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Introduction

The 2010 Global Burden of Disease has identified anxiety and depression as the most prevalent mental health conditions worldwide, contributing significantly to overall global disease burden and years lived with disability.(Ferrari et al., 2013; World Federation For Mental Health, 2012) In the UK, anxiety and depressive disorders affect approximately 15% of the adult population.(LSE and The Centre for Economic Performance, 2012)

Patients with psychiatric conditions have an increased risk of cardiovascular disease (CVD), including myocardial infarction (MI) and stroke.(De Schutter et al., 2011; Elderon and Whooley, 2013; Hare et al., 2014; Osborn et al., 2007; Tully et al., 2015) Both anxiety and depression are common mental disorders, with high prevalence in the general population. While the relationship between severe mental illness and cardiovascular disease has been widely explored, there is a paucity of evidence around the relationship between anxiety and incident cardiovascular events.(Bowen et al., 2000; Chou et al., 2012; Davies and Allgulander, 2013; Lambiase et al., 2014; Osborn et al., 2007) The burden of CVD and CVD risk factors is increasing rapidly amongst young, working-age adults. (Lavie and Milani, 2006; Moran et al., 2014; Poisson et al., 2014) Since cardiovascular disease is the leading cause of loss of in disability adjusted life-years (DALYs) worldwide, this represents the greatest loss for families and national economies. Accordingly, it is important to know whether individuals with anxiety or depressive disorders are at risk of earlier onset of MI and stroke compared to individuals without these conditions.(Murray et al., 2012)

This study aims firstly to quantify the excess risk of non-fatal stroke or MI

Abbreviations:
MI Myocardial Infarction
CVD Cardiovascular Disease
EMIS Egton Medical Information Systems
UK United Kingdom
NHS National Health Service

associated with diagnosed anxiety and depressive disorders and antidepressant use in an unselected primary care population, and secondly, to test the hypothesis that cardiovascular (CV) events may have an earlier presentation in patients with anxiety and depressive disorders compared to those without. We hypothesize that risk will be increased in patients with these psychiatric conditions compared to those without and that the increased risk can be further explained by sociodemographic and cardiovascular risk factors. This work will help to identify groups at higher risk for cardiovascular outcomes and potential areas for focusing preventive interventions.

Methods

A prospective cohort study using patients contributing to the east London primary care database held by the Clinical Effectiveness Group at Queen Mary, University of London was undertaken. The database comprises the electronic health records of approximately 950,000 individuals registered with 141 general practices across the east London boroughs of Tower Hamlets, Newham, and City & Hackney, all of which use EMIS web as their clinical computer system. The population of east London is one of the most deprived in the UK and has high levels of ethnic diversity, with over 50% of the resident population of non-white ethnicity.(Hull et al., 2014; Tower Hamlets Council, 2013)

The study sample included all adult patients aged 30 and over in March 2015 who were free from MI or stroke at the start of the study period in March 2005. Anonymised demographic, clinical and prescribing data were extracted for all individuals meeting the study entry criteria.

Read codes are the standard clinical terminology system used in general practice across the UK.(Chisholm, 1990) Diagnostic Read codes for anxiety and depressive disorders were selected by the authors, who comprised general practitioners, clinical psychiatrists, and epidemiologists. Diagnoses of diabetes mellitus, before March 2005, and MI and stroke, between March 2005 and March 2015, were defined according the quality and outcomes framework Read code specifications.(NHS Employers, 2014) Individuals without a diagnostic Read code for each condition were considered to be free from the disease of interest.

