**Title page**

Title: Antidepressant use and risk of adverse outcomes: a population-based cohort study

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**Abstract**

Background

Antidepressants are one of the most widely prescribed drugs in the global north. Recent rises in prescribing reflect an increase in treatment duration. However, little is known about the health consequences of long-term antidepressant treatment. This study aimed to investigate the association between antidepressant use and adverse events.

Method

The study cohort consisted of UK Biobank participants whose data had been linked to primary care records (N= 222,121). We assessed the association between antidepressant use by drug class (SSRI and ‘Other’) and four morbidity (diabetes, hypertension, coronary heart disease (CHD), cerebrovascular disease (CVA)) and two mortality (cardiovascular disease (CVD) and all-cause (ACM)) outcomes using Cox’s proportional hazards model at 5- and 10-years follow-up.

Results

SSRI treatment was associated with a decreased risk of diabetes at 5-years (HR: 0.64; 95%CI 0.49 to 0.83) and 10-years (HR: 0.68; 0.53 to 0.87) and hypertension at 10-years (HR: 0.77; 0.66 to 0.89). At 10-year follow-up, SSRI treatment was associated with increased risks of CVA (HR: 1.34; 1.02 to 1.77), CVD mortality (HR: 1.87; 1.38 to 2.53) and ACM (HR: 1.73; 1.48 to 2.03) and ‘Other’ class treatment was associated with increased risk of CHD (HR: 1.99; 1.31 to 3.01), CVD (HR: 1.86; 1.10 to 3.15) and ACM (HR: 2.20; 1.71 to 2.84).

Conclusions

Our findings indicate an association between long-term antidepressant usage and elevated risks of CHD, CVD mortality, and all-cause mortality. Further research is needed to assess whether the observed associations are causal and to elucidate the underlying mechanisms.

**Relevance statement**

Antidepressants are one of the most widely prescribed drugs and there has been striking increases in treatment duration across the global north over the past two decades. Yet little is known about the long-term adverse health effects of antidepressant treatment. This is particularly concerning given the increased risk of cardiovascular disease and mortality in patients with depression. Our paper extends previous work in the field by providing more precise estimates of the association between antidepressant use and adverse outcomes including diabetes, hypertension, stroke, coronary heart disease (CHD), cardiovascular disease (CVD) and all-cause mortality. Our findings suggest a need to review treatment plans for patients on long-term antidepressants, particularly those who are at greater risk of cardiovascular disease. These findings will be of interest to both patients and clinicians and will inform discussions about the long-term use of such medication.

**Introduction**

Antidepressants are one of the most widely prescribed drugs. Seventy million prescriptions were dispensed in 2018, amounting to nearly a doubling of prescriptions in a decade.1,2 This striking rise in prescribing is attributed to long-term treatment rather than an increased incidence of depression 3,4 and these trends are not limited to the UK.5-7 To reduce the risk of relapse, current guidelines recommend maintenance treatment of at least six months for patients who have recovered from depression, and at least two years for those identified at risk of recurrent depression.8 Some patients may also stay on treatment long-term due to difficulties with discontinuation and infrequent monitoring.9 One Scottish study found that over half of patients on antidepressants had been taking them for more than two years, with a mean treatment duration of 5.5 years.10 However, little is known about the health consequences of long-term antidepressant treatment. There is in vitro evidence to suggest that some antidepressants have the potential to cause adverse cardiovascular and metabolic effects.11-14 Yet, most trials assessing the efficacy of antidepressants are poorly suited to examining adverse outcomes: they are often short term, are underpowered to look at most adverse outcomes, have methodological shortcomings 15,16; and do not always report adverse effects, particularly serious ones.15,17-21

Depression is strongly associated with adverse risk profiles such as excess adiposity, smoking, poor diet and physical inactivity.22,23 These phenotypes and behaviours are established risk factors for a number of chronic conditions including cardiovascular disease.24 Therefore, careful assessment of the long-term cardiometabolic effects of antidepressant treatment is critical.25 The main challenge for observational studies examining potential adverse outcomes of long-term antidepressant use is accounting for the excess cardiovascular risk associated with depression (confounding by indication). Studies have attempted to control for this confounding by limiting analyses to patients with a diagnosis of depression. However, there are considerable challenges relating to diagnostic validity and not all primary care physicians give or record a diagnosis of depression even when it is recognised.26 Another approach is to identify and adjust for cardiometabolic risk factors that confound the association between depression and cardiometabolic outcomes. Meta-analyses of studies exploring the association between antidepressant use and a wide range of cardiometabolic outcomes reveal considerable heterogeneity between studies 27-29 and the evidence base remains weak.25 For example, a recent meta-analysis showed a 27% increased risk of diabetes with antidepressant use, but there was considerable variation in confounder adjustment within individual studies and none fully accounted for major risk factors and predictors for diabetes including key markers of the metabolic syndrome.27

Given the multifactorial nature of depression and cardiometabolic disease,30,31 information on a wide range of prospectively measured confounders including lifestyle, sociodemographic factors, and baseline biomarkers for cardiometabolic disease are needed to provide robust estimates of the risks associated with long-term antidepressant use. This requires richly phenotyped cohorts. One such cohort is UK Biobank, which is a large population-based cohort study (~500,000 participants).32 This open access resource has detailed information on socioeconomic status, demographics, anthropometric, behavioural, and biochemical risk factors, disability, and health status with linkages to routinely available national datasets including primary care records and deaths. We used the UK Biobank dataset to examine the association between antidepressant use and four cardiometabolic morbidity outcomes (diabetes, hypertension, cerebrovascular disease (CVA), coronary heart disease (CHD)) and two mortality outcomes (cardiovascular disease (CVD) mortality, and all-cause mortality (ACM)).

**Methods**

*Study cohort*

UK Biobank recruited ~500,000 participants aged 40 to 69 years between 2006 and 2010. Our cohort was restricted to participants (N= 222,121) whose data had been linked to primary care records during the first phase of primary care data extraction (extracted in 2018, released 2019). Biobank participants who were registered with a GP practice at least 12 months prior to study baseline and remained registered at study entry (Biobank entry date) were eligible for inclusion. Participants were excluded from this study if they had a prior recorded prescription for antidepressants (≤12 months before baseline); any prior recorded diagnosis for the outcome of interest; any prior recorded prescription for antipsychotics, lithium or antimanic drugs; or self-reported use of cardiometabolic drugs at baseline. We also excluded participants on antidepressant polytherapy. Participants entered our cohort at Biobank baseline assessment date. Participants who did not have the event of interest within the follow-up period were censored at the earliest of: (1) date of death; (2) date of leaving GP practice; or (3) end of follow-up period (either 5 or 10 years).

*Ethics and consent*

UK Biobank has obtained ethics approval from the North West Multi-centre Research Ethics Committee which covers the UK (approval number: 11/NW/0382) and has obtained informed consent from all participants.

*Exposure assessment*

We extracted information on antidepressant use (antidepressant type, strength of medication, date of prescription, and quantity prescribed) from linked primary care prescribing data focusing on ten of the most commonly prescribed antidepressants in England 1 (with the exclusion of: (1) Amitriptyline – often prescribed for pain or sleep problems in low doses; and (2) Dosulepin – not recommended in the UK national depression guidelines by the National Institute for Health and Care Excellence (NICE).33 Information on the dosing schedule was not available for extraction. The remaining eight antidepressants were categorised by drug class as selective serotonin reuptake inhibitors (SSRI’s) (citalopram, sertraline, fluoxetine, paroxetine) and ‘Other’ antidepressants (mirtazapine, venlafaxine, duloxetine, trazodone). Antidepressant treatment was defined as a time-varying exposure (i.e., participants were classified as unexposed prior to their first antidepressant prescription and subsequently classified as exposed at the date of the first antidepressant prescription). Antidepressant use was assessed in three ways: (1.) any antidepressant treatment; (2.) SSRI antidepressant treatment; (3.) ‘Other’ antidepressant treatment. To explore the dose-response relationship between antidepressant use and outcome, we calculated the number of defined daily doses (DDDs) using values on the average maintenance dose assigned by the World Health Organisations Collaborating Centre for Drug Statistics Methodology ([www.whocc.no/atc\_ddd\_index](http://www.whocc.no/atc_ddd_index)). These were categorised as ≤0.5, >0.5 to 1.0, and >1.0. For example, for citalopram the DDD is 20mg, 0.5 DDD is 10mg and >1.0 DDD is anything more than 20mg. In our study, DDD categories are referred to as low (≤0.5), intermediate (>0.5 to 1.0) and high (>1.0). For the purposes of calculating DDD, we used the recorded product strength and estimated the prescribed daily dose from the total amount prescribed divided by the duration of treatment. The reference category was no antidepressant use and included unexposed time periods prior to starting treatment and unexposed time for those who did not receive an antidepressant prescription during follow-up.

