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## **Anti-depressant medication use and C-reactive protein: Results from two population-based studies**

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## **Abstract**

The use of anti-depressant medication has been linked to cardiovascular disease (CVD). We examined the association between anti-depressant medication use and a marker of low grade systemic inflammation as a potential pathway linking anti-depressant use and CVD in two population based studies. Data were collected in a representative sample of 8,131 community dwelling adults (aged  $47.4 \pm 15.9$  yrs, 46.7% male) from the Scottish Health Surveys (SHS). The use of anti-depressant medication was coded according to the British National Formulary and blood was drawn for the measurement of C-reactive protein (CRP). In a second study, we attempted to replicate our findings using longitudinal data from the Whitehall II study (n=4584, aged  $55.5 \pm 5.9$  yrs, mean follow-up 5.5 years). Antidepressants were used in 5.6% of the SHS sample, with selective serotonin reuptake inhibitors (SSRIs) being the most common. There was a higher risk of elevated CRP ( $>3$  mg/L) in users of tricyclic antidepressant (TCA) medication (multivariate adjusted odds ratio (OR) = 1.52, 95% CI, 1.07 – 2.15), but not in SSRI users (multivariate adjusted OR = 1.07, 95% CI, 0.81 – 1.42). A longitudinal association between any antidepressant use and subsequent CRP was confirmed in the Whitehall cohort. In summary, the use of anti-depressants was associated with elevated levels of systemic inflammation independently from the symptoms of mental illness and cardiovascular co-morbidity. This might be a potential mechanism through which antidepressant medication increases CVD risk. Further data are required to explore the effects of dosage and duration of antidepressant treatment.

*Key words:* Cardiovascular risk, depression, inflammation, selective serotonin reuptake inhibitors, tricyclic antidepressant

## **1. Introduction**

As a result of the secular rises in mental health problems, antidepressant medication is currently commonly prescribed across Europe and the United States (Olfson & Marcus, 2009; Reid & Barbui, 2010). The use of anti-depressant medication has been linked with a greater risk of weight gain (Aronne & Segal, 2003), diabetes (Rubin et al., 2008; Andersohn et al., 2009; Kivimäki et al., 2010), and with an increased risk of cardiovascular disease (CVD) events in most (Cohen et al., 2000; Tata et al., 2005; Chen et al., 2008; Fosbøl et al., 2009; Krantz et al., 2009; Smoller et al., 2009), but not all (Taylor et al., 2005; Knol et al., 2007; O'Connor et al., 2008) studies. Low grade systemic inflammatory processes may be a key mechanism underlying some of the potential adverse effects of anti-depressant medication, particularly raised CVD risk. While a series of studies suggest an association between depressive symptoms and higher levels of inflammatory biomarkers (Dinan, 2009), the link between anti-depressant use and inflammation has not been previously tested in a large sample of the general population.

The aim of the present study was therefore to examine the association between anti-depressant medication use and C-reactive protein (CRP) in a representative sample of community dwelling adults. Additionally, we performed a replication study based on longitudinal data from the Whitehall II cohort.

## **2. Methods**

### *2.1 Scottish Health Survey*

The Scottish Health Survey is a cross-sectional study that is typically conducted serially every 3-5 years, that draws a different nationally representative sample of the general population living in households for each survey (see Scottish Health Survey publications). For the present analysis we combined data from separate surveys sampled in 1998

(n=4649), 2003 (n=2824) and 2008 (n=658). Participants from the different survey years were comparable in terms of demographics and risk factors. Study participants gave full informed consent and ethical approval was obtained from the London Research Ethics Council. Data were collected during two household visits. During the first visit, trained interviewers collected data on a range of demographic and health related behaviours, including self-reported smoking (current/ex-smoker/never), alcohol intake, and participation in any form of physical activity (including walking for any purposes, heavy domestic activity, recreational sports and exercise). Psychological distress was measured using the 12 item version of the General Health Questionnaire (GHQ-12), a widely-utilized measure of psychological distress in population-based studies (Goldberg et al., 1997). The GHQ-12 enquires about symptoms in the last 4 weeks. We employed a GHQ-12 cut off score of  $\geq 4$  to denote psychological distress. This definition has been validated against standardised psychiatric interviews and has been strongly associated with depression and anxiety (Goldberg et al., 1997).