Self-reported ethnicity was recorded at the practice during registration or routine consultation. Ethnic categories were based on the UK census and for this study were condensed into four categories: White (British, Irish, other white), Black (Black African, Black Caribbean, other Black) South Asian (Bangladeshi, Pakistani, Indian, other South Asian) and any other ethnic group. Patients with mixed ethnicity were grouped with their parent ethnic minority. Individuals with missing ethnicity information were grouped into an “unknown” category (results not shown). Deprivation was classified using the Townsend deprivation score, a census-based index of material deprivation calculated by the combination of four variables from the 2001 census: car ownership, overcrowded households, households not owner occupied, and unemployment.(Townsend, 1987)

Systolic and diastolic blood pressure, total cholesterol level, tobacco consumption and antidepressant use closest to and before March 2005 were extracted to identify baseline values at study entry. Hypertension was identified using the clinical Read code for hypertensive disease. Obesity was defined as having a body mass index of 30 kg/m^2 or above; Hyperlipidemia was defined as

having a total cholesterol value of greater than 5 mmol/L; Tobacco consumption was dichotomized into current smoker vs. not current smoker. Individuals without Read codes for tobacco consumption were considered to be non-current smokers.

Individuals entered the study in March 2005 and were followed up until they experienced an incident non-fatal event of MI or stroke during the ten years of follow-up. Follow-up time was censored at the end of the study period in March 2015 if they did not experience the outcome of interest.

Cox proportional-hazards regression analyses were used to firstly compare the risk of incident MI and stroke in patients with and without depression at baseline and secondly to compare the risk of incident MI and stroke in patient with and without anxiety at baseline. Three regression models were built; The first adjusted for age, gender, and ethnic group, the second additionally adjusted for diabetes, hypertension, hyperlipidemia, and smoking antidepressant prescribing at baseline, obesity, and Townsend deprivation score, and the third additionally adjusted for the presence of co-morbid anxiety or depression. Linear regression models adjusting for gender and ethnicity were used to compare the age at the time of MI and stroke of patients with and without anxiety and depression. All models accounted for clustering of patients within general practices using a shared frailty term for practice, which reflects the non-independence of patients attending the same health care provider.(Allison, 2014)

Results

A total of 524,952 adults aged 30 and over registered with the east London primary care database in March 2015 were identified. The characteristics of the study sample are presented in table 1. From the total population, 21,811 individuals had an existing diagnosis of depression at baseline (4.1%) while 22,128 had an existing diagnosis of anxiety (4.2%). Compared to individuals free from psychiatric disorders, individuals with depression or anxiety were older, had a higher proportion of females and a smaller proportion of individuals from ethnic minority groups ($p<0.001$). Prevalence of all clinical co-morbidities at baseline was higher in those with anxiety or depressive disorders, most notably hyperlipidemia was present in 60% of those with anxiety or depressive disorders and 40% of those without anxiety or depressive disorders ($p<0.001$). Similarly, 40% of those with anxiety or depressive disorders were identified as current smokers, compared to 27% of the general population. Incidence of both MI and stroke was doubled for those with anxiety or depressive disorders compared to those without ($p<0.001$).

(Insert table 1 here)

As all included patients were necessarily registered in the database in March 2015, all were able to contribute a full ten years of follow-up time to the study. Cumulative-hazard curves illustrating the increased cumulative incidence of MI and Stroke in individuals with anxiety or depression compared to those without are shown in figure 1.

(Insert figure 1 here)

Cox proportional hazards models for the risk of incident non-fatal MI and stroke for patients with and without anxiety are presented in table 2. After adjusting for age, gender, and ethnic group (model 1), the risk of MI was raised by 33% in those with anxiety relative to those without (HR 1.33, CI95% 1.17, 1.52). After adjustment for baseline risk factors and deprivation in model 2, the association between anxiety and MI was attenuated, and association did not reach the level of statistical significance (HR 1.10, CI95% 0.96, 1.26). This lack of association remained after, adjustment for co-morbid depression in model 3 (HR 1.08, CI95% 0.94, 1.24). An independent association between antidepressants and MI was observed in the analysis for anxiety (HR 1.25, CI95% 1.13, 1.39). No evidence for a relationship between anxiety and stroke was evident in any of the survival analysis models (Table 2).