*Outcome assessment*

We selected four morbidity (diabetes, hypertension, CHD, CVA) and two mortality (CVD and all-cause mortality) outcomes. Information on study outcomes were identified using relevant Read v2 and CTV3 codes (using QOF version 38: [https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/quality-and-outcomes-framework-qof/quality-and-outcome-framework-qof-business-rules/quality-and-outcomes-framework-qof-business-rules-v-38-2017-2018-october-code-r](https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/quality-and-outcomes-framework-qof/quality-and-outcome-framework-qof-business-rules/quality-and-outcomes-framework-qof-business-rules-v-38-2017-2018-october-code-release)) extracted from linked primary care records (diabetes, hypertension, CHD, CVA) and ICD-10 codes extracted from death records (CVD; ACM). Outcomes were only included if they occurred after the date of entry into the cohort. We defined first incidence as the first recorded outcome during follow-up and with no prior recorded diagnosis for the outcome in primary care records and no self-reported diagnosis at baseline assessment. We initially planned to look at risk of outcome over five years, however, due to small numbers of events, extended our follow-up period to ten years. We have included results from the 5-year follow-up to allow comparison.

*Confounder assessment and selection*

As highlighted earlier, depression, the main indication for antidepressants, is strongly associated with adverse risk profiles such as excess adiposity, smoking, and physical inactivity. These are established risk factors for cardiovascular disease and diabetes. To account for these shared risk factors, and given the multifactorial nature of cardiometabolic disease, we identified a wide range of personal, lifestyle, sociodemographic, and biomarker covariates as potential confounders. These were age, gender, body mass index (BMI), waist to hip ratio (WHR), smoking and alcohol intake status, physical activity, parental history of outcome, biochemical and haematological biomarkers (apolipoproteins A and B, vitamin D, triglycerides, HbA1c), socioeconomic status (accommodation status, number of vehicles per household, employment status, benefits status, urban/rural status, education, household income) and self-reported long-term illness, disability or infirmity (as a generic measure of “ill-health”). All confounders were assessed at baseline. Analyses were restricted to participants with nonmissing information on confounders. Confounders for each outcome and follow-up period were selected using a stepwise approach through backward elimination, beginning with a model that included the main exposure of interest and all potential confounders. Except for age and gender (included in all models), confounders were retained where the Wald test was p≤0.05 and excluded if p>0.05). Non-linear relationships between outcome and continuous confounders were considered by identifying, at each iterative step of the stepwise process, the best-fitting fractional polynomial terms. Details of the selected confounders for each model are shown in Appendix 3.

*Sensitivity analysis*

We did not have sufficient numbers to compare the effects of short-term antidepressant usage with long term. However, we carried out a sensitivity analysis to exclude short term usage (< 90 days) and get a better sense of long-term chronic effects, i.e. related to metabolic dysfunction.

*Statistical analysis*

All analyses were conducted in Stata version 16. The association between antidepressant treatment and each outcome (diabetes, hypertension, CVA, CHD, CVD mortality, and ACM) was quantified using Cox’s proportional hazards model with study duration as the underlying timescale. Antidepressant treatment was treated as a time-varying exposure. Hazard ratios (HR) and 95% confidence intervals (95%CI) were estimated for each antidepressant treatment category (Any, SSRI, ‘Other’) and outcome. Results are provided firstly from a model adjusting for baseline age and gender, and then secondly from the fully adjusted model using the confounders selected by the multivariable selection procedure described above. We also estimated HR and 95%CI by DDD category for the 10-year follow-up (insufficient number of events at 5-year follow-up). The proportional hazards assumption was assessed by means of the scaled Schoenfeld residuals, which were used to test the proportionality over time for each covariate in the final model being fitted. If there was evidence at the 5% level of a violation of the PH assumption for any covariate, the final model was refitted including a time-varying coefficient (i.e., an interaction term between that particular covariate and time). Kaplan Meier curves for each of the outcomes are shown in Appendix 4.

**Results**

Biobank participants who had linked primary care data were similar to participants without such data in terms of key sociodemographic and clinical characteristics (age, gender, ethnicity, socioeconomic status, BMI, long-term illness) (Appendix 1). The number of participants in the final study cohort varied by outcome (Fig. 1). Baseline participant characteristics are presented for each outcome cohort in Table 1. On average (median) participants were aged 56-57 years, around half of the participants or just over were female, and 96% were White.

On average, 8% of participants in each cohort had been prescribed an antidepressant by the five-year follow-up and 6% by the 10-year follow-up (Appendix 2). SSRIs were the most commonly prescribed antidepressant class (80-82%) and citalopram was the most commonly prescribed SSRI (46 to 47%). Mirtazapine was the most frequently prescribed antidepressant in the ‘‘Other’’ category (44 to 46%) (Appendix 2).

The number of events, person-years follow-up, and HR (95%CI) for the six outcomes by antidepressant class are presented in Tables 2 and 3 for the 5 and 10 year follow-ups, respectively.

At 5 years (Table 2), in models that adjusted for age and gender, any antidepressant use was associated with an increased risk of diabetes (HR: 1.28; 95%CI 1.03, 1.59), CHD (HR: 1.63; 1.22, 2.17), and ACM (HR: 1.79; 1.45, 2.23), with only weak evidence of an increased risk of CVD mortality (HR: 1.53; 0.89, 2.61) with the confidence interval for the latter including the null. For CHD and ACM, findings were attenuated after further adjustment for confounders (CHD: HR 1.47 [1.10, 1.95]; ACM: HR 1.37 [1.10, 1.70]) and were no longer evident in the fully adjusted models for diabetes (HR 0.83; 95%CI 0.66, 1.04) or CVD mortality (HR 1.21; 95%CI 0.70, 2.10). Looking at antidepressants by class (SSRIs and ‘Other’ AD) did not change the overall pattern of results for CHD and ACM. ‘Other’ antidepressants were associated with an increased risk of diabetes in the model adjusting for age and gender (HR 2.03; 1.47, 2.81), but this was no longer evident in the fully adjusted model (HR: 1.13; 0.81, 1.57). However, SSRIs were weakly associated with a reduced risk of diabetes in the model adjusted for age and gender, which became stronger following full adjustment (HR 0.64; 95%CI 0.49, 0.83). There was no clear evidence of any association between antidepressant use and either hypertension or CVA, although the number of CVA outcomes was small (n=31).

Antidepressant treatment was similarly associated with an increased risk of CHD and ACM at 10 years (Table 3), and these effects were only slightly attenuated in the fully adjusted model.

Antidepressants in the ‘Other’ class were associated with a higher risk of these outcomes. There was a weak association between any antidepressant use and incident diabetes (HR: 1.12; 0.92, 1.37), but the direction of this effect was reversed following adjustment for all confounders (HR: 0.77; 0.63, 0.94). Similar findings were observed for SSRIs, but ‘Other’ antidepressants were associated with a small increased risk of diabetes, although the confidence interval included the null (HR: 1.17; 0.87, 1.57). There was also evidence that any antidepressant use was associated with an increased risk of both CVA and CVD mortality at 10 years, which attenuated only slightly following full adjustment (CVA: HR 1.26; 0.97, 1.62; CVD mortality: HR 1.89; 1.44, 2.49). Looking at antidepressant class, this effect was only observed for SSRIs and CVA (fully adjusted HR 1.34) but was seen with both antidepressant groups for CVD mortality. In contrast, any antidepressant use was associated with a reduction in incident hypertension (fully adjusted HR 0.80; 0.70, 0.91), as was SSRI use (HR 0.77; 0.66, 0.89).

There was some evidence of a dose-response effect (Table 4) for all-cause mortality, with higher doses associated with an increased risk of this outcome. This was reflected in the analysis of the two antidepressant classes. A similar pattern was evident for CVA and CHD, but the results were subject to considerable uncertainty. There was no clear evidence of a dose-response effect for the other outcomes.

The results of the sensitivity analysis removing individuals with short periods of antidepressant prescription use did not markedly have an impact on the associations of interest (Appendix 5).

