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ARTICLE

Use of antidepressant medication and risk of type 2 diabetes: results from three cohorts of US adults

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Abstract
Aims/hypothesis The results of several studies have suggested a potential positive association between use of antidepressant medication (ADM) and incident type 2 diabetes mellitus. We examined this association in three cohorts of US adults.

Methods We followed 29,776 men in the Health Professionals Follow-up Study (HPFS, 1990–2006), 61,791 women in the Nurses' Health Study I (NHS I, 1996–2008) and 76,868 women in NHS II (1993–2005), who were free of diabetes mellitus, cardiovascular disease or cancer at baseline. The mean baseline ages for participants from the HPFS and NHS I and II were 56.4, 61.3 and 38.1 years, respectively. ADM use and other covariates were assessed at baseline and updated every 2 years. A time-dependent Cox proportional hazards model was used, and HRs were pooled together across the three cohorts.
Results During 1,644,679 person-years of follow-up, we documented 6,641 new cases of type 2 diabetes. ADM use was associated with an increased risk of diabetes in all three cohorts in age-adjusted models (pooled HR 1.68 [95% CI 1.27, 2.23]). The association was attenuated after adjustment for diabetes risk factors and histories of high cholesterol and hypertension (1.30 [1.14, 1.49]), and further attenuated by controlling for updated BMI (1.17 [1.09, 1.25]). Use of selective serotonin reuptake inhibitors and other antidepressants (mainly tricyclic antidepressants) were both associated with an elevated risk of diabetes, with pooled multivariate-adjusted HRs of 1.10 (1.00, 1.22) and 1.26 (1.11, 1.42), respectively.
Conclusions/interpretation The results suggest that ADM users had a moderately elevated risk of type 2 diabetes mellitus compared with non-users, even after adjustment for BMI.

Keywords Antidepressant · Depression · Diabetes mellitus · Meta-analysis · Prospective cohort study

Abbreviations
ADM Antidepressant medication
DPP Diabetes Prevention Program

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HPFS	Health Professionals Follow-up Study
MHI-5	Five-Item Mental Health Index
NHS	Nurses' Health Study
SDS	Severe depressive symptoms
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

Introduction

Use of antidepressant medication (ADM) has substantially increased in the past decade in the USA [1], becoming one of the most commonly prescribed classes of medication in outpatient medical practices [2, 3]. Antidepressants have been reported to cause considerable weight gain [4, 5] and impaired glucose homoeostasis [6, 7]. Several studies have linked ADM use and risk of type 2 diabetes, but the data are limited and inconsistent [8–13]. Previous studies are limited by the case–control study design [9, 10], or being restricted to high-risk populations [8] or small sample sizes [11, 12]. Therefore we investigated the association between ADM use (and types) and risk of developing type 2 diabetes mellitus in three large, well-established cohorts: the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS) I and II.

Methods

Study population We used data from three prospective cohort studies: HPFS (initiated in 1986, n=51,529, age range 40–75 years), NHS I (started from 1976, n=121,704, age range 30–55 years) and NHS II (established in 1989, n=116,671, age range 25–42 years). Detailed descriptions of the three cohorts have been given elsewhere [14–16]. In all three cohorts, questionnaires were administered at baseline and biennially thereafter to collect and update information on lifestyle practice and occurrence of chronic diseases. The follow-up rates for the participants in these cohorts all exceeded 90%.

In the current analysis, we excluded participants who had diabetes (including type 1 and 2 diabetes mellitus and gestational diabetes), cardiovascular disease or cancer at baseline (1990 for HPFS, 1996 for NHS I and 1993 for NHS II). In addition, we excluded participants without baseline information on ADM use or BMI. Finally, data from 29,776 HPFS, 61,791 NHS I and 76,868 NHS II participants were available for the analysis. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health. All participants provided informed consent.

ADM measurement

Regular ADM use during the preceding 2 years was first assessed in 1990 for HPFS, 1996 for NHS I and 1993 for NHS II. This information was updated biennially in each cohort, except for NHS II in 1995. Therefore data from 1993 was carried forward to 1995. The types of ADM use were first inquired about in 1996 for HPFS, 2000 for NHS I, and 1993 for NHS II. In HPFS, men were specifically asked to report their regular use during the preceding 2 years of selective serotonin reuptake inhibitors (SSRIs, e.g. fluoxetine, sertraline, paroxetine, citalopram), tricyclic antidepressants (TCAs, e.g. amitriptyline, imipramine, nortriptyline) and other antidepressants biennially since 1996. In NHS I, women provided information on SSRIs and other antidepressants, of which the TCAs were provided as examples. In NHS II, women were asked about their regular use of SSRIs and TCAs in 1993, 1997 and 1999, and SSRIs and other types (TCAs as examples) biennially since 2001.

