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Antidepressant medication use and future risk of cardiovascular disease: the Scottish Health Survey

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Aims The association between antidepressant use and risk of cardiovascular disease (CVD) remains controversial, particularly in initially healthy samples. Given that antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are now prescribed not only for depression, but also for a wide range of conditions, this issue has relevance to the general population. We assessed the association between antidepressant medication use and future risk of CVD in a representative sample of community-dwelling adults without known CVD.

Methods and results A prospective cohort study of 14 784 adults (aged 52.4 ± 11.9 years, 43.9% males) without a known history of CVD was drawn from the Scottish Health Surveys. Of these study participants, 4.9% reported the use of antidepressant medication. Incident CVD events (comprising CVD death, non-fatal myocardial infarction, coronary surgical procedures, stroke, and heart failure) over 8-year follow-up were ascertained by a linkage to national registers; a total of 1434 events were recorded. The use of tricyclic antidepressants (TCAs) was associated with elevated risk of CVD [multivariate-adjusted hazard ratio (HR) = 1.35, 95% confidence interval (CI), 1.03–1.77] after accounting for a range of covariates. There was a non-significant association between TCA use and coronary heart disease events (969 events, multivariate-adjusted HR = 1.24, 95% CI, 0.87–1.75). The use of SSRIs was not associated with CVD. Neither class of drug was associated with all-cause mortality risk.

Conclusion Although replication is required, the increased risk of CVD in men and women taking TCAs was not explained by existing mental illness, which suggests that this medication is associated with an excess disease burden.

Keywords Antidepressants • Cardiovascular disease • Epidemiology • Mortality

Introduction

There is an increasing trend for antidepressant medication use across Europe and the USA.[1,2] As such, it is important to ascertain any health risks associated with such a prevalent treatment. Recently, it has been suggested that antidepressant use may lead to an increased risk of cardiovascular disease (CVD); however, such findings remain uncertain. Data from case–control studies,[2–8] for instance, have produced conflicting results for the two main classes of antidepressant medication [tricyclic antidepressant (TCA) and selective serotonin reuptake inhibitors (SSRIs)]. Similarly, in prospective studies of participants with existing CVD, the data are also discordant, with some studies suggesting a reduced risk of recurrent myocardial infarction (MI)[9] in people taking SSRIs relative to non-users, whereas other studies have shown increased risk in TCA and SSRI users.[10–12]

Importantly, most of these studies have sampled men and women with existing CVD at study entry. Prospective studies of healthy participants provide a higher level of evidence in this context as it is possible to address the issue of reverse causality which beset case–control studies—i.e. the concern that the mental health consequences of a CVD diagnosis may be generating an increased use of antidepressant medication rather than the converse. Furthermore, given that antidepressants such as SSRIs are

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being increasingly prescribed not only for depression, but also for a wide range of conditions,[1] the risks associated with antidepressants have increasing relevance to the general population. Several prospective studies of antidepressant use and risk of CVD in initially healthy participants exist, although the findings remain equivocal.[13–16] These inconsistencies might be due to differences in the characteristics of study participants, sample size, different strategies to control for depressive symptoms, and a variation in specific outcomes and follow-up times. Importantly, none of the existing work has contained a representative sample of the general population.

Accordingly, the aim of the present study was to examine the association between antidepressant use and incident CVD in a representative sample of community-dwelling adults without known CVD at baseline. Since TCAs represent the older generation of antidepressant drugs and have been largely replaced by SSRIs, we also examined the association of these different classes of drug with CVD.

Methods

Study design and participants

The Scottish Health Survey (SHS) is a cross-sectional survey that is typically conducted serially every 3–5 years, which draws a nationally representative sample of the general population living in households. For the present analysis, we combined data from separate surveys sampled in 1995, 1998, and 2003 (comprising 28.6, 36.3, and 35.1% of the present sample, respectively) in adults aged 35 years and older as described previously.[17] We linked these data to records of hospital admissions and mortality; thus, the analyses were based on a prospective cohort design. Participants from the different survey years contributed data only once and were comparable in terms of demographics and risk factors. The main exclusion criteria for the present analysis were a history of clinically confirmed CVD, which was identified from retrospective patient hospital records. Participants gave full informed consent to take part in the study and ethical approval was obtained from the London Research Ethics Council.