***Discussion***

*Brief summary of the main findings*

This population-based cohort study investigated whether commonly prescribed antidepressants were associated with a risk of developing diabetes, hypertension, CVA, CHD, and mortality (CVD and all-cause). Our study found that long-term antidepressant use was associated with an increased risk of CHD, CVD, and all-cause mortality. These issues appear to be more problematic for antidepressants other than SSRIs (mirtazapine, venlafaxine, duloxetine, trazodone), with the use of such drugs associated with a two-fold increased risk of CHD, CVD and all-cause mortality at 10 years. There was also some evidence that antidepressants, and particularly SSRI’s, were associated with a reduced risk of developing hypertension and diabetes. The findings were particularly evident after 10 years follow-up where we had larger numbers of events.

Comparison of hazard ratios before and after adjustment for a large number of confounders suggested that the associations between antidepressant use and increased risk of diabetes are confounded by adverse clinical phenotypes commonly associated with depression. For diabetes, this confounding appears to be driven by key metabolic risk markers and factors for this condition, mainly HbA1C and BMI.34,35 This is less apparent for hypertension where there was little difference in estimates before and after adjustment for all confounders.

*Comparison with existing studies*

Previous meta-analyses have highlighted the challenges of comparing work in this field because of significant heterogeneity in study design and methods, including measurement of exposures, outcomes, and adjustment for confounders.25 A systematic review and meta-analysis of randomised trials found that SSRIs were associated with an improvement in glycemia, which was not moderated by depression status, diabetes status, or change in weight across studies.36 This work is consistent with our findings of a lower risk of diabetes with SSRI treatment. In contrast, a meta-analysis 27 and pharmaco-vigilance study 37 both found an association between treatment with antidepressants and increased rates of diabetes. The conflicting findings between these studies and our work could be explained by differences in the adjustment for confounders. For example, in the meta-analysis, none of the included studies adjusted for HbA1C and less than half adjusted for BMI.27 The lack of adjustment of key risk factors associated with depression, the main indication for treatment, and outcomes suggest a lack of sufficient control for confounding by indication in previous work. This applies to previous work related to all our studied outcomes.

There is some evidence that depression is associated with lower blood pressure,38,39 although this is contradicted by a meta-analysis of prospective cohort studies that concluded depression ‘is probably a risk factor for hypertension’.40 Licht et al. also found that antidepressant use increased the risk of developing hypertension, while the other studies mentioned did not adjust for antidepressant use.38 Our study is not in line with the findings of Licht et al. regarding the effect of antidepressant treatment. We found a reduction in the risk of developing hypertension for the ‘Any’ antidepressants and ‘SSRI’ categories, although it was less convincing for the category of ‘Other’ antidepressants.

Coupland et al. 41,42 described an increased risk of CVA with antidepressants in those with incident prescriptions at over 65 years old. However, these studies were based on primary care data and adjusted for a limited range of confounders. A meta-analysis also found that SSRIs were associated with an increased risk of CVA (RR, 1.24; 95%CI, 1.15 to 1.34).28 The results of this meta-analysis should be treated with caution because the estimates are characterized by a high between-study heterogeneity. Moreover, it was not possible to distinguish between the effects of ADs and depression itself. Our fully adjusted model at 10-year follow-up, while showing a trend towards increased risk, also includes the possibility of no association (HR 1.26; 95%CI 0.97-1.62) for all antidepressants. However, there was some evidence of an increase in risk for those on SSRIs (1.34; 95%CI 1.02, 1.77). While this may reflect a genuine risk from this class of drug, it may also be because SSRIs are widely perceived as safer than other antidepressants and are therefore more likely to be prescribed to those who are already at risk.

Our finding of an increase in the risk of developing CHD and of CVD mortality is broadly in line with published work 43. However, there are some differences. Oh et al. 44 highlighted the risk of tricyclic antidepressants in CHD and found that SSRIs did not increase risk, although most of their evidence came from case-control designs and studies that were scored as low quality. Our findings are more nuanced. We found an increase in the risk of CHD and CVD mortality in the 10 year fully adjusted model except for CHD in those taking SSRIs, where confidence intervals included the null. We did not replicate Coupland et al.’s finding of a reduced risk of myocardial infarction in a younger cohort.41

Our finding of an increase in ACM at 10-year follow-up is supported by Almeida et al..45 They described a risk that increases with the severity of depression. In their study, those who were currently well and taking antidepressants were at lower risk than those who were depressed, irrespective of whether they were taking antidepressants. This suggests that other factors related to depression, for example, suicidality, may be more important contributors to all-cause mortality than antidepressants. Our study design does not allow us to determine this.

*Strengths and limitations*

The major strength of this study is the linkage of a richly phenotyped national prospective cohort study to primary care records. This has enabled us to examine multiple cardiometabolic outcomes and thus obtain a more complete picture on the potential long-term effects of taking antidepressant medication. Importantly, the use of the linked data from Biobank has enabled adjustment for a wide range of prospectively measured confounders – both clinical and socioeconomic - in our analytical models. In addition, this data linkage ensured the availability of high-quality data in terms of measures of exposure and outcomes. We have therefore been able to overcome the limitations of previous work that have relied solely on prospective cohorts (with poorly measured exposures/outcomes) and those that utilised data from primary care records (with limited information on confounders).

Limitations include the time lag between measurement of confounders and outcomes (up to 5 and 10 years). We did not have enough events to carry out a sensitivity analysis at 1 year follow-up to allow us to assess the impact of this. Furthermore, while we adjusted for a wide range of potential confounders, we cannot rule out the possibility of residual confounding. The low number of events meant that we could not compare outcomes by individual antidepressants. However, we were able to explore findings by antidepressant class. Like previous work, we did not have information on the severity of depression at the time of prescription and outcome. This information is not included routinely in primary care records. No information on dosing schedule was available. However, we calculated defined daily doses using WHO data to explore dose response effects. Patients may not have taken their antidepressant medication as prescribed and therefore it is possible that there may be some misclassification of the antidepressant exposure. Finally, only 44% of the Biobank had linked primary care data available at the time of our analyses and this could have introduced bias. However, comparison of baseline characteristics between those with and without linked primary care data suggested few differences. Our study cohort is mostly of White British ethnic origin and our findings require replication in more ethnically diverse cohorts, particularly given ethnic differences in cardiometabolic risk and disease. Type I errors might be inflated due to testing of multiple outcomes and significant findings should be interpreted with caution.

*Conclusions and clinical implications*

Antidepressants, and especially SSRIs, may have a good safety profile in the short term, but are associated with adverse outcomes in the long term. This is important because most of the substantial increase in prescribing in the last twenty or more years is in long-term repeat prescribing. While we cannot establish causality, we have described concerning associations with increases in CHD, CVD and all-cause mortality that are broadly in line with earlier findings but undertaken in a cohort that has had detailed prospectively recorded information enabling us to adjust for important confounders. The increase in all-cause mortality is also worrying, although, as we note above, other factors related to depression, for example suicidality, may be more important contributors to all-cause mortality than antidepressants. Some of our findings are less concerning. We found some evidence that, once other clinical and socioeconomic factors are adjusted for, antidepressants – and particularly SSRIs – may reduce the risk of developing hypertension and diabetes. This is intriguing, and, if it is supported, suggests directions for research into the mechanisms involved in the association between antidepressants and CHD and CVD mortality. Since this is an observational study, our findings do not imply causality and highlight the importance of further work to investigate and elucidate potential mechanisms. In the meantime, the message for clinicians is that prescribing of antidepressants in the long term may not be harm-free, and it is particularly important to review the cardiovascular health of patients on antidepressants more proactively and have discussions around stopping treatment for those on long-term treatment, particularly those with cardiovascular disease.

**Declaration of interest**

The authors declare that there is no conflict of interest.

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**Author contributions**

Narinder Bansal: Principal investigator; Study conception; funding acquisition; data curation; formal analysis; methodology; project administration; writing – original draft, review and editing.

Mohammed Hudda: methodology; formal analysis; writing – review and editing.

Rupert Payne: Study conception; funding acquisition; writing – review and editing.

Daniel Smith: Study conception; funding acquisition; writing – review and editing.

David Kessler: Study conception; funding acquisition; writing – review and editing.

Nicola Wiles: Study conception; funding acquisition; writing – review and editing.

**Data availability**

The data was created under UK Biobank application number 46704 and is available directly from UK Biobank.