Depressive symptoms were assessed using the five-item Mental Health Index (MHI-5), a subscale of the Short-Form 36 Health Status Survey. The MHI-5 score has been shown to have high sensitivity and specificity for detecting major depressive disorder, with the area under the receiver operating characteristic curve ranging from 0.89 to 0.94 [17, 18]. The MHI-5 score was considered a dichotomous indicator of presence (MHI-5 score ≤52) or absence (MHI-5 score >52) of severe depressive symptoms (SDS). Using a score value of 52 as the cut-off point, Yamazaki et al. [18] reported a sensitivity of 91.8% and specificity of 84.6%. However, MHI-5 was only available in 1992, 1996 and 2000 for NHS I, and in 1993, 1997 and 2001 for NHS II. No information on depressive symptoms was available for men. Women in NHS II in 2001 and men in HPFS in 2002 reported their lifetime history of depression by answering the following two questions. (1) In your lifetime, have you ever had 2 weeks or more when nearly every day you felt sad, blue or depressed for most of the day (0, no; 1, yes)? (2) Did you ever tell a doctor or mental health specialist that you were feeling depressed (0, no; 1, yes)? The study flow is shown in Electronic supplementary material (ESM) Fig. 1.

Assessment of diabetes

In all three cohorts, a supplementary questionnaire regarding symptoms, diagnostic tests and hypoglycaemic therapy was mailed to participants who reported a diagnosis of diabetes mellitus. A case of type 2 diabetes mellitus was considered confirmed if at least one of the following was reported on the supplementary questionnaire according to the National Diabetes Data Group criteria [19]: (1) one or

more classic symptoms (excessive thirst, polyuria, weight loss, hunger) plus fasting plasma glucose levels of at least 7.8 mmol/l or random plasma glucose levels of at least 11.1 mmol/l; (2) at least two elevated plasma glucose concentrations on different occasions (fasting levels of at least 7.8 mmol/l, random plasma glucose levels of at least 11.1 mmol/l and/or concentrations of at least 11.1 mmol/l after 2 h or more shown by oral glucose tolerance testing) in the absence of symptoms; or (3) treatment with hypoglycaemic medication (insulin or oral hypoglycaemic agent). The diagnostic criteria changed in June 1998, and a fasting plasma glucose of 7.0 mmol/l was considered the threshold for the diagnosis of diabetes [20]. Self-reported type 2 diabetes diagnosis through supplemental questionnaire confirmation has been demonstrated to be highly accurate compared with medical record reviews in validation studies [14, 21]. Of a random sample of 62 NHS I participants who reported type 2 diabetes and were confirmed by the supplementary questionnaire, 61 (98%) were reconfirmed after their medical records were reviewed by an endocrinologist blinded to the supplementary questionnaire [21]. We conducted a similar validation study in the HPFS: of 59 type 2 diabetes cases confirmed by the supplementary questionnaire, 57 (97%) were reconfirmed by medical records [14]. In addition, in another substudy to assess the prevalence of undiagnosed diabetes in NHS I, fasting plasma glucose and plasma fructosamine were measured in a random sample of participants who did not report a previous diagnosis of diabetes. Only one (0.5%) of the women had an elevated fasting plasma glucose or plasma fructosamine level in the diabetic range, and her levels were barely above the diagnostic cut-offs [22]. By confirming all self-reported cases of diabetes, we excluded false-positive results, and the NHS I results suggest that the false-negative rate is low. We only included cases confirmed by the supplemental questionnaires in the current analysis.

Covariates In the biennial follow-up questionnaires, we inquired about and updated information on risk factors for chronic diseases, such as body weight, cigarette smoking, physical activity and a family history of diabetes mellitus, as well as a history of chronic diseases, including hypertension and hypercholesterolaemia (and their medication treatments). Marital status and living status were updated every 4 years. Dietary information (including alcohol intake) was assessed using a validated semi-quantitative food frequency questionnaire every 4 years. A low-risk diet score was defined as a diet low in *trans*-fat and glycaemic load and high in cereal fibre, and with a high ratio of polyunsaturated to saturated fat [15]. The dietary score summed the quintile values of the four nutrients, with 5 representing the lowest-risk quintile in each dietary factor [15]. Among NHS I and II participants, we ascertained menopausal status, menopausal hormone use and oral contraceptive use.