(Insert table 2 here)

Cox proportional hazards models for the risk of incident non-fatal MI and stroke for patients with and without depressive disorders are presented in table 3. After adjusting for age, gender, and ethnic group in model 1, the risk of MI was raised by 52% in those with depressive disorders compared to those without (HR 1.52 CI95% 1.34, 1.73). The risk of stroke was raised by 43% in those with depressive disorders compared to those without after adjusting for the same (HR 1.43 CI95% 1.11, 1.78). The independent effect of depressive disorders on risk of incident MI and stroke remained after additionally adjusting for cardiovascular risk factors, medication use, and deprivation in model 2 (MI HR 1.22, CI95% 1.06, 1.40, Stroke HR 1.29, CI95% 1.00-1.67). Finally, adjusting for the presence of anxiety at baseline in model 3 did not have an appreciable effect on the independent effect of depressive disorders on MI and stroke. As with the previous analysis, independent associations between antidepressants and MI were also observed in

the analysis for depression.

(Insert table 3 here)

Multivariable analyses examining differences in age at first CVD presentation according to psychiatric condition showed that anxiety was associated with an earlier presentation of MI 3.6 years (2.1-5.0) $p<0.001$ and depression was associated with an earlier presentation of strokes 4.1 years (1.1-7.1) $p=0.008$. There were no significant associations between depression and age at time of MI, or anxiety and age at the time of stroke (Table 4).

(Insert table 4 here)

Discussion

Principal Findings

This study has used a large electronic health database to highlight the heterogeneity of risk of cardiovascular outcomes according to psychiatric disorder in an ethnically and socially diverse population. While the study demonstrates a strong relationship between depression and cardiovascular disease, the evidence for a relationship between cardiovascular disease and anxiety is weaker. The study shows that the mean age at first MI is lower in those with anxiety, while mean age at first stroke is lower in those with depression. Furthermore, the study has shown a strong independent effect of antidepressant on risk of MI, but not stroke. Our findings show that traditional cardiovascular risk factors can explain part of the association between anxiety, depression and cardiovascular disease. This is encouraging as the majority of these modifiable risk factors can be managed in primary care. The association between anxiety and incident MI was reduced after adjustment for cardiovascular risk factors. Traditional cardiovascular risk factors and antidepressant use accounted for a greater amount of the association between depression and MI, as evidenced by the risk associated with depressive disorders decreasing from 52% to 21% after full adjustment, and a smaller proportion of the association between depression and stroke (reduction in risk associated with depressive disorders from 40% to 29%).

Comparisons with existing literature

The associations between depressive disorders/anxiety and MI, and between depressive disorders and stroke confirm those of previous studies.(Dong et al.,

2012; Pan et al., 2014; Roest et al., 2010; Van der Kooy et al., 2007) While strong evidence for a relationship between anxiety and fatal myocardial has been found, the evidence for a relationship with non-fatal MI is more equivocal.(Roest et al., 2010). Anxiety has been shown to increase risk of incident stroke in recent studies in a US setting.(Lambiase et al., 2014; Thurston et al., 2013) The lack of a relationship in our study may be due to lack of reliable assessment of anxiety, or the fact that we did not capture fatal events, and may have thus underestimated the relationship between anxiety and incident CVD.

The finding of increased cardiovascular risk amongst people with diagnosed depression reinforces that of recent studies: A 2014 meta-analysis of 28 cohort studies (n= 681,139) examining the risk of incident stroke in patients with depression reported a pooled estimate of 1.40 (CI95% 1.27-1.53) which aligns closely with the findings reported in above.(Barlinn and Kepplinger, 2015) Of the 28 studies, two were based in the UK; the first reported no relationship between stroke and depression or anxiety, while the second reported a relationship between depression and coronary heart disease, but not stroke. (Surtees et al., 2008)(Brunner et al., 2014)

Associations with antidepressant prescribing

The independent association between antidepressants and cardiovascular outcomes has been demonstrated before.(Pan et al., 2014) Clinical prescribing in general practice is largely guided by evidence from randomized control trials, which tend to be conducted in idealized populations and have a short duration. In the absence of RCTs, the long term observation and follow-up of patients via routine electronic health databases will provide the timeliest evidence around

the benefits and risks of medication use in the general population.(Ayerbe et al., 2014; Coupland et al., 2011) While we cannot infer causality from our observations, our results add to a significant body of evidence suggesting that antidepressants should be prescribed, balancing the benefits with the negative side effects associated with them in the long term.

