin in zimelidine-induced hyperglycemia in mice. Biol Pharm Bull. 1999; 22(11):1240–1. [PubMed: 10598036]
23. Carvalho F, Barros D, Silva J, et al. Hyperglycemia induced by acute central fluoxetine administration: role of the central CRH system and 5-HT3 receptors. Neuropeptides. 2004; 38(2–3):98–105. [PubMed: 15223272]
24. Levkovitz Y, Ben-Shushan G, Hershkovitz A, et al. Antidepressants induce cellular insulin resistance by activation of IRS-1 kinases. Mol Cell Neurosci. 2007; 36(3):305–12. [PubMed: 17728140]
25. Yamada J, Sugimoto Y, Inoue K. Selective serotonin reuptake inhibitors fluoxetine and fluvoxamine induce hyperglycemia by different mechanisms. Eur J Pharmacol. 1999; 382(3):211–5. [PubMed: 10556672]
26. Khoza S, Barner JC, Bohman TM, Rascati K, Lawson K, Wilson JP. Use of antidepressant agents and the risk of type 2 diabetes. Eur J Clin Pharmacol. 2012; 68(9):1295–1302. [PubMed: 22120432]

27. Skene DJ, Bojkowski CJ, Arendt J. Comparison of the effects of acute fluvoxamine and desipramine administration on melatonin and cortisol production in humans. Br J Clin Pharmacol. 1994; 37(2):181–6. [PubMed: 8186063]
28. Zimmermann U, Kraus T, Himmerich H, Schuld A, Pollmächer T. Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. J Psychiatr Res. 2003; 37(3):193–220. [PubMed: 12650740]
29. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care. 1994; 17(9):961–9. [PubMed: 7988316]
30. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med. 1995; 122(7):481–6. [PubMed: 7872581]
31. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006; 444(7121):840–6. [PubMed: 17167471]
32. Jindal RD. Long-term antidepressant use and risk for diabetes: cause for concern and optimism. Am J Psychiatry. 2009; 166(9):1065–6. author reply 1066. [PubMed: 19723798]
33. Jerome C, First M. Validity of the bereavement exclusion to major depression: does the empirical evidence support the proposal to eliminate the exclusion in DSM-5? World Psychiatr. 2012; 11:3–10.
34. Young AS, Klap R, Shoai R, Wells KB. Persistent depression and anxiety in the United States: prevalence and quality of care. Psychiatr Serv. 2008; 59(12):1391–8. [PubMed: 19033165]
35. Thase ME. Treatment-resistant depression: prevalence, risk factors, and treatment strategies. J Clin Psychiatry. 2011; 72(5):e18. [PubMed: 21658343]
36. Gilmer WS, Trivedi MH, Rush AJ, et al. Factors associated with chronic depressive episodes: a preliminary report from the STAR-D project. Acta Psychiatr Scand. 2005; 112(6):425–33. [PubMed: 16279871]
37. Rush AJ. STAR*D: what have we learned? Am J Psychiatry. 2007; 164(2):201–4. [PubMed: 17267779]
38. Eaton WW, Armenian H, Gallo J, Pratt L, Ford DE. Depression and risk for onset of type II diabetes. A prospective population based study. Diabetes Care. 1996; 19(10):1097–102. [PubMed: 8886555]
39. Kawakami N, Takatsuka N, Shimizu H, Ishibashi H. Depressive symptoms and occurrence of type 2 diabetes among Japanese men. Diabetes Care. 1999; 22(7):1071–6. [PubMed: 10388970]
40. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia. 2006; 49(5):837–45. [PubMed: 16520921]
41. Mojtabai R, Olfson M. Proportion of antidepressants prescribed without a psychiatric diagnosis is growing. Health Aff (Millwood). 2011; 30(8):1434–42. [PubMed: 21821561]
42. Pigott HE, Leventhal AM, Alter GS, Boren JJ. Efficacy and effectiveness of antidepressants: current status of research. Psychother Psychosom. 2010; 79(5):267–79. [PubMed: 20616621]