Statistical analysis Person-years for each participant was calculated from the date of return of the baseline questionnaire to the date of diagnosis of type 2 diabetes mellitus, death, the end of the follow-up (31 January 2006 for HPFS, 30 June 2008 for NHS I or 30 June 2007 for NHS II) or the date of return of their last questionnaire, whichever came first. Participants with missing information on ADM use during the follow-up were censored. Time-dependent Cox proportional hazards models were used to estimate age- and multivariate-adjusted HRs. In multivariate analysis, we adjusted for age, ethnicity, marital and living status, smoking status, alcohol intake, physical activity, current multivitamin and aspirin use, a family history of diabetes, quintile of dietary score and major comorbidities (hypertension, hypercholesterolaemia and their treatments). Among nurses, we also adjusted for menopausal status and hormone use, and oral contraceptive use (NHS II participants only). Finally, we further adjusted for BMI. All the covariates were chosen by prior knowledge of their potential associations with diabetes or depression. ADM use and all the covariates were updated every 2–4 years and were treated as time-dependent variables, except for ethnicity and a family history of diabetes mellitus. Because ADM use may contribute to diabetes through weight gain, baseline BMI and subsequent weight gain in each 2-year interval were adjusted in a sensitivity analysis.

We investigated the association between different types of ADM and diabetes risk by categorising the participants into four groups: non-users, only SSRI users, only TCA/other users and multiple ADM users. Furthermore, we evaluated the association between ADM use and diabetes risk in participants with or without SDS in NHS I and II.

We also summarised the estimates of association across the three studies via a meta-analysis. Heterogeneity of HRs across studies was evaluated by the Cochrane Q statistic ($p < 0.10$ was considered to indicate significant heterogeneity). The HRs were pooled using the random-effects model if significant heterogeneity was detected, or the fixed-effect model otherwise. All p values were two-sided, and 95% CIs were calculated for HRs. Data were analysed with the Statistical Analysis Systems software package, version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

We documented 1,287 incident cases of type 2 diabetes mellitus during 16 years of follow-up in HPFS (300,084 person-years), 3,514 cases during 12 years in NHS I (566,746 person-years) and 1,840 cases during 14 years in NHS II (777,930 person-years). Table 1 describes the distribution of baseline characteristics according to current ADM use status. The mean age was 56.4 years in HPFS

Table 1 Age-standardised baseline characteristics according to ADM use status in the three cohorts. Data are presented as means for continuous variables and percentages for categorical variables

Characteristic	HPFS (1990)		NHS I (1996)		NHS II (1993)	
	No ADM	ADM	No ADM	ADM	No ADM	ADM
n	29,411	365	57,655	4,136	68,257	8,611
Age (years)	56.4	56.3	61.4	59.8	37.9	39.3
Race (white, %)	95.6	95.5	97.5	98.7	96.4	97.5
Family history of diabetes (%)	20.3	22.6	26.3	26.8	33.8	36.3
BMI (kg/m^2)	25.5	25.6	26.2	27.2	25.0	26.5
Physical activity (MET-h/week)	38.3	27.3	18.4	14.5	21.6	19.4
Smoking status (%)						
Current smoker	7.5	10.8	12.6	13.8	10.4	17.4
Past smoker	41.7	46.0	42.1	46.7	22.8	26.1
Never smoked	50.8	43.2	45.3	39.5	66.8	56.5
Marital status (with spouse, %)	89.3	81.8	78.7	74.2	81.3	69.9
Living status (alone, %)	6.7	11.8	14.5	17.5	8.4	14.0
Dietary score[a]	12.0	11.4	12.0	11.9	12.0	11.9
Alcohol (g/day)	10.3	9.1	5.3	4.7	3.2	3.2
Current aspirin user (%)	31.0	32.0	52.8	47.9	9.5	14.4
Multivitamin supplement user (%)	36.9	42.5	52.0	57.3	43.6	48.0
Menopausal status (premenopausal, %)	NA	NA	12.1	13.2	95.4	90.9
Ever menopause hormone use (%)[b]	NA	NA	57.9	71.2	14.8	26.3
Ever oral contraceptive use (%)[b]	NA	NA	NA	NA	84.2	90.2
Hypertension (%)	23.8	29.5	36.4	43.8	6.8	12.2
Hypercholesterolaemia (%)	28.4	40.5	50.3	60.0	16.0	25.4
MHI-5 score	NA	NA	80.2	68.5	72.7	62.2
Severe depressive symptoms (%)[c]	NA	NA	4.6	20.9	11.1	30.8