During the second household visit, conducted within a few days of the first, trained nurses collected information about physician-diagnosed CVD (stroke, ischemic heart disease, angina symptoms), diabetes, and hypertension, recorded medication usage, measured weight and height to calculate body mass index [BMI; weight (kilograms)/height (meters) squared], and took blood samples from consenting participants. The use of antidepressant medication was coded according to the British National Formulary (<http://bnf.org/bnf>) (codes; 040301 to 040304). Peripheral blood was collected in serum tubes and spun at room temperature. All blood samples were frozen at  $-70^{\circ}\text{C}$  until assay. The analysis of CRP levels was performed using the N Latex high sensitivity CRP monoimmunoassay on the Behring Nephelometer II analyser. The limit of detection was 0.17 mg/L and the coefficient of variation was less than 6% for this assay. All analyses from

each survey were carried out in the same laboratory according to Standard Operating Procedures by State Registered Medical Laboratory Scientific Officers.

Antidepressant medication use was split into four categories, [none, tricyclics (TCAs), selective serotonin reuptake inhibitor (SSRIs), other]. We used  $\chi^2$  and one-way ANOVA to examine differences in baseline characteristics between non-medicated and medicated groups. C-reactive protein was log transformed to normalise the data and we excluded any participants reporting an acute infection (bronchitis, influenza, etc) in the 3 weeks prior to the nurse visit since this may contribute to elevated levels of CRP. Associations between anti-depressant medication use and CRP were examined using general linear models. We fitted several models that included a basic model adjusted for age and sex; and several mutually exclusive models including further adjustments for physical activity (<1 hr/wk; 1-3 hrs/wk; >3 hrs/wk), alcohol (never/ex drinker; trivial; moderate; heavy) and smoking (never; previous; current) (model 1); adjustment for body mass index (<18.5 kg/m<sup>2</sup>; ≥18.5 <25 kg/m<sup>2</sup> ; ≥25 <30 kg/m<sup>2</sup> ; ≥30 kg/m<sup>2</sup>) (model 2); adjustment for psychological distress (GHQ-12 score of zero; 1 – 3; ≥4) (model 3). Finally we performed a fully adjusted model that contained all of the aforementioned variables plus physician diagnosed CVD, diabetes, hypertension. This modelling strategy allowed us to examine the relative importance of each co-variable in the model and crucially if the associations between anti-depressant use and CRP were independent of important confounding factors. We also used multivariate logistic regression to compute odds ratios (OR) with accompanying 95% confidence intervals (CI) for the association between medication use and CRP as a binary outcome (>3 mg/L). This cut point was based on previous clinical guidelines (Pearson et al., 2003).

## *2.2 Whitehall II study*

We performed a replication study based on data from the Whitehall II prospective cohort study of British civil servants. CRP was measured from 4584 participants in 1991-1993 (baseline) and again in 2003-2004 (follow-up). The analysis of CRP from serum stored at -80°C was performed using a high-sensitivity immunonephelometric assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK) (Kivimäki et al., 2008). All other baseline characteristics were assessed in 1997-1999 and included age, sex, smoking (current vs other), physical activity (sedentary vs non-sedentary), BMI, prevalent CHD (history of myocardial infarction [MI] or definite angina), diabetes (according to World Health Organization definition) and hypertension (systolic/diastolic blood pressure  $\leq$ 140/90 mm Hg or on antihypertensive treatment) and psychological distress (GHQ-12 caseness). Use of antidepressants (yes/no) was requested at baseline in 1997-1999 and at follow-up in 2003-2004 (mean follow-up  $5.5 \pm 0.5$  years).