Baseline assessment

Survey interviewers visited eligible households and collected data on demographics and lifestyle (e.g. smoking, alcohol, physical activity) variables and measured height and weight. Psychological distress was assessed using the 12-item version of the General Health Questionnaire (GHQ-12), a widely utilized measure of psychological distress in population-based studies.[18] The GHQ-12 enquires about symptoms of anxiety and depression in the last 4 weeks. We employed a GHQ-12 cut-off score of $\geq$4 to denote psychological distress that has been validated against standardized psychiatric interviews.[18] On a separate visit, nurses collected information on medical history and medication and recorded the average of three seated blood pressure readings (Omron HEM-907 blood pressure monitor). Hypertension was confirmed from a self-report of a physicians diagnosis, the use of antihypertensive medication, or identified from a direct measurement of blood pressure ($\geq$140/90 mmHg). The use of antidepressant medication was coded according to the British National Formulary (codes: 040301–040304).[19] Information on history of psychiatric hospital admissions was also recorded at baseline, including the number of continuous in patient stays and ICD diagnosis, as described previously.[20] Psychiatric admissions cover conditions related to major depressive disorder, psychoactive substance abuse, schizophrenia, non-specific delirium, diseases related to the nervous system, and suspected mental and behavioural disorder.

Clinical events follow-up

The surveys were linked to a patient-based database of hospital admissions and deaths with follow-up until December 2007 [Information Services Division (ISD) Scotland].[21] The ISD database has demonstrated 94% accuracy and 99% completeness when samples of computerized CVD records from the Scottish national database were compared with the original patient case notes. Classification of the underlying cause of death is based on information collected on the death certificate together with any additional information provided subsequently by the certifying doctor. The primary endpoint for the present analyses was a composite of fatal and non-fatal CVD events. Mortality from cardiovascular causes was coded according to International Classification of Diseases—Version 9 (ICD-9) (390–459) and ICD-10 (I01-I99), and non-fatal events included CVD-related hospital admissions incorporating acute MI, coronary artery bypass surgery (CABG), percutaneous coronary angioplasty (PTCA), stroke, and heart failure. For secondary endpoints, we specifically examined CHD events (including CHD death, nonfatal MI, CABG, PTCA) and cause specific mortality (cancer and CVD).

Statistical analysis

Cox's proportional hazards models were used with months as the time scale to estimate the risk of CVD events according to antidepressant medication use [categorized as: none (referent), TCAs, SSRIs, other antidepressants). Study members that survived were censored at 31 December 2007. In preliminary analyses, there were no clear differences in our results between men and women, so the data were pooled and sex- and age-adjusted in the basic model. In further models, we first adjusted for psychological distress (GHQ-12 $\geq$ 4) and history of psychiatric continuous inpatient stays (none, one, more than one) in order to account for existing mental illness. We then further added health behaviours, including frequency of weekly physical activity (split into tertiles), smoking (never, previous, current), alcohol intake (never/rarely, moderate, heavy), and also socioeconomic group (using the Registrar General Classification; I/II professional/intermediate, III skilled non-manual/skilled manual, IV/V part-skilled/unskilled), marital status (married or partnered/single/divorced/widowed), and body mass index category (underweight, normal weight, overweight, obese). Lastly, we adjusted for pre-clinical CVD risk factors including the use of cardiovascular medication (β-blockers, diuretics, angiotensin-converting enzyme-inhibitors, calcium blockers, lipid-lowering medications) and hypertension. Participants with missing body mass index values ($n = 1238$) were recoded with a dummy variable in order to retain them in the analyses. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure, although no appreciable violations were noted. To estimate the attributable risk in relation to the use of antidepressants, the following calculation was performed: $(a/(a+b)) - (c/(c+d)) \times 100$ where 'a' and 'b' represents the number of events and non-events in the exposed group, respectively, and 'c' and 'd' the number of events and non-events in the non-exposed group. Differences in the characteristics of participants with relation to antidepressant use were analysed using ANOVA tests to examine continuous variables and χ^2 tests to examine categorical variables. All analyses were performed using SPSS (version 14) and all tests of statistical significance were based on two-sided probability ($P < 0.05$).

Results

The overall response rate ranged between 60 and 76% for the different survey years. The initial sample consisted of 16 144 participants, although after exclusion of 699 participants with clinically confirmed CVD at baseline, and participants with missing demographic variables, the analytical sample comprised 14 784 adults (aged 52.4 ± 11.9 years, 43.9% males). Excluded participants were older (60.5 vs. 52.4, $P < 0.001$) and were more likely to be using antidepressant medication (6.9 vs. 4.9%, $P = 0.001$). In particular, those participants excluded because of existing CVD demonstrated the highest use of antidepressants (8.1%) compared with those excluded due to missing data (4.4%).