[a] Dietary score was defined as sum of quintiles of consumption of cereal fibre, glycaemic load (reverse), polyunsaturated to saturated fat ratio and *trans* fat (reverse) consumption

[b] Current plus past users

[c] Severe depressive symptoms were defined as MHI-5 score 0–52

MET-h/week, metabolic equivalent-hours/week; NA, not available

(range 43–80), 61.3 years in NHS I (range 50–79) and 38.1 years in NHS II (range 29–46). The baseline prevalence of current ADM use in the three cohorts was 1.2% in 1990 (HPFS), 6.7% in 1996 (NHS I), and 11.2% in 1993 (NHS II), respectively. There was a substantial increase in the prevalence of ADM use in all three cohorts over time (7.1% in 2004 for HPFS, 12.3% in 2006 for NHS I and 22.2% in 2005 for NHS II, respectively). Current ADM users were less likely to be physically active, and more likely to be smokers, use multivitamin supplements, live alone and be unmarried. The prevalence of hypertension and hypercholesterolaemia was higher in current ADM users. Current female ADM users tended to have a higher BMI than female non-users, but this was not the case for men. In addition, current ADM use was associated with a worse MHI-5 score in women.

In age-adjusted models, ADM users had an elevated risk of developing type 2 diabetes mellitus across the three cohorts (Table 2). The average absolute risk difference between ADM users and non-users was 2.87 per 1,000 person-years. Adjustment for updated BMI attenuated the associations in women, but not in men. The final multivariate-adjusted HRs (95% CIs) were 1.37 (1.07, 1.76) for HPFS, 1.10 (1.00, 1.21) for NHS I and 1.23 (1.11, 1.37) for NHS II. The HRs were slightly attenuated with further adjustment for MHI-5 scores in NHS I and II, and became non-significant for NHS I (HR 1.08 [0.97, 1.19]). After pooling of the estimates across the three studies, the HR for developing type 2 diabetes associated with current ADM use was 1.17 (1.09, 1.25).

We further analysed the association between different types of ADM and diabetes risk (Table 3). Neither type of ADM was associated with diabetes risk in NHS I and HPFS. Both SSRIs and TCAs/others were associated with increased risks in NHS II, which were not substantially

Table 2 ADM use and risk of type 2 diabetes in the three cohorts

	HPFS (1990–2006)		NHS I (1996–2008)		NHS II (1993–2007)		Pooled (random-effects model)	
	No ADM	ADM	No ADM	ADM	No ADM	ADM	No ADM	ADM
Cases/person-years	1,219/290,794	68/9,290	3,040/511,713	474/55,033	1,337/672,931	503/104,999	5,596/1,475,438	1,045/169,241
Crude incidence, per 1,000 person-years	4.19	7.32	5.94	8.61	1.99	4.79	3.79	6.17
Age-adjusted model	1.00	1.66 (1.30, 2.12)	1.00	1.40 (1.27, 1.54)	1.00	2.05 (1.84, 2.27)	1.00	1.68 (1.27, 2.23)
Multivariate-adjusted model[a]	1.00	1.34 (1.04, 1.72)	1.00	1.19 (1.08, 1.31)	1.00	1.42 (1.28, 1.58)	1.00	1.30 (1.14, 1.49)
Further adjusted for BMI[b]	1.00	1.37 (1.07, 1.76)	1.00	1.10 (1.00, 1.21)	1.00	1.23 (1.11, 1.37)	1.00	1.17 (1.09, 1.25)[d]
Further adjusted for MHI-5 score[c]	NA	NA	1.00	1.08 (0.97, 1.19)	1.00	1.21 (1.08, 1.35)	NA	NA

Data are HR (95% CI)

[a] HRs were adjusted for age (continuous), ethnicity (whites, non-whites), marital status (having spouse or not), living status (alone, with others), smoking status (never smoked, past smoker, current smoker), alcohol intake (0, 0.1–4.9, 5.0–14.9, ≥15.0 g/day in women, 0, 0.1–4.9, 5.0–29.9, ≥30.0 g/day in men), multivitamin and aspirin use (yes, no), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9 and ≥27.0 metabolic equivalent-hours/week), family history of diabetes, major comorbidities (history of hypertension, hypercholesterolaemia and their treatments) and quintile of dietary score. Among women, we also adjusted for menopausal status and hormone use, and oral contraceptive use (NHS II participants only)