Replication analyses with longitudinal data from Whitehall II used linear and logistic regression analyses to examine the association of antidepressant use in 1997-1999 with CRP in 2003-2004 after adjustment for baseline characteristics (i.e., smoking, physical activity, alcohol consumption, psychological distress, CHD, diabetes, hypertension, body mass index, and psychological distress in 1997-1999 and CRP in 1991-1993). To assess dose-response associations we repeated this analysis with antidepressant use in 1997-1999 and 2003-2004 (0, 1 or 2 times) as the exposure variable. There were no clear differences in our results between men and women, so the data were pooled and sex-adjusted. Analyses were conducted using SPSS version 14 (Scottish Health Survey) and SAS version 9.2 (Whitehall II).

### **3. Results**

#### *3.1 Scottish Health Survey*

The initial sample with available data on CRP consisted of 10,518 participants, although after exclusions (n=854 with infection in last 3 wks; n=863 missing BMI; n=670 missing demographics), the analytical sample comprised 8131 adults (aged  $47.4 \pm 15.9$  yrs, 3797 male, 4334 women). Excluded participants were older (52.3 vs. 47.4,  $p < 0.001$ ) and were somewhat more likely to be using anti-depressant medication (8.3% vs. 5.6%,  $p < 0.001$ ).

In this sample, SSRIs were the most commonly used type of anti-depressants. The medicated study participants were older, more likely to be female, smokers, ex-drinkers, more sedentary, obese, displayed higher levels of psychological distress and greater morbidity (Table 1). TCA users were on average older than SSRI users (54.8 vs 47.2 yrs,  $p < 0.001$ ); TCA users had lower levels of psychological distress (34.2 vs 42.7%,  $p < 0.001$ ); although levels of obesity (31.6 vs 25.4%,  $p = 0.12$ ) and smoking rates (41.3 vs 42.3%,  $p = 0.88$ ) did not significantly differ between TCA and SSRI users, respectively.

In linear analyses that examined the associations between anti-depressants and CRP, the use of TCAs remained consistently associated with CRP after a series of adjustments for potential confounders (Table 2). There was also an association between SSRI use and CRP, although this association was largely confounded by smoking. All of the covariates were strongly associated with CRP ( $p < 0.001$ ). We re-ran the models replacing BMI with waist/hip ratio as a marker of central adiposity but this did not impact on the results, and there remained an elevated level of CRP in TCA users (fully adjusted  $\beta = 0.35$ , 95% CI, 0.17 – 0.53). Sex stratified analyses suggested that the associations of TCA anti-depressant use were somewhat stronger in women (fully adjusted  $\beta = 0.37$ , 95% CI, 0.17 – 0.58) than in men ( $\beta = 0.30$ , 95% CI, -0.04 – 0.64).

A similar pattern of results emerged using logistic regression, that showed a greater risk of elevated CRP ( $> 3$  mg/L) in users of TCA medication (multivariate adjusted OR =



1.52, 95% CI, 1.07 – 2.15), but not in SSRI users (multivariate adjusted OR = 1.07, 95% CI, 0.81 – 1.42). We performed a number of sensitivity analyses to examine potential effect modification by obesity, psychological distress, and smoking. The removal of obese participants (n=1842) or smokers (n=2281), or participants with history of CVD (n=518) essentially did not alter the results, while removal of participants with psychological distress (n=1113) strengthened the association between TCA use and CRP (multivariate adjusted OR = 1.73, 95% CI, 1.13 – 2.64).

### *3.2 Whitehall II study*

Clinical characteristics of the 3313 men and 1271 women at mean age of 55.5 years are presented in table 1. A lower proportion of the Whitehall II sample were taking medication for depression (2.6%) compared to the Scottish Health Survey (5.6%). Those on antidepressants at baseline displayed higher levels of psychological distress and were more likely to be female, obese, non-drinkers, and use lipid-lowering medication compared with those not using anti-depressants (Table 1).