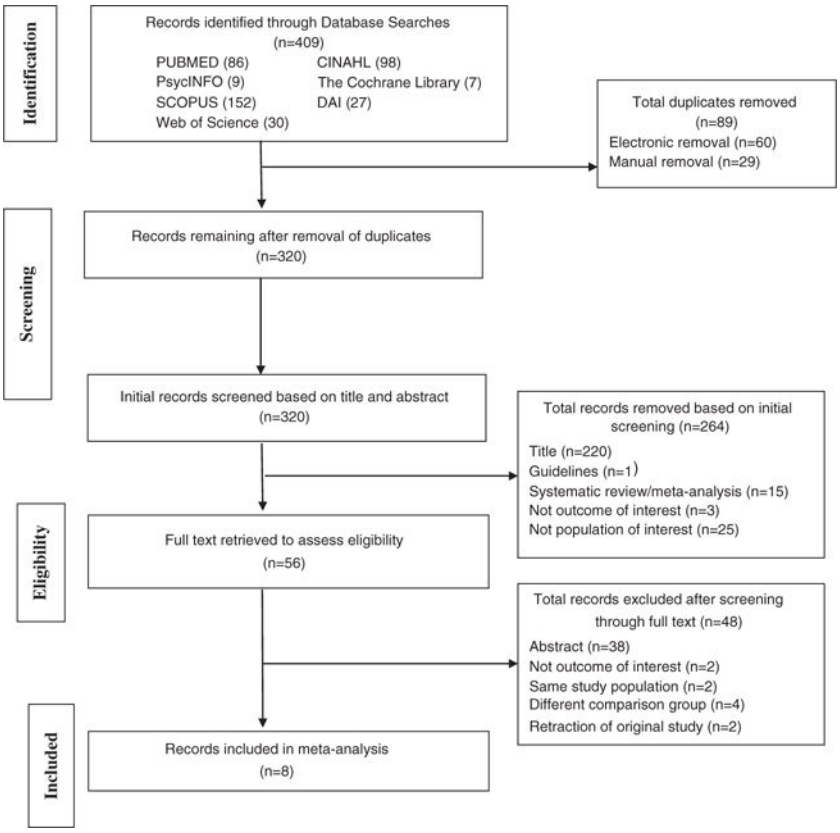


Figure 1.
Flowchart of screened articles

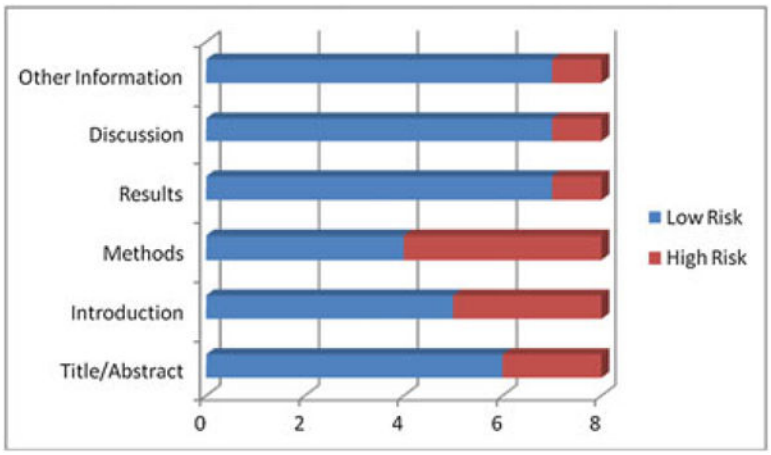
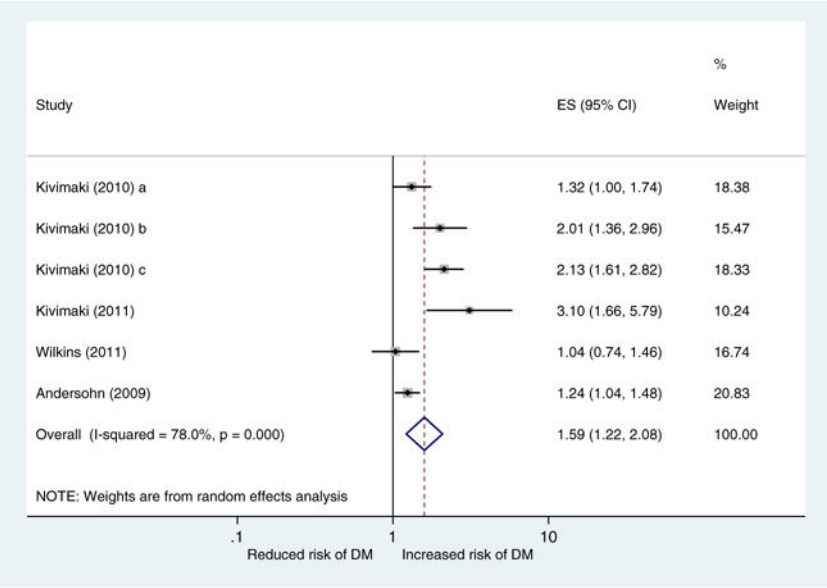