Among those included in the analytical sample, 2.2, 2.0, and 0.7% reported taking TCAs, SSRIs, or other antidepressants (including monoamine oxidase inhibitors), respectively. Antidepressant users were older, more likely to be female, from lower socioeconomic groups, smokers, none alcohol drinkers, more sedentary, displayed higher levels of obesity, psychological distress, and hypertension and were more likely to have a psychiatric continuous inpatient stay (*Table 1*).

Over an average of 8 years of follow-up, there were 1434 CVD events (26.2% fatal), and 67.5% of the events were related to CHD ($n = 211$ death, $n = 241$ non-fatal MI, $n = 517$ surgical procedures). The co-variables that were independently associated with CVD and all-cause mortality are shown in Supplementary material online, *Table S1*. The risk of CVD events was elevated in TCA users, although the association was considerably attenuated after further adjustments for potential confounding factors, especially indicators of mental illness including psychological distress and psychiatric continuous inpatient stays (*Table 2*). Nevertheless, there remained a 35% [95% confidence interval (CI), 3–77%] increased risk of CVD associated with TCA use in the fully adjusted model. The results remained largely unchanged for TCA use and CVD risk when we removed 487 participants with psychiatric inpatient history (age- and sex-adjusted hazard ratio (HR) = 2.00, 95% CI, 1.51–2.66) or 2395 participants reporting psychological distress (age- and sex-adjusted HR = 2.14, 95% CI, 1.53–3.00). The attributable risk percentage for CVD, comparing TCA users and non-users, was 8.4%. When we repeated the main analyses using CHD events as the outcome (*Table 2*), there was evidence of increased risk in TCA users, although the association was less precisely estimated after adjustments for confounding factors (multivariate-adjusted HR = 1.24, 95% CI, 0.87–1.75). The use of SSRIs was not associated with CVD.

A total of 1238 all-cause deaths (459 cancer and 375 CVD) were recorded during the 8 years of follow-up. There were no significant associations between antidepressant use and all-cause mortality (*Table 3*). We repeated the analyses looking specifically at cancer deaths, although there were no associations with any antidepressant medication use. There was an association between TCA use and CVD death (age- and sex-adjusted HR = 2.23, 95% CI, 1.39–3.60), although the association was no longer significant after adjustment for co-variables. There was also elevated risk for stroke specific death in both TCA (age- and sex-adjusted HR = 2.23, 95% CI, 0.85–6.39) and SSRI users (age- and sex-adjusted HR = 3.32, 95% CI, 1.20–9.18). However, the findings on risk of stroke should be interpreted with caution since there were only 78 events and the associations with SSRIs became considerably less precise after multivariate adjustment (multivariate-adjusted HR = 2.46, 95% CI, 0.87–6.96).

Table 1 Characteristics of the study sample at baseline ($n = 14\,784$)

Variable	Non-medicated ($n = 14\,055$)	Medicated ($n = 729$)	*P*-value
Age (years)	52.4 ± 11.9	53.3 ± 11.8	0.035
Male (%)	44.9	26.3	<0.001
Socioeconomic group (%)			
Professional	30.6	25.5	0.01
Part skilled/ unskilled	23.6	28.5	
Marital status (%)			
Married/ partnered	63.4	49.8	<0.001
Single/separated/ widowed	36.6	50.2	
Smoking (%)			
Never	42.1	29.6	<0.001
Ex-smoker	27.7	27.8	
Current	30.2	42.5	
Alcohol (%)[a]			
Never/trivial	19.1	29.9	<0.001
Ex-drinker	4.6	11.8	
Moderate	60.4	48.1	
Heavy	15.9	10.0	
Physical activity (%)			
Bottom tertile	37.6	52.7	<0.001
Top tertile	34.8	26.6	
BMI category (%)[b]			
<18.5 kg/m^2	1.0	1.8	<0.001
≥18.5 < 25 kg/m^2	30.9	25.2	
≥25 < 30 kg/m^2	37.5	35.3	
≥30 kg/m^2	22.4	27.4	
GHQ-12 score (%)			
0–3	85.3	54.9	<0.001
≥4	14.7	45.1	
Psychiatric inpatient stays (%)	2.8	13.3	<0.001
Hypertension (%)	26.3	31.0	0.005

[a]Moderate alcohol refers to >1 to <21 U/week; heavy refers to ≥21 U/wk (based on UK government safe drinking guidelines; http://www.drinking.nhs.uk/questions/recommended-levels/). 1 U = half pint beer, a small glass of wine, or a measure of spirits.
[b]Missing BMI values (8.2% in controls and 10.3% in antidepressant users).