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**Figures and tables**

Figure 1. Cohort selection

Table 1. Participant baseline characteristics at 5-year follow up

Footnote: $Parental history of outcome, for mortality outcomes this is parental history of cardiometabolic and vascular disease SD: Standard deviation

Table 2. Hazard ratios by outcome and antidepressant class at 5-year follow-up

Footnote: The number of events for SSRI’s and Other AD do not always equate to Any AD due to differential confounder selection (see Appendix 3)

Table 3. Hazard ratios by outcome and antidepressant class at 10-year follow-up

Footnote: The number of events for SSRI’s and Other AD do not always equate to Any AD due to differential confounder selection (see Appendix 3)

Table 4: DDD hazard ratios by outcome and antidepressant class at 10-year follow-up

Footnote: The number of events for SSRI’s and Other AD do not always equate to Any AD due to differential confounder selection (see Appendix 3)

**Supplementary**

Appendix 1: Biobank participant characteristics by primary care data linkage status

Appendix 2: Antidepressant prescriptions by cohort

Appendix 3a: List of confounders included in the models looking at the exposure of any antidepressant treatment

Footnote: $non-linear term \*p<0.05, \*\*p<0.01, \*\*\*p<0.001

Appendix 3b: List of confounders included in the models looking at the exposure of SSRI treatment

Footnote: $non-linear term \*p<0.05, \*\*p<0.01, \*\*\*p<0.001

Appendix 3c: List of confounders included in the models looking at the exposure of ‘Other’ class of antidepressants

Footnote: $non-linear term \*p<0.05, \*\*p<0.01, \*\*\*p<0.001

Appendix 4a: Kaplan Meier curves at 5-year follow up

Appendix 4a: Kaplan Meier curves at 10-year follow up

Appendix 5: Sensitivity analysis excluding short term antidepressant use (<90 days)

Figure 1. Cohort selection

Biobank participants with primary care data linkage

n= 222,121

*Total exclusions by outcome and follow-up period*

*(5 and 10 year):*

Diabetes: 69,624 and 70,340

Hypertension: 100,080 and 100,617

CVA: 99,455 and 99,996

CHD: 102,064 and 102,589

CVD mortality: 101,883 and 102,409

ACM: 101,883 and 102,409

*Final n by outcome and follow-up period (5 and 10 year):*

Diabetes: 152,497 and 151,781

Hypertension: 122,041 and 121,504

CVA: 122,666 and 122,125

CHD: 120,057 and 119,532

CVD mortality: 120,238 and 119,712

ACM: 120,238 and 119,712

*Exclusion reasons:*

Less than 12 months GP registration prior to study entry

Antidepressant prescribed less than 12 months prior to study entry

Prior GP record of outcome

No longer registered with GP on study entry

Participant study withdrawal

Self-reported history of outcome at study entry

Antidepressant polytherapy

Self-reported use of medication for cholesterol, diabetes or blood pressure

Antipsychotic prescription (before and during follow-up period)

Table 1. Participant baseline characteristics at 5-year follow up

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Diabetes**(N= 152,497**)** | **Hypertension**(N= 122,041) | **CVA**(N= 122,666) | **CHD**(N= 120,057) | **CVD mortality**(N= 120,238) | **ACM**(N= 120,238) |
| Age (years): median [IQR] | 57 (49-63) | 56 (48-62) | 56 (49-62) | 56 (48-62) | 56 (48-62) | 56 (48-62) |
| Gender: n (%)MaleFemale | 76,948 (50.5)75,549 (49.5) | 53,219 (43.6)68,822 (56.4) | 53,587 (43.7)69,079 (56.3) | 51,670 (43.0)68,387 (57.0) | 51,813 (43.1)68,425 (56.9) | 51,813 (43.1)68,425 (56.9) |
| Ethnic group: n (%)WhiteEthnic minority | 146,057 (96.2)5,755 (3.8) | 116,665 (96.0)4,811 (4.0) | 117,206 (96.0)4,861 (4.0) | 115,227 (96.3)4,494 (3.7) | 115,399 (96.3)4,501 (3.7) | 115,399 (96.3)4,501 (3.7) |
| Apolipoprotein A (g/L): mean (SD) | 1.5 (0.3) | 1.5 (0.3) | 1.5 (0.3) | 1.5 (0.3) | 1.5 (0.3) | 1.5 (0.3) |
| Apolipoprotein B (g/L): mean (SD) | 1.0 (0.2) | 1.0 (0.2) | 1.0 (0.2) | 1.0 (0.3) | 1.1 (0.2) | 1.1 (0.2) |
| HbA1c (mmol/mol): median [IQR] | 34.9 (32.5-37.2) | 34.7 (32.4-37.1) | 34.7 (32.4-37.1) | 34.6 (32.3-37.0) | 34.6 (32.3-37.0) | 34.6 (32.3-37.0) |
| BMI (kg/m2): median [IQR] | 26.5 (24.0-29.5) | 26.1 (23.7-28.9) | 26.1 (23.7-28.9) | 26.1 (23.7-28.9) | 26.0 (23.7-28.9) | 26.0 (23.7-28.9) |
| WHR: median [IQR] | 0.87(0.80-0.94) | 0.86 (0.79-0.92) | 0.86 (0.79-0.92) | 0.85 (0.79-0.92) | 0.86 (0.79-0.92) | 0.86 (0.79-0.92) |
| Triglycerides (mmol/L): median [IQR] | 1.46 (1.03-2.12) | 1.47 (1.00-2.04) | 1.41 (1.00-2.04) | 1.4 (1.0-2.0) | 1.40 (1.0-2.0) | 1.40 (1.0-2.0) |
| Vitamin D (nmol/L): median [IQR] | 46.9 (32.5-62.4) | 47.0 (32.5-62.4) | 46.9 (32.5-62.4) | 47.1 (32.6-62.5) | 47.1 (32.6-62.5) | 47.1 (32.6-62.5) |
| Long-standing illness: n (%)NoYes | 107,350 (72.1)41,552 (27.9 | 90,123 (75.5)29,277 (24.5) | 90,458 (75.4)29,515 (24.6) | 89,751 (76.3)27,955 (23.7) | 89,843 (76.2)28,040 (23.8) | 89,843 (76.2)28,040 (23.8) |
| Ever smoked: n (%)NoYes | 61,895 (40.8)89,902 (59.2) |  51,453 (42.4)70,009 (57.6) | 51,699 (42.4)70,351 (57.6) | 50,794 (42.4)68,913 (57.6) | 50,855 (42.4)69,033 (57.6) | 50,855 (42.4)69,033 (57.6) |
| Alcohol intake: n (%)NeverSpecial occasions only1 to 3 times per monthOnce or twice a week3 to 4 times a weekDaily | 10,348 (6.8)15,102 (9.9)16,713 (11.0)41,117 (27.0)37,419 (24.6)31,456 (20.7) | 8,439 (6.9)12,438 (10.2)13,984 (11.5)33,446 (27.5)29,725 (24.4)23,718 (19.5) | 8,507 (6.9)12,517 (10.2)14,044 (11.5)33,616 (27.5)29,842 (24.4)23,818 (19.5) | 8,151 (6.8)12,172 (10.1)13,777 (11.5)33,026 (27.5)29,409 (24.5)23,455 (19.5) | 8,168 (6.8)12,191 (10.1)13,797 (11.5)33,069 (27.5)29,450 (24.5)23,495 (10.6) | 8,168 (6.8)12,191 (10.1)13,797 (11.5)33,069 (27.5)29,450 (24.5)23,495 (10.6) |
| Number of days/week of moderate physical activity: n (%)012 to 34 to 56 to 7 | 17,824 (12.3)11,635 (8.0)43,323 (29.8) 36,946 (25.4)35,498 (24.4) | 13,830 (11.9)9,408 (8.1)35,167 (30.2)29,515 (25.4)28,450 (24.4) | 13,914 (11.9)9,440 (8.0)35,312 (30.2)29,658 (25.4)28,599 (24.5) | 13,540 (11.8)9,251 (8.1)34,718 (30.2)29,171 (25.4)28,092 (24.5) | 13,563 (11.8)9,261 (8.1)34,762 (30.2)29,214 (25.4)28,141 (24.5) | 13,563 (11.8)9,261 (8.1)34,762 (30.2)29,214 (25.4)28,141 (24.5) |
| Parental history$: n (%)NoYes | 131,802 (86.4)20,695 (13.6) | 86,802 (71.1)35,239 (28.9) | 110,316 (89.9)12,350 (10.1) | 98,445 (82.0)21,612 (18.0) | 47,156 (39.2)73,082 (60.8) | 47,156 (39.2)73,082 (60.8) |
| Type of accommodation: n (%)HouseFlat/apartmentOther | 138,745 (91.4)12,765 (8.4)359 (0.2) | 111,365 (91.6)9,927 (8.2)240 (0.2) | 111,897 (91.6)9,987 (8.2)243 (0.2) | 109,821 (91.7)9,695 (8.1)234 (0.2) | 109,977 (91.7) 9,719 (8.1)234 (0.2) | 109,977 (91.7) 9,719 (8.1)234 (0.2) |
| Household vehicles: n (%)NoneOneTwoThree or more | 10,601 (7.0)62,830 (41.5)60,717 (40.1)17,282 (11.4) | 8,006 (6.6)49,416 (40.8)49,560 (40.9)14,210 (11.7) | 8,067 (6.6)49,679 (40.8)49,777 (40.9)14,257 (11.7) | 7,792 (6.5)48,689 (40.8)48,944 (41.0)14,008 (11.7) | 7,807 (6.5)48,771 (40.8)49,010 (50.0)14,024 (11.7) | 7,807 (6.5)48,771 (40.8)49,010 (50.0)14,024 (11.7) |
| Employment status: n (%)PaidRetiredUnpaid role/studentUnable to workUnemployed | 92,616 (61.3)47,225 (31.3)4,998 (3.3)3,889 (2.6)2,266 (1.5) | 77,652 (64.3)34,478 (28.5)4,481 (3.7)2,477 (2.0)1,732 (1.4) | 77,914 (64.2)34,763 (28.6)4,492 (3.7)2,503 (2.1)1,742 (1.4) | 76,683 (64.4)33,953 (28.5)4,411 (3.7)2,376 (2.0)1,660 (1.4) | 76,762 (64.4)34,048 (28.5)4,413 (3.7)2,379 (2.0)1,661 (1.4) | 76,762 (64.4)34,048 (28.5)4,413 (3.7)2,379 (2.0)1,661 (1.4) |
| Educational qualifications: n (%)School levelNVQ/HND or equivalentA level or equivalentUniversity/Professional | 40,258 (31.9)10,650 (8.4)16,846 (13.3)58,631 (46.4) | 33,019 (32.0)7,746 (7.5)13,912 (13.5)48,591 (47.0) | 33,146 (40.0)7,788 (7.5)13,969 (13.5)48,781 (47.0) | 25,863 (25.4)7,589 (7.4)20,460 (20.1)47,990 (47.1) | 25,885 (25.4)7,601 (7.4)20,486 (20.1)48,055 (47.1) | 25,885 (25.4)7,601 (7.4)20,486 (20.1)48,055 (47.1) |
| Disability allowance: n (%)No benefitsDisability benefits | 144,265 (95.5)6,752 (4.5) | 116,671 (96.5)4,247 (3.5) | 117,185 (96.5)4,306 (3.5) | 115,148 (96.6)4,089 (3.4) | 115,307 (96.6)4,108 (3.4) | 115,307 (96.6)4,108 (3.4) |
| Urban/rural home status: n (%)Rural/small townUrban | 23,973 (15.9)127,210 (84.1) | 19,320 (16.0)101,642 (84.0) | 19,391 (16.0)102,189 (84.0) | 19,089 (16.0)99,904 (84.0) | 19,114 (16.0)100,060 (84.0) | 19,114 (16.0)100,060 (84.0) |
| Household income (£GBP): n (%)<18,00018,000 to 30,99931,000 to 51,99952,000 to 100,000Greater than 100,000 | 27,504 (20.8)33,938 (25.7)36,104 (27.4)27,653 (20.9)6,825 (5.2) | 20,304 (19.2)26,450 (25.1)29,593 (28.0)23,391 (22.2)5,855 (5.5) | 20,449 (19.3)26,582 (25.1)29,698 (28.0)23,465 (22.1)5,873 (5.5) | 19,866 (19.1)26,045 (25.0)29,268 (28.1)23,156 (22.2)5,781 (5.6) | 19,904 (19.1)26,088 (25.0)29,300 (28.1)23,179 (22.2)5,792 (5.6) | 19,904 (19.1)26,088 (25.0)29,300 (28.1)23,179 (22.2)5,792 (5.6) |