Figure 2.
Risk of bias assessment



Note: Kivimaki [2010]a- 1-99 defined daily dose of antidepressant compared to no use
Kivimaki [2010]b- 199-399 defined daily dose of antidepressant compared to no use
Kivimaki [2010]c- ≥ 400 defined daily dose of antidepressant compared to no use

Figure 3.
Forest plot of included studies with odds ratio (group level)

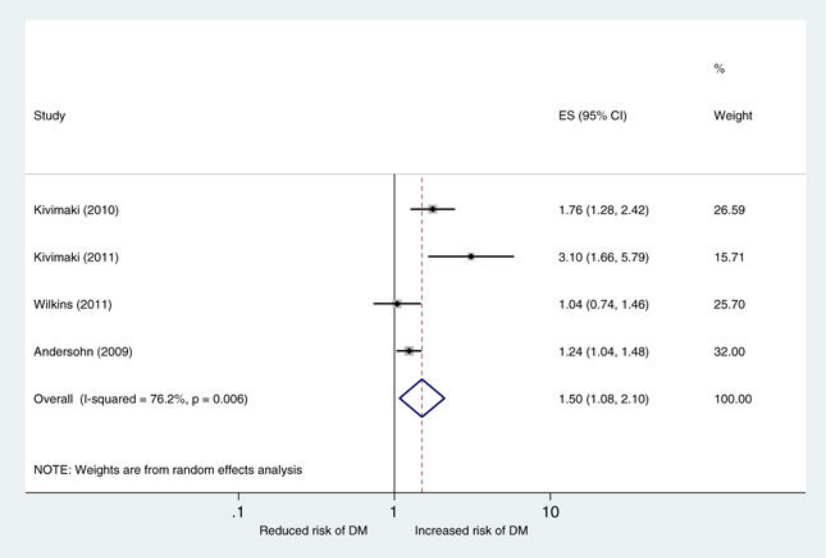


Figure 4.
Forest plot of included studies with odds ratio (study level)

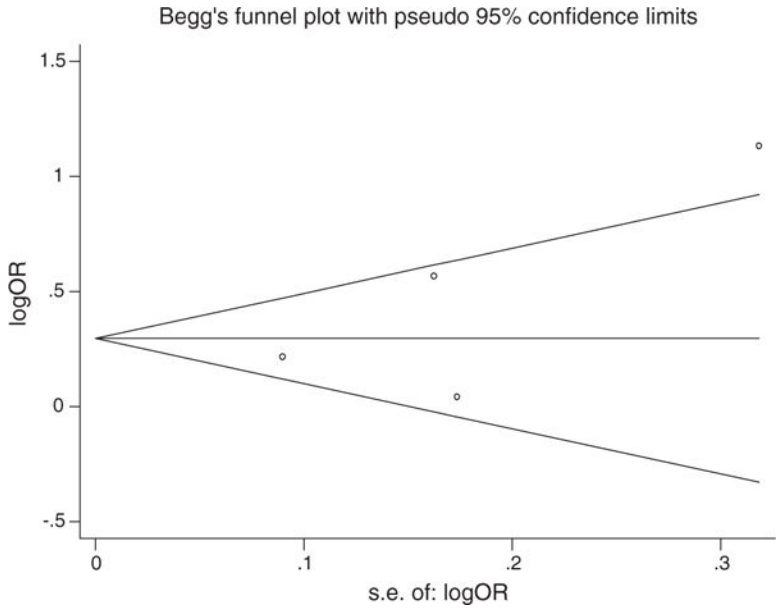
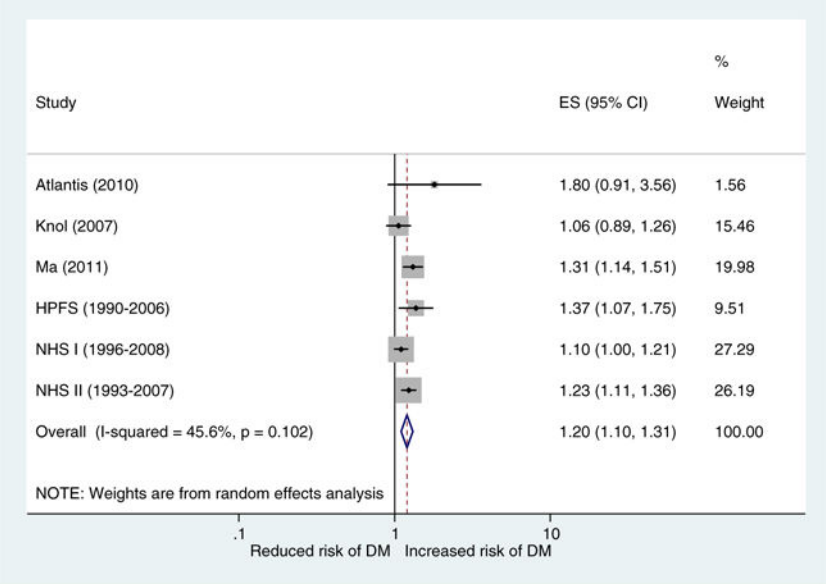