Table 2 Hazard ratios (95% confidence interval) for the relation between use of antidepressant medication and risk of cardiovascular disease events

	Events/total *N*	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)	Model 4, HR (95% CI)
All cardiovascular disease events[a]					
Non-medicated	1333/14 055	1.00 (ref)	1.00	1.00	1.00
TCAs	58/324	1.96 (1.50–2.55)	1.59 (1.21–2.08)	1.34 (1.02–1.76)	1.35 (1.03–1.77)
SSRIs	31/299	1.63 (1.14–2.33)	1.34 (0.93–1.92)	1.24 (0.86–1.78)	1.11 (0.77–1.60)
Other	12/106	1.47 (0.83–2.60)	1.05 (0.59–1.86)	0.99 (0.55–1.75)	0.88 (0.49–1.57)
Any [yes vs. no (reference)]		1.77 (1.45–2.18)	1.42 (1.15–1.75)	1.26 (1.02–1.55)	1.19 (0.97–1.48)
Coronary heart disease events[b]					
Non-medicated	909/14 055	1.00 (ref)	1.00	1.00	1.00
TCAs	35/324	1.78 (1.27–2.49)	1.45 (1.03–2.04)	1.24 (0.87–1.75)	1.24 (0.87–1.75)
SSRIs	16/299	1.21 (0.74–1.99)	0.99 (0.60–1.63)	0.90 (0.55–1.49)	0.81 (0.49–1.33)
Other	8/106	1.40 (0.70–2.81)	1.00 (0.49–2.02)	0.92 (0.46–1.87)	0.80 (0.40–1.63)
Any [yes vs. no (reference)]		1.53 (1.17–1.99)	1.22 (0.93–1.60)	1.08 (0.82–1.42)	1.00 (0.76–1.32)

Model 1: adjusted for age and sex. Model 2: additional adjustment for psychological distress (GHQ-12 $\geq$ 4) and psychiatric continuous inpatient stays. Model 3: additional adjustment for socioeconomic group, marital status, physical activity, smoking, alcohol, and body mass index. Model 4: additional adjustment for CVD medication and hypertension (physician diagnosed or BP > 140/90 mmHg).
[a]Includes CVD death, non-fatal myocardial infarction, coronary artery bypass, percutaneous transluminal coronary angioplasty, stroke, and heart failure.
[b]Includes CHD death, non-fatal myocardial infarction, coronary artery bypass, and percutaneous transluminal coronary angioplasty.

Table 3 Hazard ratios (95% confidence interval) for the relation between use of antidepressant medication and risk of death

	Events/total *N*	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)	Model 4, HR (95% CI)
All-cause mortality					
Non-medicated	1155/14 055	1.00	1.00	1.00	1.00
TCAs	44/324	1.65 (1.22–2.23)	1.21 (0.89–1.64)	1.09 (0.80–1.49)	1.09 (0.80–1.49)
SSRIs	23/299	1.29 (0.85–1.95)	0.97 (0.64–1.47)	0.84 (0.56–1.29)	0.82 (0.55–1.26)
Other	16/106	2.47 (1.51–4.04)	1.43 (0.86–2.35)	1.43 (0.86–2.35)	1.40 (0.85–2.31)
Any [yes vs. no (reference)]		1.63 (1.30–2.04)	1.16 (0.92–1.46)	1.05 (0.83–1.33)	1.05 (0.83–1.32)
Cardiovascular disease death					
Non-medicated	348/14 055	1.00	1.00	1.00	1.00
TCAs	18/324	2.23 (1.39–3.60)	1.72 (1.06–2.79)	1.38 (0.84–2.26)	1.39 (0.85–2.28)
SSRIs	6/299	1.10 (0.49–2.47)	0.87 (0.38–1.96)	0.77 (0.35–1.78)	0.74 (0.33–1.70)
Other	3/106	1.56 (0.50–4.87)	0.94 (0.30–2.95)	0.86 (0.27–2.70)	0.83 (0.26–2.50)
Any [yes vs. no (reference)]		1.75 (1.18–2.60)	1.31 (0.87–1.97)	1.11 (0.74–1.68)	1.09 (0.72–1.65)
Cancer death					
Non-medicated	433/14055	1.00	1.00	1.00	1.00
TCAs	13/324	1.27 (0.73–2.21)	1.09 (0.62–1.91)	1.04 (0.59–1.81)	1.02 (0.58–1.79)
SSRIs	9/299	1.32 (0.70–2.56)	1.13 (0.58–2.21)	1.01 (0.51–1.96)	0.99 (0.50–1.93)
Other	4/106	1.60 (0.60–4.30)	1.21 (0.45–3.28)	1.27 (0.46–3.41)	1.23 (0.45–3.33)
Any [yes vs. no (reference)]		1.33 (0.89–1.98)	1.12 (0.79–1.69)	1.06 (0.70–1.59)	1.04 (0.69–1.57)

Model 1: adjusted for age and sex. Model 2: additional adjustment for psychological distress (GHQ-12 $\geq$ 4) and psychiatric continuous inpatient stays. Model 3: additional adjustment for socioeconomic group, marital status, physical activity, smoking, alcohol, and body mass index. Model 4: additional adjustment for CVD medication and hypertension (physician diagnosed or BP > 140/90 mmHg).