$Parental history of outcome, for mortality outcomes this is parental history of cardiometabolic and vascular disease

SD: Standard deviation

|  |  |  |  |
| --- | --- | --- | --- |
|  | Age & gender adjusted |  | Fully adjusted |
| **Antidepressant class** | Participants | Observations | Events | Person years | HR | 95% CI |  | HR | 95% CI |
|  |  |  |  |  |  |  |  |  |  |
| Diabetes | 114,076 | 124239 | 961 | 545,735 |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| No AD  |   |  | 872 | 495,551 | 1.00 |  |  |  |  |
| Any AD |   |  | 89 | 50,185 | 1.28 | (1.03-1.59)  |  | 0.83 | (0.66-1.04)  |
| SSRI's |   |  | 62 | 46,557 | 0.91 | (0.72-1.14)  |  | 0.64 | (0.49-0.83)  |
| Other AD |   |  | 38 | 11,503 | 2.03 | (1.47-2.81)  |  | 1.13 | (0.81-1.57)  |
|  |  |  |  |  |  |  |  |  |  |
| Hypertension | 107,316 | 117025 | 2621 | 508,852 |  |  |  |  |  |
|  |   |  |  |  |  |  |  |  |  |
| No AD  |   |  | 2411 | 460,887 | 1.00 |  |  | 1.00 |  |
| Any AD |   |  | 210 | 47,965 | 1.02 | (0.89-1.18)  |  | 0.93 | (0.81-1.08)  |
| SSRI's |   |  | 161 | 38,986 | 1.02 | (0.89-1.18)  |  | 0.91 | (0.77-1.07)  |
| Other AD |   |  | 49 | 8,991 | 1.15 | (0.87-1.53)  |  | 1.02 | (0.77-1.36)  |
|  |  |  |  |  |  |  |  |  |  |
| CVA | 121,190 | 132313 | 337 | 581,598 |  |  |  |  |  |
|  |   |  |  |  |  |  |  |  |  |
| No AD  |   |  | 306 | 526,413 | 1.00 |  |  | 1.00 |  |
| Any AD |   |  | 31 | 55,186 | 1.17 | (0.81-1.70)  |  | 1.04 | (0.72-1.52)  |
| SSRI's |   |  | 25 | 43,784 | 1.24 | (0.86-1.79)  |  | 1.12 | (0.74-1.69)  |
| Other AD |   |  | 7 | 10,619 | 1.18 | (0.56-2.49)  |  | 1.15 | (0.54-2.43)  |
|  |  |  |  |  |  |  |  |  |  |
| CHD | 80,964 | 87972 | 545 | 388,540 |  |  |  |  |  |
|  |   |  |  |  |  |  |  |  |  |
| No AD  |   |  | 492 | 353,972 | 1.00 |  |  | 1.00 |  |
| Any AD |   |  | 53 | 34,568 | 1.63 | (1.22-2.17)  |  | 1.47 | (1.10-1.95)  |
| SSRI's |   |  | 41 | 28,448 | 1.55 | (1.15-2.08)  |  | 1.44 | (1.04-1.99)  |
| Other AD |   |  | 13 | 6,177 | 1.78 | (1.03-3.09)  |  | 1.59 | (0.91-2.77)  |
|  |  |  |  |  |  |  |  |  |  |
| CVD mortality | 113,800 | 124084 | 150 | 546,926 |  |  |  |  |  |
|  |   |  |  |  |  |  |  |  |  |
| No AD  |   |  | 135 | 495849 | 1.00 |  |  | 1.00 |  |
| Any AD |   |  | 15 | 51077 | 1.53 | (0.89-2.61)  |  | 1.21 | (0.70-2.10)  |
| SSRI's |   |  | 11 | 41,490 | 1.24 | (0.68-2.25)  |  | 1.16 | (0.62-2.18)  |
| Other AD |   |  | 4 | 10,220 | 1.50 | (0.56-4.05)  |  | 1.14 | (0.42-3.11)  |
|  |  |  |  |  |  |  |  |  |  |
| All-cause mortality | 101,609 | 110788 | 746 | 488,286 |  |  |  |  |  |
|  |   |  |  |  |  |  |  |  |  |
| No AD  |   |  | 649 | 442,834 | 1.00 |  |  | 1.00 |  |
| Any AD |   |  | 97 | 45,452 | 1.79 | (1.45-2.23)  |  | 1.37 | (1.10-1.70)  |
| SSRI's |   |  | 76 | 36,649 | 1.44 | (1.14-1.83)  |  | 1.41 | (1.11-1.80)  |
| Other AD |   |  | 27 | 9,686 | 1.89 | (1.29-2.78)  |  | 1.30 | (0.88-1.92)  |