Strengths

Clinical data on anxiety and depression have been widely used for research purposes since large electronic databases have become available. Electronic health databases provide a platform to conduct high resolution research on very specific and clinically meaningful outcomes that are difficult to investigate with smaller cohorts. (Daskalopolou et al., 2016; Chou et al., 2012).The east London database covers a large, unselected, and geographically contiguous population, allowing for the capture of sufficient numbers of patients with the two most common psychiatric conditions to explore the relationship with cardiovascular outcomes. Given that 99% of the UK population is registered with a general practitioner, we are likely to have captured an accurate cross-section of the population of east London. The findings of this study can be generalized to other primary care populations in urban settings with high ethnic and social diversity.

The east London database captures all prescriptions issued by the general practice team. Though the database does not provide information on whether the prescriptions are filled, a comparison of prescribing data from electronic health databases and NHS dispensing data shows the two sources to be highly comparable, with 97% of cardiovascular medications dispensed as prescribed. (The NHS Information Centre, 2011)

The prospective nature of this study ensured that we captured incident cardiovascular events recorded after the onset of depression or anxiety, limiting the possibility of reverse causality. All data were entered into the medical record prospectively, minimizing the risk of recall bias or inaccurate self-report. The study accounted for the presence of well-established risk factors for cardiovascular disease and benefitted from high levels of ethnicity recording and patient level deprivation data, which allowed for a more accurate estimation of the independent effect of anxiety and depressive disorders on the CVD outcomes. This study has demonstrated that it is possible to replicate and confirm results from non-observational studies and trials in an electronic health database setting using observational epidemiology methodology.

The capture and coding of both anxiety and depressive disorders is clearly outlined in the UK National Institute for Health and Care Excellence guidelines, and thus we expect that general practitioners will code this information consistently and to a high level. (NICE, 2014; NICE, 2011) Furthermore, incentive payments for the accurate recording of depression as part of the Quality and Outcomes Framework were introduced in 2006. A systematic review of the validity of diagnoses in the General Practice Research Database, which collects data identical to that used in our study has shown that 83% of cases with mental and behavioural disorders present in the GPRD were confirmed by general practitioners. (Herrett et al., 2010)

Limitations

Anxiety and depressive disorders tend to be under-diagnosed in primary care settings. (Rait et al., 2009; Robert et al., 1997; Stein and Sareen, 2015) Furthermore, lower rates of healthcare usage amongst patients with these

conditions may limit the opportunity to recognize major cardiovascular conditions in these populations.(Yeomans et al., 2014).

The over diagnosis of depressive disorders, coupled with the under diagnosis of those who have depressive disorders but don't seek medical help due to reduced motivation, may lead to an underestimation of the associations between depressive disorders and cardiovascular disease. (Mitchell et al., 2009) As a result, this study may have had reduced power to detect the true relationship between anxiety and depressive disorders and subsequent cardiovascular events. Furthermore, due to the nature of the data, we were unable to assess disease stage (for example, current, remitted, mild, moderate, severe), which could have an impact on the risk of incident cardiovascular disease. Data on physical activity were only available for 27.6% of the study sample and therefore adjustment for this confounder was not possible.

The study included all patients currently registered in the database in 2015 and thus we did not have any patients that died during the course of follow-up. Lack of linkage to hospital episode statistics or mortality data meant that we were unable to examine all-cause mortality or CV related mortality in the study population. Furthermore we were unable to determine whether any hospital admissions for MI or stroke had occurred prior to study entry, and thus we had to assume that the first recorded event in the primary care database was truly incident.

Though our study accounted for ever use of antidepressants, it did not take consider the dosage, drug type, or continuity of prescribing. The study also did not consider antipsychotic medication which has been shown to increase risk of

stroke, but not MI. (Brauer et al., 2011; Douglas and Smeeth, 2008)

We examined incidence of cardiovascular outcomes over the previous 10 years; this was due to confidence in the quality of the recorded covariate and diagnostic data following the introduction of the Quality and Outcomes Framework in 2004, which rewarded general practices for high quality and complete recording of priority clinical conditions and risk factors across the UK.(NHS Employers, 2014)

We were unable to examine a “disease-free” cohort and follow them up prospectively to compare CVD outcomes between patients who developed anxiety/depression and those who did not. Furthermore, our use of baseline measures of key cardiovascular risk factors did not fully account for the time varying nature of risk factor control, which can change in response to both pharmacological and non-pharmacological intervention by the clinician, and in response to changes in morbidity status of the patient.