Fifty-four participants (1.2%) were treated with antidepressants both at baseline and follow-up. Linear regression analyses on the longitudinal association showed a dose-response relation between antidepressant use and subsequent CRP, which was strongest for participants that used antidepressants at both time points (Table 3). This association was largely robust to adjustment for confounders. The association between use of antidepressants only at baseline and CRP at follow up was not statistically significant.

## **4. Discussion**

In this study of a representative sample of community dwelling adults we observed an association between antidepressant medication use and CRP, which was particularly strong for TCAs. A longitudinal association between any antidepressant use and subsequent CRP

was replicated in the Whitehall study, although we were unable to investigate the role of medication type as this information had not been collected. These associations were independent of psychological distress, a measure of common mental disorder that is reflective of symptoms of anxiety and depression. In addition, antidepressant users were more likely to be obese and have cardiovascular disease co-morbidity at baseline. The use of TCA therapy in clinical practise has largely been replaced by newer antidepressant medication such as SSRIs, which demonstrated weaker associations with CRP in the present study and could be largely explained through confounding effects of lifestyle risk factors such as smoking. This is consistent with recent work that showed the association between depressive symptoms and CRP was largely explained through smoking, weight gain and physical inactivity (Hamer et al., 2009).

The association between antidepressant use and risk of CVD is controversial. In prospective studies of participants with existing CVD some studies have shown protective effects of SSRIs on recurrent MI and death (Taylor et al., 2005) whilst other studies have shown increased risk in TCA and SSRI users (Fosbøl et al., 2009; Krantz et al., 2009). In another study, the increased risk of mortality associated with antidepressants was not robust to adjustment for depressive symptoms, thus suggesting an effect of depression but not medication (O'Connor et al., 2008). In an occupational cohort study of initially healthy participants, use of TCAs, but not SSRIs, was associated with increased risk of MI over 4.5 years follow up (Cohen et al., 2000). In the Women's Health Initiative study of post-menopausal women, TCAs and SSRIs were associated with increased risk of mortality, and SSRIs with greater risk of hemorrhagic and fatal stroke, although not with MI over 5.9 years of follow up (Smoller et al., 2009).

Short term trials of antidepressant medication in patients with major depression have produced inconsistent findings with regards to systemic markers of inflammation such as CRP (O'Brien et al., 2006; Dawood et al., 2007; Tousoulis et al., 2009). However, these inconsistencies might reflect the different types of patients contained in each study, which included patients with coronary heart disease, heart failure, and patients with depression but otherwise healthy. Thus the underlying medical condition and other medications may have also impacted on levels of inflammation. The mechanisms that might link anti-depressants with low grade inflammation remain poorly understood. However, it is possible that factors such as weight gain and impaired glucose tolerance play a role. In addition antidepressants might impact on glucocorticoid receptors and the hypothalamic pituitary adrenal axis, which has both anti- and pro-inflammatory effects (Pariante, 2009; Pace & Miller, 2009). Elevated levels of systemic inflammation might be a potential mechanism through which antidepressant medication increases CVD risk (Danesh et al., 2004). However, the role of CRP in CVD aetiology is highly controversial, since the evidence from Mendelian randomisation studies does not support a causal role (Kivimäki et al., 2008; Zacho et al., 2008; Elliot et al., 2009) whereas there is supportive evidence of causality from experimental work in animals and humans (Venugopal et al., 2002; Verma et al., 2002; Bischoff et al., 2005). Therefore, further studies are required to better understand the association between antidepressant use, low grade inflammation, and CVD risk. Other mechanisms might also be important. For example, tricyclic antidepressants may induce weight gain 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 (Roose et al., 1998; Licht et al., 2009; Kemp et al., 2010).