[b] HRs were further adjusted for BMI (<23.0, 23.0–24.9, 25.0–29.9, 30.0–34.9 and ≥35.0 kg/m^2)

[c] HRs were further adjusted for MHI-5 score (0–52, 53–75, 76–85, 86–100)

[d] Fixed-effect model was chosen because of non-significant heterogeneity statistic (p>0.10)

NA, not available

Table 3 Different types of ADM use and diabetes risk in the three cohorts

Variable	Cases/person-years	Crude incidence, per 1,000 person-years	Age-adjusted model	Multivariate-adjusted model[a]	Further adjusted for BMI[b]	Further adjusted for MHI-5 score[c]
HPFS (1996–2006)						
No ADM	827/172,521	4.79	1.00	1.00	1.00	NA
SSRIs	33/4,988	6.62	1.45 (1.02, 2.06)	1.17 (0.82, 1.67)	1.13 (0.79, 1.60)	NA
TCAs, others	20/2,614	7.65	1.69 (1.08, 2.63)	1.37 (0.88, 2.14)	1.50 (0.96, 2.35)	NA
Multiple	3/346	8.67	2.07 (0.67, 6.46)	1.39 (0.45, 4.33)	1.22 (0.39, 3.84)	NA
NHS I (2000–2008)						
No ADM	1,890/303,466	6.23	1.00	1.00	1.00	1.00
SSRIs	206/25,728	8.01	1.28 (1.10, 1.47)	1.11 (0.96, 1.28)	1.01 (0.87, 1.17)	0.99 (0.85, 1.15)
TCAs, others	109/12,619	8.64	1.38 (1.14, 1.68)	1.19 (0.98, 1.44)	1.14 (0.93, 1.38)	1.12 (0.92, 1.36)
Multiple	26/3,253	7.99	1.26 (0.85, 1.86)	0.98 (0.66, 1.44)	0.87 (0.59, 1.29)	0.84 (0.57, 1.25)
NHS II (1993–2007)						
No ADM	1,337/672,931	1.99	1.00	1.00	1.00	1.00
SSRIs	306/59,796	5.12	2.01 (1.78, 2.28)	1.44 (1.27, 1.64)	1.18 (1.04, 1.34)	1.16 (1.02, 1.32)
TCAs, others	137/33,788	4.05	1.91 (1.60, 2.28)	1.35 (1.12, 1.61)	1.33 (1.11, 1.59)	1.31 (1.09, 1.57)
Multiple	60/11,415	5.26	2.70 (2.08, 3.51)	1.52 (1.17, 1.98)	1.30 (1.00, 1.69)	1.26 (0.96, 1.65)
Pooled results (random-effects model)						
No ADM	4,054/1,148,918	3.53	1.00	1.00	1.00	NA
SSRIs	545/90,512	6.02	1.56 (1.11, 2.20)	1.25 (1.02, 1.52)	1.10 (1.00, 1.22)[d]	NA
TCAs, others	266/49,021	5.43	1.64 (1.29, 2.08)	1.28 (1.13, 1.45)[d]	1.26 (1.11, 1.42)[d]	NA
Multiple	89/15,014	5.93	1.91 (1.04, 3.35)	1.25 (0.81, 1.92)	1.09 (0.74, 1.61)	NA

Data are HR (95% CI)

[a] HRs were adjusted for age (continuous), ethnicity (whites, non-whites), marital status (having spouse or not), living status (alone, with others), smoking status (never smoked, past smoker, current smoker), alcohol intake (0, 0.1–4.9, 5.0–14.9, ≥15.0 g/day in women, 0, 0.1–4.9, 5.0–29.9, ≥30.0 g/day in men), multivitamin and aspirin use (yes, no), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9 and ≥27.0 metabolic equivalent-hours/week), family history of diabetes, major comorbidities (history of hypertension, hypercholesterolaemia and their treatments), and quintile of dietary score. Among women, we also adjusted for menopausal status and hormone use and oral contraceptive use (NHS II participants only)

[b] HRs were further adjusted for BMI (<23.0, 23.0–24.9, 25.0–29.9, 30.0–34.9 and ≥35.0 kg/m^2)

[c] HRs were further adjusted for MHI-5 (0–52, 53–75, 76–85, 86–100)

[d] Fixed-effect model was chosen because of non-significant heterogeneity statistic (p>0.10)

NA, not available

attenuated after adjustment for MHI-5 score. In HPFS, HR of diabetes for TCA/other use was 1.50 (95% CI 0.96, 1.35), while HR for TCA-only use was 2.67 (95% CI 1.66, 4.29). The pooled HRs (95% CIs) for use of SSRIs, TCAs/others and multiple types were 1.10 (1.00, 1.22), 1.26 (1.11, 1.42) and 1.09 (0.74, 1.61), respectively.