Table 2. Hazard ratios by outcome and antidepressant class at 5-year follow-up

Table 3. Hazard ratios by outcome and antidepressant class at 10-year follow-up

|  |  |  |  |
| --- | --- | --- | --- |
|  | Age & gender adjusted |  | Fully adjusted |
| **Antidepressant class** | Participants | Observations | Events | Person years | HR | 95% CI |  | HR | 95% CI |
|  |  |  |  |  |  |  |  |  |  |
| Diabetes | *98,338* | *109,681* | 1,456 | 890,085 |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| No AD  |   |  | 1,352 | 817,492 | 1.00 |  |  |  |  |
| Any AD |   |  | 104 | 72,592 | 1.12 | (0.92-1.37)  |  | 0.77 | (0.63-0.94)  |
| SSRI's |   |  | 72 | 59,606 | 1.13 | (0.94-1.36)  |  | 0.68 | (0.53-0.87)  |
| Other AD |   |  | 47 | 15,814 | 2.01 | (1.50-2.68)  |  | 1.17 | (0.87-1.57)  |
|  |  |  |  |  |  |  |  |  |  |
| Hypertension | 92,524 | 103,416 | 3,777 | 825,174 |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| No AD  |   |  | 3,545 | 755,910 | 1.00 |  |  | 1.00 |  |
| Any AD |   |  | 232 | 69,263 | 0.86 | (0.75-0.98)  |  | 0.80 | (0.70-0.91)  |
| SSRI's |   |  | 182 | 57,514 | 0.83 | (0.73-0.94)  |  | 0.77 | (0.66-0.89)  |
| Other AD |   |  | 51 | 11,835 | 1.19 | (0.97-1.46)  |  | 0.96 | (0.73-1.26)  |
|  |  |  |  |  |  |  |  |  |  |
| CVA | 105,536 | 118,030 | 693 | 962,201 |  |  |  |  |  |
|  |   |  |  |  |  |  |  |  |  |
| No AD  |   |  | 625 | 882,022 | 1.00 |  |  | 1.00 |  |
| Any AD |   |  | 68 | 80,179 | 1.42 | (1.10-1.83)  |  | 1.26 | (0.97-1.62)  |
| SSRI's |   |  | 57 | 66,283 | 1.44 | (1.13-1.84)  |  | 1.34 | (1.02-1.77)  |
| Other AD |   |  | 11 | 14,035 | 1.12 | (0.62-2.04)  |  | 0.97 | (0.54-1.77)  |
|  |  |  |  |  |  |  |  |  |  |
| CHD | 79,938 | 89,029 | 1,015 | 728,001 |  |  |  |  |  |
|  |   |  |  |  |  |  |  |  |  |
| No AD  |   |  | 934 | 669,588 | 1.00 |  |  | 1.00 |  |
| Any AD |   |  | 81 | 58,413 | 1.49 | (1.18-1.87)  |  | 1.32 | (1.04-1.66)  |
| SSRI's |   |  | 56 | 76,620 | 1.38 | (1.10-1.73)  |  | 1.15 | (0.87-1.51)  |
| Other AD |   |  | 23 | 9,320 | 2.25 | (1.48-3.40)  |  | 1.99 | (1.31-3.01)  |
|  |  |  |  |  |  |  |  |  |  |
| CVD mortality | 103,567 | 115,732 | 454 | 947,147 |  |  |  |  |  |
|  |   |  |  |  |  |  |  |  |  |
| No AD  |   |  | 389 | 868,874 | 1.00 |  |  | 1.00 |  |
| Any AD |   |  | 65 | 78,273 | 2.54 | (1.94-3.32)  |  | 1.89 | (1.44-2.49)  |
| SSRI's |   |  | 50 | 64,864 | 1.92 | (1.43-2.57)  |  | 1.87 | (1.38-2.53)  |
| Other AD |   |  | 15 | 13,409 | 2.71 | (1.62-4.55)  |  | 1.86 | (1.10-3.15)  |
|  |  |  |  |  |  |  |  |  |  |
| All-cause mortality | 81,279 | 90,508 | 1,752 | 745,059 |  |  |  |  |  |
|  |   |  |  |  |  |  |  |  |  |
| No AD  |   |  | 1,511 | 685,708 | 1.00 |  |  | 1.00 |  |
| Any AD |   |  | 241 | 59,352 | 2.23 | (1.94-2.56)  |  | 1.86 | (1.61-2.14)  |
| SSRI's |   |  | 181 | 49,651 | 1.68 | (1.44-1.96)  |  | 1.73 | (1.48-2.03)  |
| Other AD |   |  | 63 | 10,127 | 2.82 | (2.19-3.63)  |  | 2.20 | (1.71-2.84)  |

Table 4: DDD hazard ratios by outcome and antidepressant class at 10-year follow-up

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Any Antidepressant |  | SSRI class |  | Other class |
| **DDD category** | Events | PY | HR | 95% CI |  | Events | PY | HR | 95% CI |  | Events | PY | HR | 95% CI |
| Diabetes |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No AD | 1,352 | 817,492 | 1.00 |  |  | 1,352 | 817,492 | 1.00 |  |  | 1681 | 979,614 | 1.00 |  |
| <=0.5 | 21 | 40,984 | 0.34 | (0.22-0.53) |  | 15 | 33,374 | 0.32 | (0.19-0.54) |  | 10 | 9,285 | 0.54 | (0.29-1.00) |
| >0.5 to 1.0 | 7 | 15,306 | 0.23 | (0.11-0.49) |  | 4 | 13,140 | 0.15 | (0.06-0.41) |  | 4 | 2,683 | 0.65 | (0.24-1.74) |
| >1.0 | 56 | 15,924 | 0.65 | (0.33-1.31) |  | 40 | 12,945 | 1.45 | (1.05-1.99) |  | 23 | 3,760 | 0.31 | (0.09-1.04) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hypertension |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No AD | 3,563 | 759,428 | 1.00 |  |  | 3,563 | 759,428 | 1.00 |  |  | 3563 | 759,428 | 1.00 |  |
| <=0.5 | 80 | 40,415 | 0.51 | (0.40-0.63) |  | 62 | 33,114 | 0.49 | (0.38-0.63) |  | 18 | 7,301 | 0.58 | (0.36-0.92) |
| >0.5 to 1.0 | 29 | 14,487 | 0.13 | (0.04-0.41) |  | 21 | 12,605 | 0.40 | (0.26-0.61) |  | 8 | 1,883 | 0.90 | (0.45-1.80) |
| >1.0 | 88 | 14,458 | 0.55 | (0.33-0.93) |  | 69 | 11,893 | 0.55 | (0.30-0.99) |  | 19 | 2,565 | 1.49 | (0.95-2.35) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CVA |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No AD | 625 | 882,022 | 1.00 |  |  | 625 | 882,022 | 1.00 |  |  | 630 | 885,445 | 1.00 |  |
| <=0.5 | 29 | 882,022 | 0.95 | (0.66-1.39) |  | 25 | 38,023 | 1.08 | (0.72-1.62) |  | 4 | 8,644 | 0.56 | (0.21-1.51) |
| >0.5 to 1.0 | 12 | 46,576 | 1.09 | (0.61-1.93) |  | 9 | 14,591 | 0.98 | (0.51-1.89) |  | 3 | 2,255 | 1.74 | (0.56-5.43) |
| >1.0 | 18 | 16,828 | 1.45 | (0.90-2.32) |  | 15 | 13,377 | 1.51 | (0.90-2.52) |  | 3 | 3,047 | 1.24 | (0.40-3.87) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CHD |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No AD | 938 | 673,779 | 1.00 |  |  | 938 | 673,779 | 1.00 |  |  | 887 | 638,727 | 1.00 |  |
| <=0.5 | 31 | 34,372 | 0.90 | (0.63-1.29) |  | 20 | 28,340 | 0.75 | (0.48-1.16) |  | 11 | 5,711 | 1.53 | (0.84-2.79) |
| >0.5 to 1.0 | 16 | 12,335 | 1.24 | (0.75-2.03) |  | 11 | 10,716 | 1.01 | (0.56-1.84) |  | 4 | 1,516 | 2.03 | (0.76-5.45) |
| >1.0 | 24 | 11,819 | 1.73 | (1.15-2.60) |  | 19 | 9,727 | 1.71 | (1.08-2.71) |  | 5 | 2,000 | 1.92 | (0.79-4.65) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CVD mortality |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No AD | 426 | 903,678 | 1.00 |  |  | 392 | 872,950 | 1.00 |  |  | 426 | 903,678 | 1.00 |  |
| <=0.5 | 37 | 47,545 | 1.73 | (1.23-2.44) |  | 25 | 37,227 | 1.76 | (1.17-2.65) |  | 9 | 8,710 | 1.56 | (0.80-3.03) |
| >0.5 to 1.0 | 12 | 17,529 | 1.56 | (0.87-2.78) |  | 10 | 14,393 | 1.73 | (0.92-3.26) |  | 2 | 2,278 | 1.46 | (0.36-5.87) |
| >1.0 | 15 | 17,300 | 1.55 | (0.92-2.63) |  | 8 | 13,370 | 1.21 | (0.60-2.46) |  | 6 | 3,143 | 3.06 | (1.35-6.93) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| All-cause mortality |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No AD | 1,364 | 638,409 | 1.00 |  |  | 1,511 | 685,708 | 1.00 |  |  | 1566 | 705,811 | 1.00 |  |
| <=0.5 | 93 | 32,768 | 1.38 | (1.12-1.71) |  | 81 | 28,818 | 1.40 | (1.12-1.76) |  | 29 | 6,260 | 1.60 | (1.10-2.31) |
| >0.5 to 1.0 | 55 | 11,775 | 2.33 | (1.77-3.06) |  | 40 | 10,873 | 1.78 | (1.30-2.45) |  | 16 | 1,637 | 3.34 | (2.04-5.49) |
| >1.0 | 55 | 11,303 | 2.12 | (1.61-2.79) |  | 51 | 9,752 | 2.15 | (1.62-2.86) |  | 15 | 2,155 | 2.70 | (1.61-4.50) |