Several limitations should be noted. We did not have information regarding dosage in either of our studies, which is a clear limitation. Furthermore, we did not have detailed information on the duration of anti-depressant treatment, although we attempted to examine this issue in the Whitehall II study by defining long term use as participants that reported taking antidepressants at baseline and follow up. The results showed that those participants taking antidepressants at baseline and follow up did demonstrate significantly elevated CRP, although use of anti-depressants at one time point only was not associated with CRP. These data therefore suggest that chronic use might be an important factor, although further studies will be required to fully examine this issue. The associations of antidepressant use with CRP were independent of psychological distress, which reflects symptoms of depression and anxiety. However, we were unable to adjust specifically for a clinically diagnosed depression. Nevertheless, the strengths of our analyses include the sampling of a large, representative general population-based group, thus our results can be generalised to the wider community. In addition, the findings were replicated in a second study. The findings were generally more robust in women, who demonstrated higher levels of CRP, greater psychological distress and more use of anti-depressants compared with men. However, these results should be treated cautiously since they might reflect a lack of statistical power in men.

In summary, previous evidence suggests an association between depressive symptoms and higher levels of inflammatory biomarkers. The present study suggests that the use of antidepressants was associated with elevated levels of systemic inflammation independently from symptoms of mental illness. This might be a potential mechanism through which antidepressant medication increases CVD risk.

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**Table 1.** Baseline characteristics of the study samples in Scottish Health Surveys (n=8131) and Whitehall II (n=4584)

Variable	Scottish Health Surveys			Whitehall II		
	Non-medicated (n=7675)	Medicated (n=456)	p-value	Non-medicated (n=4470)†	Medicated (n=114)†	p-value
Age (yrs)	47.2±16.0	50.5±14.1	<0.001	55.5±5.9	55.2±5.9	0.56
Male (%)	48.0	24.8	<0.001	72.7	55.3	<0.001
Smoking (%)						
Never/quit	72.7	57.9	<0.001	91.7	90.4	0.61
Current	27.2	42.1		8.3	9.6	
Physical activity (%)						
None (<1 hr/wk)	27.6	39.1	<0.001	11.5	17.5	0.07
Active	72.4	60.9		88.5	82.5	
Alcohol (%)*						
Never/ex-drinkers	4.9/3.8	5.1/11.4	<0.001	13.9	19.3	0.04
Trivial	11.4	20.0		2.1	5.3	
Moderate	62.8	53.2		61.7	56.1	
Heavy	17.1	10.3		22.3	19.3	
BMI category (%)						
<18.5 kg/m <sup>2</sup>	3.7	4.8	0.019	0.6	1.0	0.15
≥18.5 <25 kg/m <sup>2</sup>	34.0	28.3		43.0	42.0	

$\geq 25 < 30 \text{ kg/m}^2$	39.8	39.7		42.9	36.0	
$\geq 30 \text{ kg/m}^2$	22.4	27.2		13.5	21.0	
GHQ-12 score (%)						
zero	64.8	32.2	<0.001	53.4	30.7	<0.001
1 – 3	23.1	27.4		22.6	18.4	
$\geq 4$	12.1	40.4		24.0	51.9	
Cardiovascular disease (%)	6.1	11.4	<0.001	5.3	7.0	0.42
Diabetes (%)	2.7	6.4	<0.001	4.7	4.4	0.88
Hypertension (%)	18.8	25.1	0.001	26.7	31.6	0.24
Lipid lowering medication	5.0	8.8	<0.001	2.8	6.1	0.01

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\*Trivial consumption refers to 1 unit per week, moderate alcohol refers to >1<21 units per week; heavy refers to  $\geq 21$  units/wk. (based on UK government safe drinking guidelines; <http://www.drinking.nhs.uk/questions/recommended-levels/>). 1 unit = half pint beer, a small glass of wine, or a measure of spirits.

†Analysis is based on complete data on all the measures except that 17 (14.9%) antidepressant users and 247 (5.5%) non-users had missing data on physical activity and 14 (12.3%) antidepressant users and 567 (12.7%) non-users had missing data on BMI.