Figure 5.
Funnel plot for assessing publication bias of studies with odds ratio



HPFS: Health Professionals Follow-up Study (1990-2006)
NHS I: Nurses' Health Study I (1996-2008)
NHS II: Nurses' Health Study II (1993-2007)

Figure 6.
Forest plot of included studies with hazards ratio pooled (group level)

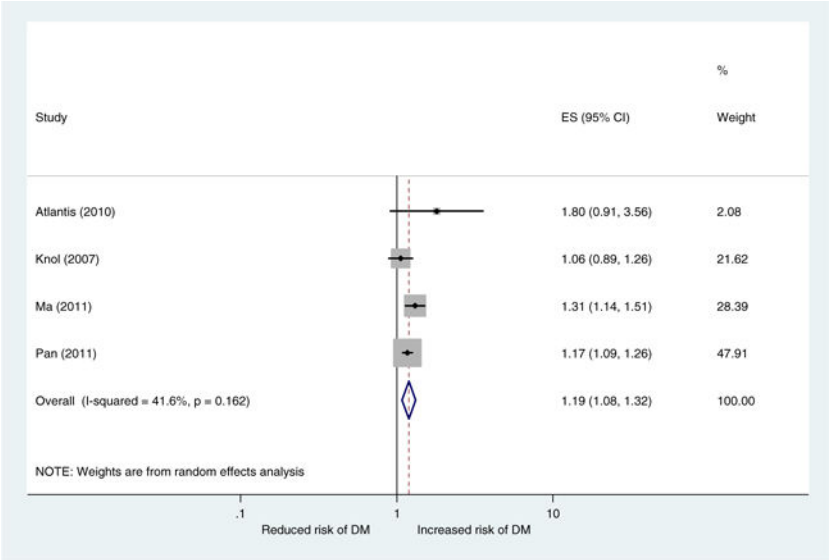


Figure 7.
Forest plot of included studies with hazards ratio pooled (study level)

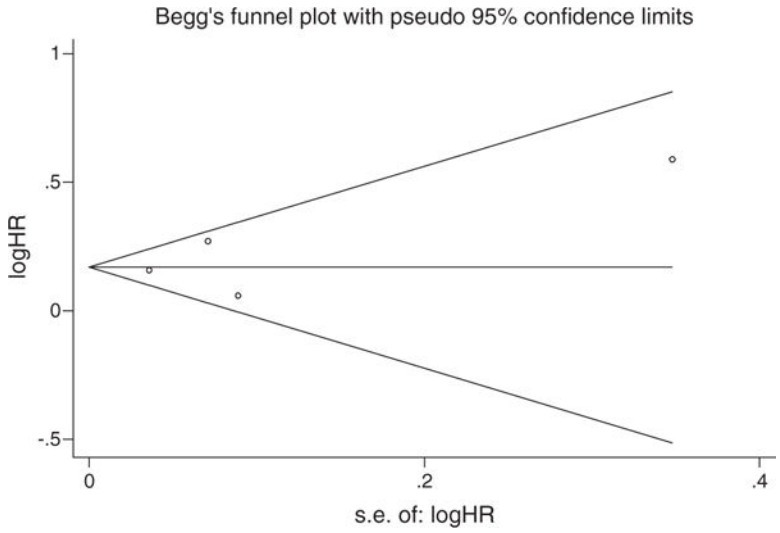


Figure 8.
Funnel plot for assessing publication bias of studies with hazards ratio

Table 1

Decision rules for risk of bias using Strengthening the Reporting of Observational Studies in Epidemiology