We also investigated the joint association of current ADM use and SDS with diabetes risk in women (Table 4). In the old-age cohort (NHS I), participants with both SDS and ADM use had an increased risk, while those with only SDS or ADM use had no increased risk. In the young-age cohort (NHS II), SDS and ADM use were individually and jointly associated with increased risk. However, no significant interaction was found in either NHS I (p for interaction=0.60) or NHS II (p for interaction=0.20). After the results from the two cohorts had been pooled, compared with women without SDS and ADM use, ADM use alone and SDS alone were associated with a 15% (95% CI 6%, 24%) and 14% (95% CI 1%, 28%) increased risk of type 2 diabetes, respectively, while the combination of SDS and ADM use was associated with a 25% (9%, 44%) increased risk.

In a sensitivity analysis of controlling for baseline BMI along with weight change in each interval instead of updated BMI, the results were similar (HR 1.20 [95% CI 1.12, 1.28]). The results were also similar for adjustment of updated BMI as a continuous variable (HR 1.16 [95% CI 1.08, 1.25]). Analyses stratified by age, overweight, significant weight gain (defined as weight gain of more than 5%) and history of hypertension or hypercholesterolaemia revealed similar risk estimates and no indications of interactions (ESM Table 1). Only baseline ADM use was not a predictor for incident type 2 diabetes (pooled HR 1.07 [95% CI 0.94, 1.22]), while the incident ADM use (excluding the baseline prevalent ADM users from the analysis) was associated with a significantly increased risk

Table 4 Risk of type 2 diabetes according to SDS and ADM use in the NHS[a]

Variable	No SDS		SDS	
	No ADM use	ADM use	No ADM use	ADM use
NHS I (1996–2008)				
Cases/person-years	2,810/478,455	376/44,980	128/18,707	90/8,520
Crude incidence, per 1,000 person-years	5.87	8.36	6.84	10.56
Age-adjusted model	1.00	1.37 (1.23, 1.52)	1.20 (1.01, 1.43)	1.77 (1.43, 2.18)
Multivariate-adjusted model[b]	1.00	1.18 (1.05, 1.31)	1.05 (0.88, 1.26)	1.38 (1.12, 1.71)
Further adjusted for BMI[c]	1.00	1.09 (0.97, 1.21)	1.10 (0.92, 1.31)	1.30 (1.05, 1.61)
NHS II (1993–2007)				
Cases/person-years	1,107/573,190	342/74,137	162/61,832	131/25,689
Crude incidence, per 1,000 person-years	1.93	4.61	2.62	5.10
Age-adjusted model	1.00	1.98 (1.75, 2.24)	1.48 (1.25, 1.75)	2.42 (2.02, 2.90)
Multivariate-adjusted model[b]	1.00	1.44 (1.27, 1.63)	1.20 (1.02, 1.42)	1.37 (1.14, 1.65)
Further adjusted for BMI[c]	1.00	1.23 (1.08, 1.39)	1.17 (0.99, 1.38)	1.22 (1.01, 1.47)
Pooled results[d]				
Final multivariate adjusted model	1.00	1.15 (1.06, 1.24)	1.14 (1.01, 1.28)	1.25 (1.09, 1.44)

Data are HR (95% CI)

[a] SDS were defined as MHI-5 score 0–52

[b] HRs were adjusted for age (continuous), ethnicity (whites, non-whites), marital status (having spouse or not), living status (alone, with others), smoking status (never smoked, past smoker, current smoker), alcohol intake (0, 0.1–4.9, 5.0–14.9, ≥15.0 g/day in women, 0, 0.1–4.9, 5.0–29.9, ≥30.0 g/day in men), multivitamin and aspirin use (yes, no), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9 and ≥27.0 metabolic equivalent-hours/week), family history of diabetes, major comorbidities (history of hypertension, hypercholesterolaemia and their treatments), and quintile of dietary score. Among women, we also adjusted for menopausal status and hormone use and oral contraceptive use (NHS II participants only)

[c] HRs were further adjusted for BMI (<23.0, 23.0–24.9, 25.0–29.9, 30.0–34.9 and ≥35.0 kg/m^2)

[d] Results were pooled by fixed-effect models because of non-significant heterogeneity statistic (p for heterogeneity all >0.10)

of type 2 diabetes (pooled HR 1.27 [95% CI 1.08, 1.48]), suggesting that recent ADM use might be more relevant to the elevated risk.