Appendix 1: Biobank participant characteristics by primary care data linkage status

|  |  |  |
| --- | --- | --- |
|  | Linked(n=222,121) | Unlinked(n=280,403) |
| Age (years): median [IQR] | 58 [50-63] | 58 [50-63] |
| Male: n (%) | 100,149 (45.1%) | 128,980 (46.0%) |
| White: n (%) | 210,733 (95.3%) | 261,981 (94.0%) |
| University/professional education: n (%) | 81,917 (45.7%) | 105,057 (46.1%) |
| Urban location: n (%)  | 186,597 (84.9%) | 242,203 (87.2%) |
| Disability allowance: n (%) | 13,925 (6.3%) | 16,089 (5.8%) |
| Median BMI (kg/m2): median [IQR] | 26.8 [24.2-30.0] | 26.6 [24.1-29.8] |
| Long term illness: n (%) | 72,599 (33.6%) | 87,307 (32.0%) |

Appendix 2: Antidepressant prescriptions by outcome

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Diabetes | Hypertension | CVA | CHD | CVD mortality | ACM |
| 5-year  |
| Antidepressant N (%) | 11,978 (7.9) | 9,582 (7.9) | 9,709 (7.9) | 9,406 (7.8) | 9,559 (7.9) | 9,546 (7.9) |
| SSRI N (% of AD) | 9,574 (79.9)  | 7,726 (80.6) | 7,778 (80.1) | 7,627 (81.1) | 7,703 (80.6) | 7,716 (80.8) |
| CitalopramN (% of SSRI) | 7,247 (46.3) | 5,924 (46.6) | 5,951 (46.6) |  5,831(46.7) | 5,839 (46.7) | 5,839 (46.7) |
| MirtazapineN (% of Other class) | 1,750 (46.6) | 1,321 (45.0) | 1,334 (45.0) | 1,297 (45.4) | 1,298 (45.5) | 1,298 (45.5) |
| 10-year  |
| Antidepressant N (%) | 9,126 (6.0) | 7,242 (6.0) | 7,449 (6.1) | 7,124 (6.0) | 7,240 (6.1) | 7,269 (6.1) |
| SSRI N (% of AD) | 7,379 (80.9) | 5,941 (82.0) | 6,121 (82.2) | 5,824 (81.2) | 5,941 (82.1) | 5,931 (81.6) |
| CitalopramN (% of SSRI) | 7,175 (46.5) | 5,865 (46.7) | 5,892 (46.7) | 5,771 (46.8) | 5,779 (46.8) | 5,779 (46.8) |
| MirtazapineN (% of Other class) | 1,673 (46.2) | 1,258 (44.5) | 1,272 (44.6) | 1,234 (44.9) | 1,234 (44.9) | 1,234 (44.9) |

Appendix 3a: List of confounders included in the models looking at the exposure of any antidepressant

|  |  |  |
| --- | --- | --- |
| Follow-up period | Outcome | Confounders selected by model |
| *5-year*  |
|  |
|  | Diabetes | Age$, gender, HbA1c$\*\*\*, BMI\*\*\*, WHR$\*\*\*, triglycerides\*\*\*, long-term illness\*\*, smoking status, parental diabetes history\*\*, benefits status\*\*, urban/rural status\*\*\*, household income$ |
| Hypertension | Age$\*\*\*, gender\*\*, BMI\*\*\*, WHR\*\*, triglycerides\*\*\*, vitamin D$\*\*\*, parental hypertension history\*\*\*, alcohol intake status$, urban/rural status\*\*\* |
| CVA | Age$, gender\*\*, accommodation status$\*\*, benefits status\*\*\* |
| CHD | Age$\*\*\*, gender\*\*\*, apolipoprotein A\*\*\*, apolipoprotein B\*\*\*, vitamin D\*\*, long-term illness\*\*\*, parental CHD history\*, education$\*\*\* |
| CVD mortality | Age$\*, gender\*\*, WHR\*\*\*, employment status$\*\*\*, physical activity$ |
| ACM | Age$\*, gender\*, BMI$, WHR\*\*\*, long-term illness\*\*\*, benefits status\*\*\*, household income$\*\* |
| *10-year*  |
|  |
|  | Diabetes | Age$, gender\*, apolipoprotein A\*\*\*, HbA1c$\*\*\*, BMI\*\*\*, WHR$\*\*\*, triglycerides\*\*\*, vitamin D\*\*\*, long-term illness\*\*, parental diabetes history\*\*\*, benefits status\*\*\*, urban/rural status\*\*\*, household income$ |
| Hypertension | Age$\*\*\*, gender\*\*\*, BMI\*\*\*, WHR\*\*\*, triglycerides\*\*\*, vitamin D$\*\*\*, parental hypertension history\*\*\*, benefits status, urban/rural status\*\*\*, household income$\* |
| CVA | Age$\*\*, gender\*\*\*, vitamin D\*\*\*, long-term illness\*\*, parental CVA history\*\*, number of vehicles per household$\*\*\*, benefits status\*\*\* |
| CHD | Age$\*\*\*, gender\*\*\*, apolipoprotein A\*\*\*, apolipoprotein B\*\*\*, BMI\*\*, vitamin D, long-term illness\*\*\*, parental CHD history, employment status$\*, education$\*\*\* |
| CVD mortality | Age$\*, gender\*\*\*, HbA1c\*\*\*, WHR\*\*\*, long-term illness\*\*\*, smoking status\*\*, number of vehicles per household$\*\*\*, employment status$\*\*, benefits status\*\*, physical activity$ |
| ACM | Age$\*\*\*, gender\*\*\*, HbA1c\*\*, BMI$\*\*\*, WHR\*\*\*, vitamin D\*\*, long-term illness\*\*\*, smoking status\*\*\*, number of vehicles per household$\*\*\*, employment status$\*\*, benefits status\*\*\*, education$\*, physical activity$\* |

$non-linear term

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001

Appendix 3b: List of confounders included in the models looking at the exposure of SSRI treatment