Unanswered questions and future research

Coded diagnoses for anxiety and depressive disorders do not provide any information as to the severity of the condition, which is likely to affect subsequent healthcare usage and cardiovascular risk. Using additional information to refine the classification of disease severity would improve the estimation of the independent effect of anxiety and depressive disorders on subsequent cardiovascular outcomes.(Kubzansky et al., 1998)

Small numbers of patients with diagnosed psychiatric conditions other than

anxiety and depressive disorders meant that we were unable to extend the same analysis to other relevant conditions such as those with schizophrenia, bipolar disorder, or personality disorders, which have been found to have a significant relationship with cardiovascular outcomes.(Ringen et al., 2014) For the same reason, we were unable to estimate CV risk in individuals with more than one prevalent psychiatric condition at baseline. Conducting the analysis in larger or multiple electronic health databases would allow for the study of a wider range of psychiatric disorders would be valuable in confirming or refuting the findings, and also exploring risk in patients with concurrent anxiety and depressive disorders.

Clinical Relevance

In conclusion, the evidence provided in this paper contributes to a better understanding of the association between anxiety and CVD, which has received little attention and confirms existing literature around the relationship between depression and MI/stroke. The weaker relationship between anxiety and excess risk of MI (after adjustment for traditional cardiovascular risk factors) is of clinical importance and highlights that control of traditional risk factors is the cornerstone of cardiovascular disease prevention, even in populations with psychiatric disorders. Our findings suggest that strict control of cardiovascular risk factors among patients with anxiety disorders may reduce the risk of coronary or cerebrovascular events to a level equivalent to that for patients without anxiety. Our findings for depressive disorders suggest an independent effect of depression which persists despite accounting for cardiovascular risk factor control. Targeting more intensive management of cardiovascular risk factors and evaluating the benefit risk ratio of antidepressant prescribing should be prioritized amongst primary care teams.