Part	Decision rule
Title and abstract	If the design of the study is not mentioned in the title and/or abstract and/or an adequate summary is not provided, then it is high risk. If addressed, then is it low risk.
Introduction	If the objective of the study is not clearly specified and proper study rationale not given, then it is high risk. If addressed, then it is low risk.
Methods	If explicit mention is not made of the study design, setting, participants, variables, data source, bias, statistical methods used, study size and sensitivity analysis, then it is high risk. If all addressed, then it is low risk.
Results	If adequate information is not provided with respect to participant numbers, characteristics of study participants, outcome data, main results, other analyses, then it is high risk. If all addressed, then it is low risk.
Discussion	If there is not a proper summary of key findings, discussion of limitations, cautious interpretation of results and generalizability explained, then it is high risk. If addressed, then it is low risk.
Other information	If no explicit mention of funding source, then it is high risk. If addressed, then it is low risk.

Table 2

Characteristics of included studies

Study and year	Country	Methods	Participant characteristics, follow-up	Interventions/comparison	Outcomes	Factors controlled	Notes
Andersohn *et al.* (2009)	UK	Nested case–control study of depressed individuals receiving antidepressants between 1 January 1990 and 30 June 2005.	A total of 165 958 patients fulfilled cohort definition. 2243 cases of incident diabetes mellitus matched with 8963 matched comparisons **Gender**-male (40%) female (60%) **Follow-up**-mean follow-up of 2.8 years	**Intervention**-antidepressant Use **Comparison**-no antidepressant use	Diabetes was identified using predefined diabetes codes and prescriptions of oral anti-diabetics and insulin	BMI, smoking, hypertension, hyperlipidemia, and recent use of beta-blockers, thiazides, antipsychotics, carbamazepine, phenytoin, valproate, litium, glucocoticoids	Supported partly by a grant from the Canadian Foundation for innovation and the Canadian Institutes of Health Research and an unrestricted grant from Bayer Schering Pharma AG for database acquisition
Atlantis *et al.* (2010)	Australia	Prospective cohort study followed up biennially between 1994 and 2004	A total of 826 patients after exclusion of prevalent diabetes cases at baseline aged 65 years and older **Gender**-male (47%)female (53%)**Follow-up**-10 years	**Intervention**-antid epressant use **Comparison**-no antidepressant use	Diabetes incidence assessed by 'self-report' and then prescriptions evaluated	Demographic factors, lifestyle factors, functional health, prevalent chronic disease	Funded by Victorian Health Promotion Foundation, the Australian Research Council and NHMRC
Knol *et al.* (2007)	Netherlands	Historical cohort study	Individuals 18 years or older at the index date; new users of antidepressants (AD) and benzodiazepines (BD); had at least two prescriptions of AD or BD in the year after the index date **Mean age**-45.5 (±17) years **Gender**-male (42%)female (58%) **Follow-up**-7 years	**Intervention**-(1) participants using AD but no BD; (2) participants using AD and BD **Control**-participants using no AD and no BD	Initiation of diabetes medication, defined as the first prescription for any glucose-lowering drug, either hypoglycemic agents and/or insulin, after index date	Age, sex, chronic disease score	Source of funding mentioned (pharmaceutical company-Novo Nordisk and the Scientific Institute of Dutch Pharmacists) and it is a Netherland study
Kivimaki *et al.* (2010)	Finland	Series of nested studies within prospective cohort	Working aged men and women; 851 individuals with incident type 2 diabetes and 42 343 individually matched diabetes-free control subjectsAge range-20–64 years **Gender**-male (34%)female (66%) **Follow-up**-4 years	**Intervention**-antidepressant use over a fixed period of 4 years before type 2 diabetes diagnosis between 1 January 2001 and 31 December 2005 **Comparison**-no antidepressant users	Incident diabetes	Mutually diagnosed depression and antidepressant use entered in the same model	Publicly funded study
Kivimaki *et al.* (2011)	England	Longitudinal follow-up study	A total of 10 308 civil servants aged 35–55 years at recruitment in 1985/1988; data collected in different phases – at phase 5 (n = 5290), 7 (n = 4663), 9 (n = 4663) **Mean age**-49.2 (±6) years (never user)48.9 (±5.8) years (ever user)	**Intervention**-antidepressant use assessed with generic name, brand name, or both coded with British National Formulary **Comparison**-no antidepressant use	Incident diabetes assessed by physician	Age, sex, ethnicity	Supported by RO1 grant (Continues)