Discussion

In the three cohorts of more than 160,000 US men and women with 12–16 years of follow-up, ADM users were at a moderately increased risk of developing type 2 diabetes mellitus after adjustment of the figures for diabetes risk factors. The increased risk did not appear to differ by types of ADM (SSRIs or others). The association was in part, but not completely, explained by BMI.

The relationship between depression and diabetes is of particular interest, since both conditions are major contributors to the global burden of chronic diseases. Several epidemiological studies have documented a bidirectional association between depression and diabetes: depression increases the risk of developing diabetes and, vice versa, diabetes is also associated with an increased risk of being depressed [23, 24]. However, whether antidepressant treatment could elevate diabetes risk remains controversial. Rubin et al. [8] found in the Diabetes Prevention Program (DPP) study that ADM use (78% were SSRIs) was associated with a more than twofold increased risk of type 2 diabetes among participants with impaired glucose tolerance who were assigned to lifestyle or placebo diabetes prevention interventions, even after depressive symptoms had been controlled for. However, the increased risk was not detected in participants in the metformin intervention arm [8]. Recently, two large nested case–control studies using medical record databases in the UK [9] and Finland [10] both found an increased diabetes risk associated with long-term ADM use of moderate and/or high daily doses for depression treatment, and the association was independent of depression severity. The associations were found for both SSRIs and TCAs in these two studies [9, 10]. A cohort study among 1,000 older Australians found that ADM use was associated with an 80% (95% CI −9%, 257%) non-significant increased risk [12]. Campayo et al. [13] found in a Spanish community sample of adults aged ≥55 years (n=3,521) that the HR for ADM use was 1.26 (95% CI 0.63, 2.50). Knol et al. [11] used prescription data from the PHARMO database and did not find an increased risk in antidepressant users. However, this study lacked information on BMI and lifestyle factors, and included only patients with hypoglycaemic treatment as diabetes

cases. We also found that only baseline ADM use did not predict risk of type 2 diabetes, suggesting that recent ADM use might be more relevant to the elevated risk. The results concurred with the findings of Andersohn et al. [9] that recent ADM use was positively associated with the risk of type 2 diabetes, but not past use of antidepressants.

To the best of our knowledge, the current analysis is the largest prospective cohort study investigating the association between ADM use and diabetes risk. Despite heterogeneity in study design, population characteristics and risk estimates, our findings are largely consistent with those from previous studies. The results from NHS I were somewhat weaker than those from NHS II and HPFS. Despite homogeneity in study design and target population (health professionals or nurses, mostly white), the cohorts have considerable heterogeneity. First, the age ranges are different. The NHS I encompasses middle-aged and elderly women (50–79 years old at baseline), while NHS II consists of a group of younger women (29–46 years old at baseline). One potential reason for the null association in NHS I was that early-onset diabetes had been excluded, and participants with severe depression were more likely to withdraw from the study during the early follow-up of the entire cohort before 1996 (1976–1996), and thus the remaining participants in NHS I were relatively less depressed. Whether the increased risk found in NHS II but not in NHS I reflects an age-specific effect of ADM on diabetes risk remains unclear and deserves further investigation. Second, the prevalence of ADM use was substantially lower in men than women. This may reflect the sex difference of depression prevalence [25], as well as the reluctance of men to seek [26] or receive treatment [27] compared with women. In the present study, the baseline prevalence of ADM use in HPFS was 1.2% in 1990, which was consistent with the National Comorbidity Survey 1990–1992, where 1.4% of male participants reported ADM use [28]. This prevalence climbed to 2.9% in 1996 and 7.1% in 2004 in HPFS. The prevalence of ADM use over time in our studies was consistent with several national datasets [1, 28]. Finally, the results of specific types of ADM use should be interpreted cautiously because the reasons for prescribing the specific types of ADM may be different. The prevalence of SSRI use increased in all three cohorts over time, which was coincident with SSRIs becoming the first-line treatment for depression during follow-up [29]. Individuals using TCAs or multiple types of ADM were more likely to be non-responsive to the initial medication [29].