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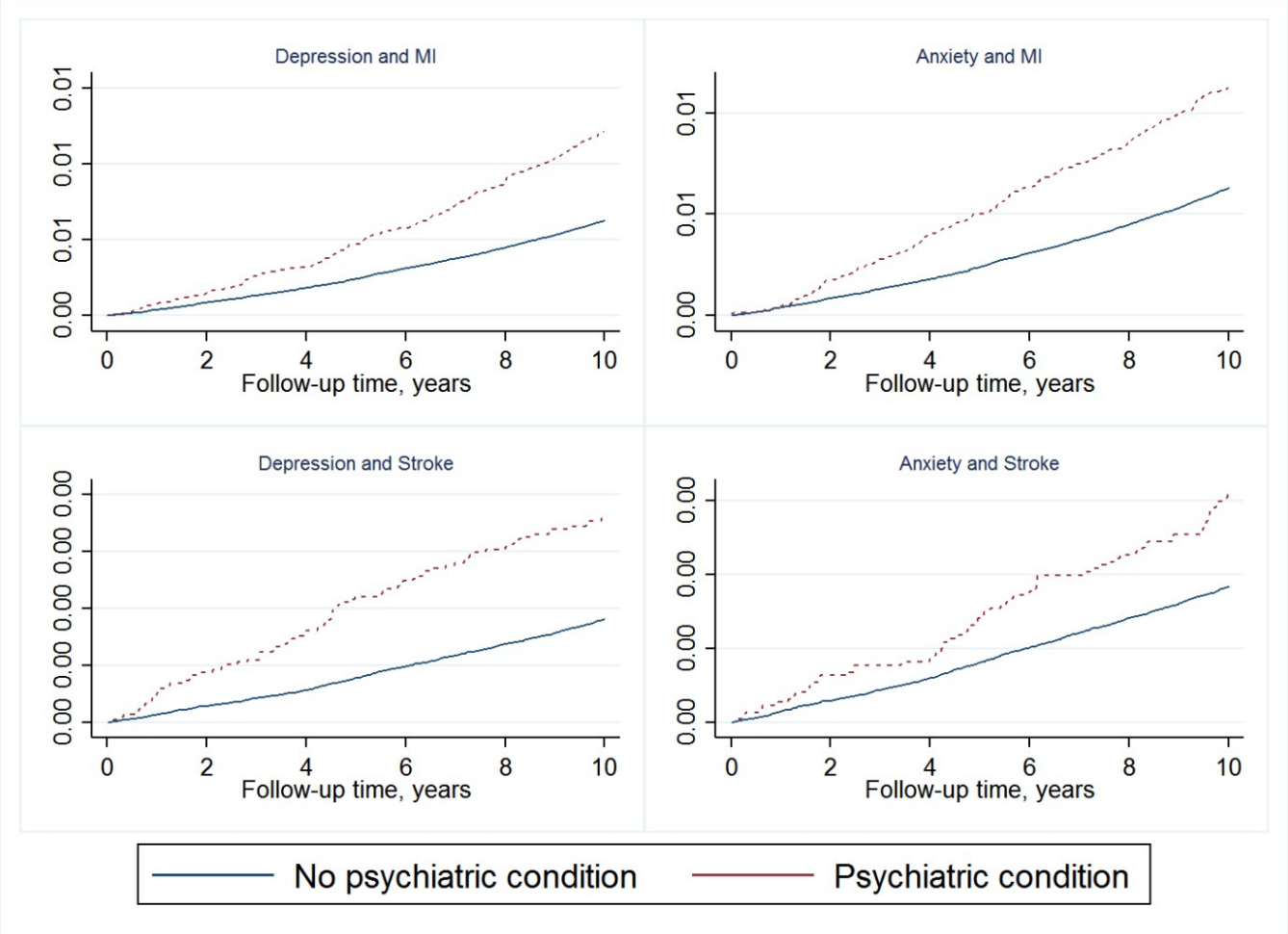

Figure 1. Cumulative Hazard Curves for incidence of MI and Stroke in patients with Anxiety or Depression