**Table 2.** Adjusted regression coefficients (95% CI) for the relation of antidepressant medication use with C-reactive protein in the Scottish Health Survey

Drug class	N	Mean± SD (mg/L)	Age & sex adjusted $\beta$ (95% CI)*	<b>Model 1</b> $\beta$ (95% CI)*	<b>Model 2</b> $\beta$ (95% CI)*	<b>Model 3</b> $\beta$ (95% CI)*	<b>Fully adjusted</b> $\beta$ (95% CI)*
None	7675	3.02±5.80	Reference	Reference	Reference	Reference	Reference
TCAs	155	5.72±9.00	0.54 (0.35 to 0.73)	0.44 (0.25 to 0.62)	0.48 (0.30 to 0.66)	0.50 (0.31 to 0.69)	0.35 (0.17 to 0.52)
SSRIs	260	3.56±5.19	0.20 (0.06 to 0.35)	0.13 (-0.02 to 0.27)	0.17 (0.03 to 0.31)	0.15 (0.01 to 0.30)	0.06 (-0.07 to 0.20)
Other	41	4.02±4.39	0.24 (-0.12 to 0.60)	0.16 (-0.20 to 0.51)	0.28 (-0.06 to 0.62)	0.18 (-0.18 to 0.54)	0.16 (-0.18 to 0.49)

\* Regression coefficients represent log transformed CRP values.

**Model 1;** adjusted for age, sex, smoking, physical activity, alcohol

**Model 2;** adjusted for age, sex, body mass index

**Model 3,** adjusted for age, sex, psychological distress

**Fully adjusted;** age, sex, smoking, physical activity, alcohol, psychological distress (GHQ-12 $\geq$ 4), physician diagnosed CVD, diabetes, hypertension, lipid lowering medication, body mass index

**Table 3.** Adjusted regression coefficients (95% CI) for the relation of antidepressant medication use with C-reactive protein at follow up in Whitehall II.

		Age, sex and baseline					
	Mean± SD	CRP adjusted	<b>Model 1</b>	<b>Model 2</b>	<b>Model 3</b>	<b>Fully adjusted</b>	
N	(mg/L)	β (95% CI)*	β (95% CI)*	β (95% CI)*	β (95% CI)*	β (95% CI)*	β (95% CI)*
Antidepressant use at baseline							
No	4470	2.51±4.69	Reference	Reference	Reference	Reference	Reference
Yes	114	2.77±3.71	0.15 (-0.03 to 0.32)	0.14 (-0.04 to 0.31)	0.14 (-0.03 to 0.31)	0.13 (-0.05 to 0.30)	0.11 (-0.07 to 0.28)
Antidepressant use over 2 time points							
0	4382	2.51±4.68	Reference	Reference	Reference	Reference	Reference
1	148	2.66±4.55	0.09 (-0.06 to 0.24)	0.08 (-0.07 to 0.23)	0.10 (-0.05 to 0.25)	0.07 (-0.09 to 0.22)	0.07 (-0.09 to 0.22)
2	54	3.37±4.64	0.28 (0.03 to 0.54)	0.27 (0.02 to 0.52)	0.24 (-0.01 to 0.49)	0.27 (0.01 to 0.52)	0.21 (-0.04 to 0.45)

\* Regression coefficients represent log transformed CRP values. A category of "missing data" was added to measures of BMI and physical activity.

**Model 1;** adjusted for age, sex, baseline CRP, smoking, physical activity, alcohol consumption.

**Model 2;** adjusted for age, sex, baseline CRP, body mass index

**Model 3,** adjusted for age, sex, baseline CRP, psychological distress (GHQ-12≥4)

**Fully adjusted;** age, sex, baseline CRP, smoking, physical activity, alcohol consumption, psychological distress, CHD, diabetes, hypertension, body mass index, lipid lowering medication.