Antidepressants may be associated with an increased diabetes risk through a variety of mechanisms. First, ADM use may primarily be a marker of depression severity and/or chronicity, and depression has been shown to increase the risk of subsequent diabetes [23, 24]. ADM users may have been more severely depressed or have a history of chronic or recurrent depression. Second, ADM use was associated with poor health behaviours (i.e. smoking and physical inactivity) and a high prevalence of major comorbidities in this study. Although we controlled for a large number of health behaviour factors and other medical conditions, residual confounding is still possible. Furthermore, weight gain is a common side effect in short- and long-term treatment with TCAs [4]. There is evidence of an initial stable weight or even weight loss with the use of SSRIs, followed by weight gain in the long-term phase [5]. Kivimaki et al. [10] found that ADM use (and different types) was associated with significantly more weight gain compared with non-users in a nested case–control study. The association between ADM use and diabetes was largely attenuated, but remained significant even after we controlled for updated BMI or weight gain in our study, which is consistent with the DPP results [8], suggesting that other mechanisms beyond weight gain may have a role. Moreover, a mechanistic study found that some SSRIs could act as inhibitors of insulin signalling and as potential inducers of cellular insulin resistance [6]. Different ADMs have varied binding affinities to various receptors, which may be involved in different effects on insulin secretion and action [30]. The associations with different types of ADM, even within a certain type, have been suggested by a recent report [9]. Therefore future studies need to be more specific on types of ADM, beyond those of SSRIs and TCAs, and should examine more recent forms of ADM, such as serotonin–norepinephrine reuptake inhibitors.

Strengths, limitations and implications Strengths of the present study include the large sample size, long-term follow-up and biennially updated information on medication use, disease onset and lifestyle risk factors. Time-dependent Cox models were performed to incorporate these repeated measures, which minimised the possibility of residual and time-dependent confounding.

This study also has several limitations and the results should be interpreted with caution. First, our study populations primarily consisted of health professionals with European ancestry. Although their concern about health status and better understanding of health-related issues enhanced the reliability and validity of our questionnaire data, the generalisability to other populations may be limited. Nevertheless, it appears unlikely that the fundamental biology underlying a relationship between ADM and diabetes would be different between our cohorts and the general population.

Second, the diabetes cases were self-reported, but we only included cases confirmed by the supplemental questionnaires. Moreover, information on ADM use was self-reported, and we

could not assess the association between specific agents, doses and duration of drug use with diabetes risk. Furthermore, we lacked clinical data on participants' depression history, severity and chronicity. Notably, ADM use may be a marker of depression severity and/or chronicity, and it is possible that the underlying more severe depressive disorder rather than ADM use increases risk of diabetes. We attempted to account for this by adjusting for a depressive score in women, but residual confounding may remain, since this score could not capture the history and chronicity of depression and we did not have depressive symptom information for men. A specific depression symptoms measure (such as the Diagnostic Interview Schedule, Center for Epidemiologic Studies Depression Scale) may better capture the severity of depression.

Another limitation is that ADMs can be used for conditions other than depression, such as anxiety disorders, insomnia, neuropathic pain, and premenstrual syndrome and hot flushes in women. We could not distinguish different indications for ADMs in our cohorts. In a secondary analysis, we found that 79% of ADM users in HPFS reported a lifetime history of depression in 2002, and the proportion was 91% in NHS II in 2001, when questions about lifetime history of depression were asked. These data indicate that the majority of participants used ADM for treating depression or related symptoms.

In addition, surveillance bias due to the disease diagnosis is also possible in our analyses, although our participants had regular physical examinations and ready access to healthcare systems. Finally, our results cannot prove causality, like any other observational data. Studies with post-intervention follow-up of existing randomised placebo-controlled antidepressant trials can be used to evaluate the effects on glucose homoeostasis, insulin sensitivity and diabetes risk.

Conclusions The results from the three large long-term cohort studies suggest that individuals with antidepressant treatment had a moderately increased risk of developing type 2 diabetes. This association appeared to be partly mediated through BMI, particularly in women. However, this study cannot determine whether ADM use is a causal risk factor for type 2 diabetes, or serves as a marker of depression severity/chronicity. Additional research is needed to confirm these results with more detailed information on dose and duration of treatment and other clinical variables. Mechanistic studies are also required to better understand the influence of antidepressants on glucose tolerance and carbohydrate metabolism. Before conclusive evidence on this relationship is obtained, patients with depression are advised to adhere to their treatment strategies with careful attention to their body weight and blood glucose level.

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