Table 1. Description of study sample

	Whole cohort	Anxiety cohort	Non-Anxiety cohort	p.val for difference	Depression cohort	Non-Depression cohort	p.val for difference
	n (%)	n (%)	n (%)		n (%)	n (%)	
N	524,952 (100)	22,128 (4.2)	502,824 (95.8)		21,811 (4.1)	503,141 (95.9)	
Demographic characteristics at baseline							
Mean age (SD)	35.9 (13.9)	42.7 (13.9)	35.6 (13.8)	<0.001	43.2 (13.5)	35.6 (13.8)	<0.001
Median age (IQR)	32 (25-44)	41 (32-52)	32 (24-43)		42 (33-52)	32 (24-43)	
Female	247,528 (47.1)	13,267 (60.0)	234,261 (46.6)	<0.001	13,777 (63.2)	233,751 (46.5)	<0.001
Male	277,423 (52.8)	8,861 (40.0)	268,562 (53.4)		8034 (36.8)	269,389 (53.5)	
White	220,079 (41.9)	13,863 (62.6)	206,216 (41.0)	<0.001	13,436 (61.6)	206,643 (41.1)	<0.001
South Asian	144,666 (25.6)	3,507 (15.8)	141,159 (28.1)		3,182 (14.6)	141,484 (28.1)	
Black	89,186 (17.0)	2,739 (12.4)	86,447 (17.2)		3,155 (14.5)	86,031 (17.1)	
Other	32,425 (6.2)	889 (4.0)	31,536 (6.3)		869 (4.0)	31,556 (6.3)	
Unknown	38,596 (7.4)	1,130 (5.1)	37,466 (7.5)		1,169 (5.4)	37,427 (7.4)	
Mean Townsend score (SD)	5.2 (1.8)	5.4 (1.8)	5.2 (1.8)	<0.001	5.5 (1.7)	5.2 (1.8)	<0.001
Prevalent cardiovascular risk factors and medication use at baseline							
Diabetes mellitus	50,081 (9.5)	2,804 (12.7)	47,277 (9.4)	<0.001	3,098 (14.20)	46,983 (9.3)	<0.001
Current smoker	145,862 (27.8)	8,378 (37.9)	137,484 (27.3)	<0.001	8,897 (40.8)	136,965 (27.2)	<0.001
Hypertension	86,946 (16.6)	5,829 (26.3)	81,117 (16.1)	<0.001	5,613 (25.7)	81,333 (16.2)	<0.001
Hyperlipidemia (≥5 mmol/L)	204,682 (40.0)	13,223 (59.8)	191,459 (38.1)	<0.001	13,392 (61.4)	191,290 (38.0)	<0.001
Antidepressant use	125,532 (23.9)	15,228 (68.8)	110,304 (21.9)	<0.001	16,659 (76.4)	108,873 (21.6)	<0.001
Obesity (≥30 kg/m^2)	36,195 (6.9)	3,417 (15.4)	32,778 (6.5)	<0.001	3,791 (17.4)	32,404 (6.4)	<0.001
Anxiety		--	--		5,132 (23.5)	16,996 (3.4)	<0.001
Depression		5,132 (23.2)	16,679 (3.3)	<0.001	--	--	
Incident CVD 2005-2015							
Incident MI	3,390 (0.7)	247 (1.1)	3,143 (0.6)	<0.001	263 (1.2)	21,327 (0.6)	<0.001
Mean age at first MI (SD)	59.5 (13.4)	58.5 (11.2)			61.2 (12.9)		
Incident Stroke	987 (0.2)	68 (0.3)	919 (0.2)	<0.001	79 (0.4)	908 (0.2)	<0.001
Mean age at first Stroke (SD)	61.6 (15.3)	63.4 (12.7)			59.2 (13.0)		

*Comparisons between patients with/without anxiety and with/without depression were made using t-tests for continuous variables, and from chi-squared test for unordered categorical variables

Table 2. Association between anxiety and MI/Stroke (n=524,916)

	Risk of MI						Risk of Stroke					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
Anxiety at baseline	1.33***	[1.17,1.52]	1.10	[0.96,1.26]	1.08	[0.94,1.24]	1.17	[0.91,1.51]	1.09	[0.84,1.41]	1.06	[0.81,1.38]
Age	1.07***	[1.07,1.08]	1.07***	[1.07,1.07]	1.07***	[1.07,1.07]	1.08***	[1.07,1.08]	1.07***	[1.07,1.08]	1.07***	[1.07,1.08]
Gender												
Female (ref)	1	--	1	--	1	--	1	--	1	--	1	--
Male	2.87***	[2.66,3.10]	2.82***	[2.61,3.05]	2.84***	[2.62,3.06]	1.43***	[1.26,1.62]	1.43***	[1.26,1.63]	1.44***	[1.26,1.63]
Ethnic Group												
White (ref)	1	--	1	--	1	--	1	--	1	--	1	--
South Asian	1.86***	[1.71,2.02]	1.86***	[1.71,2.03]	1.87***	[1.72,2.04]	1.24*	[1.04,1.48]	1.18	[0.99,1.42]	1.19	[1.00,1.43]
Black African/Caribbean	0.52***	[0.46,0.59]	0.51***	[0.45,0.57]	0.51***	[0.45,0.58]	1.40***	[1.19,1.65]	1.29**	[1.09,1.52]	1.29**	[1.09,1.53]
Other ethnic group	0.76**	[0.63,0.92]	0.81*	[0.68,0.98]	0.82*	[0.68,0.99]	1.09	[0.80,1.49]	1.10	[0.80,1.50]	1.10	[0.81,1.51]
Hypertension			1.17***	[1.07,1.28]	1.17***	[1.07,1.28]			1.47***	[1.25,1.73]	1.47***	[1.25,1.73]
Diabetes Mellitus			1.48***	[1.33,1.63]	1.48***	[1.33,1.63]			1.46***	[1.21,1.75]	1.46***	[1.21,1.75]
Hyperlipidemia			1.12*	[1.02,1.22]	1.12*	[1.02,1.22]			0.89	[0.75,1.05]	0.89	[0.75,1.05]
Current smoker			2.03***	[1.87,2.20]	2.02***	[1.86,2.19]			1.33**	[1.12,1.59]	1.33**	[1.11,1.58]
Antidepressant use			1.25***	[1.13,1.39]	1.20***	[1.08,1.34]			1.07	[0.87,1.30]	1.01	[0.82,1.24]
Townsend deprivation score			1.06***	[1.04,1.09]	1.06***	[1.04,1.08]			1.03	[0.99,1.07]	1.03	[0.99,1.07]
Obesity			1.73***	[1.60,1.87]	1.73***	[1.60,1.87]			1.45***	[1.25,1.68]	1.45***	[1.25,1.68]
Depression					1.21**	[1.05,1.39]					1.29	[1.00,1.66]