Discussion

In this study of a representative sample of community-dwelling adults without known CVD at study baseline, we observed an elevated risk of CVD in TCA users, but not for SSRIs. There were no significant associations between antidepressant use and all-cause mortality. There remained a 35% increased risk of CVD associated with TCA use after accounting for potential confounding factors, which, importantly, included symptoms of depression and anxiety. Depression and psychological distress are risk factors for CVD,[17,22,23] and some previous evidence has suggested that the association between antidepressant use and CVD risk is explained by depressive symptoms and is not a direct effect of the pharmacological agents.[12] On the basis of our findings, the association between antidepressant use and CVD risk is partly independent of psychiatric symptoms which suggests that there maybe some characteristic of TCA that is raising CVD risk. Equally, it is plausible that an elevated rate of CVD of 35% could be explained by residual confounding due to unmeasured or unknown risk factors.

Previous prospective studies on antidepressant use and CVD risk have largely focused on populations with existing CVD.[9–12] Our findings are comparable with one of the few cohort study of healthy participants who showed that the use of TCAs, but not SSRIs, was associated with increased risk of MI over 4.5 years follow-up.[13] However, in large study of initially healthy postmenopausal women, TCAs and SSRIs were associated with increased risk of mortality, and SSRIs with greater risk of haemorrhagic and fatal stroke, although not with CHD over 5.9 years of follow-up.[14] In addition, women without known CHD taking antidepressants were at greater risk of incident sudden cardiac death and a marginally significant increased risk of fatal CHD in the Nurse's Health Study.[15] Our findings also tended to suggest increased risk of stroke in SSRI users, although we had limited stroke events to examine this in detail. In contrast, several case-controlled studies have found protective effects of SSRI use on MI,[5,6,8] although others have found increased risk for both TCA and SSRI use.[3,4] Some of these discrepancies might be due to the differences in characteristics of the populations. Prospective studies also provide a higher level of evidence in this context as it is possible to address the issue of reverse causality which beset case–control studies.

Tricyclic antidepressants may induce weight gain[24,25] and have been shown to have a number of other cardio-toxic effects that might explain the increased risk of CVD, including orthostatic hypotension, reduced heart rate variability, QT interval prolongation, and greater risk of hypertension.[26–28] Short-term trials of SSRI medication in patients with major depression have also been shown to adversely effect inflammatory risk markers such as C-reactive protein,[29] although results have been inconsistent.[30,31] In the present cohort of participants, we also observed elevated levels of inflammatory markers in users of antidepressants.[32]

The strengths of our study include the sampling of a large, representative general population-based group, detailed information about hospital admissions, and the well-characterized study members which facilitate insights into the role of potential confounding factors, particularly existing depression and mental illness. It is also important to note the limitations. We did not capture compliance to medication or the new use of antidepressants after the start of follow-up. It is likely both are changeable over time. Nevertheless, exposure misclassification is likely to have weakened rather than strengthened the antidepressant–CVD association herein. In addition, we did not have information regarding medication dosage. The GHQ-12 is not specifically designed to assess anxiety and depression individually and might have failed to identify chronic mental ill-health. However, measuring symptoms of anxiety, depression, and dysfunction as a unidimensional construct of psychological distress is particularly relevant in community-based samples, such as ours, as mental health problems in the community are frequently characterized by shifting patterns of symptoms that resist precise clinical classification.[33] It is therefore hard to tease apart if the use of antidepressants may mark the existence of mental health problems not captured by the GHQ. Lastly, since this was an observational study, we cannot infer causation, and it is plausible that the results could be explained by residual confounding due to unmeasured or unknown risk factors.

In conclusion, we found evidence that the use of TCAs, but not SSRIs, was associated with elevated risk of CVD, beyond that explained by the symptoms of psychiatric illness.

Author contributions

M.H. had full access to the data and takes responsibility for the integrity of the data and accuracy of the data analyses. All authors contributed to the concept and design of study, drafting, and critical revision of the manuscript.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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