Study and year	Country	Methods	Participant characteristics, follow-up	Interventions/comparison	Outcomes	Factors controlled	Notes
			Gender-male (71.9%) (never user) male (58.2%) (ever user) **Follow-up**-18 years				
Ma *et al.* (2011)	USA	Longitudinal analysis based on 70 874 women from the Women's Health Initiative-an Observational Study (WHI-OS) arm with data available on both depressive symptoms and antidepressant use	A total of 70 874 post-menopausal women **Follow-up**-average of 7.6 years	**Intervention**-antidepressant Use **Comparison**-no antidepressant use	Diabetes status was determined by self-report of ever having received a physician diagnosis of and/or treatment for diabetes when not pregnant	Age, race/ethnicity, education, smoking status at baseline, BMI, hours of recreational activity per week, alcohol intake, total daily energy intake, family history of diabetes, hormone therapy use	This study was funded by a grant from the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK)
Pan A *et al.* (2012)	USA	Longitudinal follow-up study using data from three prospective cohort studies	A total of 29 776 men in HPFS (1990–2006), 61 791 women in the NHS I (1996–2008) and 76 868 women in NHS II (1993–2005) free of diabetes **Mean age** in HPFS-56.4 years (No ADM); 56.3 years (ADM) **Follow-up**-16 years **Mean age** in NHS I-61.4 years (No ADM)59.8 years (ADM) **Follow-up**-12 years **Mean age** in NHS II-37.9 years (No ADM)39.3 years (ADM) **Follow-up**-12 years	**Intervention**-antidepressant use as defined in the categories of SSRIs, TCAs and other antidepressants **Comparison**-no antidepressant use	Incident diabetes defined as classic symptoms plus fasting or plasma glucose, or treatment with hypoglycemic meds (insulin or oral), or two incidents of high blood glucose	Age, ethnicity, marital status, living status, smoking status, alcohol intake, multi-vitamin and aspirin use, physical activity, family history of diabetes, major comorbidities (hypertension, hypercholesterolemia), quintiles of dietary score, BMI, menopausal status, hormone use, oral contraceptive use (women)	Funded by public grants
Wilkins TR *et al.* (2011)	USA	Longitudinal follow-up for 2 years	Adults over 21 years of age at baseline who were alive for the entire observation period **Gender**-male (48%)female (52%)	**Intervention**-antidepressant use and depression; antidepressant use and no depression **Comparison**-no antidepressant use	Incident diabetes, positively responded to the query of ever-having diabetes or had clinical classification code or had a prescription for insulin	Sex, race/ethnicity, age, marital status, metro status, poverty status, education, employment	No sources of funding mentioned

NHMRC, National Health and Medical Research Council; BMI, body mass index; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Table 3

Influence analysis.

Study omitted	Estimate	95% CI
OR	1.69	0.99–2.9
Andersohn *et al.* 2009		
Kivimaki *et al.* 2010	1.44	0.94–2.21
Kivimaki *et al.* 2011	1.31	1.01–1.69*
Wilkins *et al.* 2011	1.73	1.13–2.67*
HR	1.18	1.08–1.3*
Atlantis *et al.* 2010		
Knol *et al.* 2007	1.23	1.1–1.38*
Ma *et al.* 2011	1.15	1.03–1.28*
Pan *et al.* 2011	1.22	1.0–1.49

OR, odds ratio; HR, hazards ratio; 95% CI, 95% confidence interval.

*Statistically significant (CI does not include 1.0).

Table 4

Sensitivity analysis using individual categories of antidepressant drugs

				Overall	
Study name	**Antidepressant category**	**OR**	**95%CI**	I^2	***p*-value**
Andersohn *et al.* 2009	SSRIs	1.19	0.99–1.43		
Kivimaki *et al.* 2010	SSRIs	1.58	1.19–2.11 *		
Pooled results (random effects model)	SSRIs	1.34	1.02–1.77 *	63%	0.1
Andersohn *et al.* 2009	TCAs	1.28	1.05–1.56 *		
Kivimaki *et al.* 2010	TCAs	1.85	0.70–4.91		
Pooled results (random effects model)	TCAs	1.3	1.07–1.58 *	0%	0.47
Andersohn *et al.* 2009	Others	1.84	1.20–2.80 *		
Kivimaki *et al.* 2010	Others	1.06	0.79–1.42		
Pooled results (random effects model)	Others	1.37	0.80–2.34	77%	0.04

OR, odds ratio; 95% CI, 95% confidence intervals.

* Statistically significant (CI does not include 1.0).