|  |  |  |
| --- | --- | --- |
| Follow-up period | Outcome | Confounders selected by model |
| *5-year* |
|  |
| SSRI | Diabetes | Age$, gender\*, HbA1c$\*\*\*, BMI\*\*\*, WHR$\*\*\*, triglycerides, long-term illness\*\*, parental diabetes history\*\*\*, benefits status\*\*, urban/rural status\*\*\* |
| Hypertension | Age$\*\*\*, gender\*\*, BMI\*\*\*, WHR\*\*, triglycerides\*\*\*, vitamin D$\*\*\*, parental hypertension history\*\*\*, alcohol intake status, urban/rural status$\*\*\* |
| CVA | Age$, gender\*\*, long-term illness\*\*\*, accommodation status$\*\* |
| CHD | Age$\*\*, gender\*\*\*, apolipoprotein A\*\*\*, apolipoprotein B\*\*\*, WHR\*\*, vitamin D\*, long-term illness\*\*, parental CHD history, education$\*\*\* |
| CVD mortality | Age$, gender\*\*, WHR\*\*\*, employment status$\*\*\*, physical activity$ |
| ACM | Age$\*, gender\*\*, WHR\*\*\*, long-term illness\*\*\*, number of vehicles per household$\*\*\*, benefits status\*\*\*, urban/rural status, household income$ |
| *10-year* |
|  |
| SSRI | Diabetes | Age$, gender\*, apolipoprotein A\*\*\*, HbA1c$\*\*\*, BMI$\*\*\*, WHR$\*\*\*, triglycerides\*\*\*, vitamin D\*\*\*, long-term illness\*\*, smoking status, parental diabetes history\*\*\*, benefits status\*\*\*, urban/rural status\*\*\*, household income$ |
| Hypertension | Age$\*\*\*, gender\*\*\*, BMI\*\*\*, WHR\*\*\*, triglycerides\*\*\*, vitamin D$\*\*\*, parental hypertension history\*\*\*, benefits status, urban/rural status\*\*\*, household income$ |
| CVA | Age$\*\*, gender\*\*\*, vitamin D\*\*\*, long-term illness\*\*, parental CVA history\*\*, number of vehicles per household$\*\*, benefits status\*\*\* |
| CHD | Age$\*\*\*, gender\*\*\*, apolipoprotein A\*\*\*, apolipoprotein B\*\*\*, BMI\*\*, vitamin D\*\*\*, long-term illness\*\*\*, parental CHD history, employment status$\*, education$\*\*\* |
| CVD mortality | Age$\*, gender\*\*\*, HbA1c\*\*\*, WHR\*\*\*, long-term illness\*\*\*, smoking status\*, number of vehicles per household$\*\*\*, employment status$\*\*, benefits status\*\*, physical activity$\* |
| ACM | Age$\*\*\*, gender\*\*\*, HbA1c\*\*\*, BMI$\*\*\*, WHR\*\*\*, vitamin D\*\*, long-term illness\*\*\*, smoking status\*\*\*, number of vehicles per household$\*\*\*, employment status$, benefits status\*\*\*, education$, physical activity$\* |

$non-linear term

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001

Appendix 3c: List of confounders included in the models looking at the exposure of ‘Other’ class of antidepressants

|  |  |  |
| --- | --- | --- |
| Follow-up period | Outcome | Confounders selected by model |
| *5-year*  |
|  |
| Other | Diabetes | Age$, gender\*\*, HbA1c$\*\*\*, BMI\*\*\*, WHR$\*\*\*, triglycerides\*\*\*, long-term illness\*\*, parental diabetes history\*\*\*, benefits status\*\*, urban/rural status\*\*\* |
| Hypertension | Age$\*\*\*, gender, BMI\*\*\*, WHR\*\*\*, triglycerides\*\*\*, vitamin D\*\*\*, parental hypertension history\*\*\*, urban/rural status\*\*\* |
| CVA | Age$, gender\*\*, accommodation status$\*\* |
| CHD | Age$\*\*, gender\*\*\*, apolipoprotein A\*\*\*, apolipoprotein B\*\*\*, HbA1c\*\*\*, long-term illness\*\*\*, parental CHD history, employment status$, education$ |
| CVD mortality | Age$\*, gender\*\*, WHR\*\*\*, employment status$\*\* |
| ACM | Age$\*\*\*, gender\*, BMI$\*\*\*, WHR\*\*\*, long-term illness\*\*\*, smoking status\*\*\*, number of vehicles per household$\*\*\*, benefits status\*\*\* |
| *10-year*  |
|  |
| Other | Diabetes | Age$\*, gender, apolipoprotein A\*\*\*, HbA1c$\*\*\*, BMI\*\*\*, WHR$\*\*\*, triglycerides\*\*\*, long-term illness\*\*, smoking status, parental diabetes history\*\*\*, benefits status\*\*\*, urban/rural status\*\*\* |
| Hypertension | Age$\*\*\*, gender\*\*\*, BMI\*\*\*, WHR\*\*\*, triglycerides\*\*\*, vitamin D\*\*\*, parental hypertension history\*\*\*, urban/rural status\*\*\*, household income$ |
| CVA | Age$\*\*, gender\*\*\*, vitamin D\*\*\*, long-term illness\*\*\*, parental CVA history\*\*, accommodation status$, number of vehicles per household$ |
| CHD | Age$\*\*\*, gender\*\*\*, apolipoprotein A\*\*\*, apolipoprotein B\*\*\*, HbA1c\*\*, BMI\*\*\*, vitamin D\*\*\*, long-term illness\*\*\*, parental CHD history, education$ |
| CVD mortality | Age$, gender\*\*\*, HbA1c\*\*\*, WHR\*\*\*, long-term illness\*\*, smoking status\*, number of vehicles per household$\*\*, employment status$, benefits status\*\*\*, physical activity$ |
| ACM | Age$\*\*\*, gender\*\*\*, HbA1c\*\*, BMI$\*\*\*, WHR\*\*\*, vitamin D\*\*, long-term illness\*\*\*, smoking status\*\*\*, number of vehicles per household$\*\*\*, employment status$, benefits status\*\*\*, education$ |

$non-linear term

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001

Appendix 4a: Kaplan Meier curves at 5-year follow up



Appendix 4b: Kaplan Meier curves at 10-year follow up



Appendix 5: Sensitivity analysis excluding short term antidepressant use (<90 days)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Participants | Observations | Events | Person years | HR | 95% CI |
| *5-year follow-up* |  |  |  |  |  |  |
| Diabetes | 112,207 | 120,582 | 950 | 537,018 |  |  |
| No AD |  |  | 865 | 491,174 | 1.00 |  |
| Any AD |  |  | 85 | 45,843 | 0.83 | (0.67-1.06) |
|  |  |  |  |  |  |  |
| Hypertension | 105,440 | 113,375 | 2,584 | 500,154 |  |  |
| No AD |  |  | 2394 | 456,496 | 1.00 |  |
| Any AD |  |  | 190 | 43,657 | 0.91 | (0.79-1.06) |
|  |  |  |  |  |  |  |
| CVA |  119,069 | 128,165 | 336 | 571,681 |  |  |
| No AD |  |  | 306 | 521465 | 1.00 |  |
| Any AD |  |  | 30 | 50,215 | 1.10 | (0.75-1.60) |
|  |  |  |  |  |  |  |
| CHD | 79,596 | 85,304 | 538 | 382,139 |  |  |
| No AD |  |  | 488 | 350,725 | 1.00 |  |
| Any AD |  |  | 50 | 31,413 | 1.52 | (1.13-2.05) |
|  |  |  |  |  |  |  |
| CVD mortality |  111,840 | 120,250 | 147 | 537,761 |  |  |
| No AD |  |  | 135 | 491,290 | 1.00 |  |
| Any AD |  |  | 12 | 46,471 | 1.04 | (0.57-1.90) |
|  |  |  |  |  |  |  |
| All-cause mortality | 99,894 | 107,426 | 703 | 480,230 |  |  |
| No AD |  |  | 645 | 438,834 | 1.00 |  |
| Any AD |  |  | 58 | 41,396 | 0.87 | (0.66-1.14) |
|  |  |  |  |  |  |  |
| *10-year follow-up* |  |  |  |  |  |  |
| Diabetes | 95,576 | 104,342 | 1,422 | 865,671 |  |  |
| No AD |  |  | 1,327 | 806,344 | 1.00 |  |
| Any AD |  |  | 95 | 59,327 | 0.83 | (0.67-1.03) |
|  |  |  |  |  |  |  |
| Hypertension | 89,765 | 98,112 | 3,688 | 800,999 |  |  |
| No AD |  |  | 3,497 | 744,779 | 1.00 |  |
| Any AD |  |  | 191 | 56,220 | 0.79 | (0.68-0.92) |
|  |  |  |  |  |  |  |
| CVA |  102,353 | 111,864 | 674 | 933,859 |  |  |
| No AD |  |  | 620 | 869,053 | 1.00 |  |
| Any AD |  |  | 54 | 64,805 | 1.23 | (0.92-1.63) |
|  |  |  |  |  |  |  |
| CHD | 77,613 | 84,532 | 990 | 707,320 |  |  |
| No AD |  |  | 921 | 660,150 | 1.00 |  |
| Any AD |  |  | 69 | 47,170 | 1.37 | (1.07-1.76) |
|  |  |  |  |  |  |  |
| CVD mortality |  100,533 | 109,845 | 434 | 920,051 |  |  |
| No AD |  |  | 388 | 856,516 | 1.00 |  |
| Any AD |  |  | 46 | 63,534 | 1.61 | (1.17-2.21) |
|  |  |  |  |  |  |  |
| All-cause mortality | 78,953 | 85,995 | 1,671 | 724,214 |  |  |
| No AD |  |  | 1505 | 676,204 | 1.00 |  |
| Any AD |  |  | 166 | 48,009 | 1.54 | (1.31-1.82) |

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