* Columns display hazard ratio, and 95% confidence interval, *p<0.05 **p<0.01 ***p<0.0001, all models account for clustering by general practice.

Table 3. Association between depressive disorders and MI/Stroke (n=524,916)

	Risk of MI						Risk of Stroke					
	Model 1		Model 2		Model 3		Model1		Model2		Model 3	
Depression at baseline	1.52***	[1.34,1.73]	1.22***	[1.06,1.40]	1.21***	[1.05,1.39]	1.40***	[1.11,1.78]	1.29*	[1.00,1.67]	1.29	[1.00,1.66]
Age	1.07***	[1.07,1.08]	1.07***	[1.07,1.07]	1.07***	[1.07,1.07]	1.08***	[1.07,1.08]	1.07***	[1.07,1.08]	1.07***	[1.07,1.08]
Gender												
Female (ref)	1	--	1	--	1	--	1	--	1	--	1	--
Male	2.89***	[2.68,3.12]	2.83***	[2.62,3.06]	2.84***	[2.62,3.06]	1.44***	[1.27,1.63]	1.43***	[1.26,1.63]	1.44***	[1.26,1.63]
Ethnic Group												
White (ref)	1	--	1	--	1	--	1	--	1	--	1	--
South Asian	1.87***	[1.72,2.03]	1.87***	[1.72,2.04]	1.87***	[1.72,2.04]	1.25*	[1.05,1.49]	1.19	[1.00,1.43]	1.19	[1.00,1.43]
Black African/Caribbean	0.52***	[0.46,0.59]	0.51***	[0.45,0.58]	0.51***	[0.45,0.58]	1.41***	[1.20,1.66]	1.29**	[1.09,1.53]	1.29**	[1.09,1.53]
Other ethnic group	0.77**	[0.64,0.92]	0.82*	[0.68,0.98]	0.82*	[0.68,0.99]	1.10	[0.80,1.50]	1.10	[0.81,1.51]	1.10	[0.81,1.51]
Hypertension			1.17***	[1.07,1.28]	1.17***	[1.07,1.28]			1.47***	[1.25,1.73]	1.47***	[1.25,1.73]
Diabetes Mellitus			1.47***	[1.33,1.63]	1.48***	[1.33,1.63]			1.45***	[1.21,1.75]	1.46***	[1.21,1.75]
Hyperlipidemia			1.12*	[1.02,1.22]	1.12*	[1.02,1.22]			0.89	[0.75,1.05]	0.89	[0.75,1.05]
Current smoker			2.02***	[1.86,2.19]	2.02***	[1.86,2.19]			1.33**	[1.12,1.58]	1.33**	[1.11,1.58]
Antidepressant use			1.22***	[1.10,1.35]	1.20***	[1.08,1.34]			1.02	[0.83,1.25]	1.01	[0.82,1.24]
Townsend deprivation score			1.06***	[1.04,1.08]	1.06***	[1.04,1.08]			1.03	[0.99,1.07]	1.03	[0.99,1.07]
Obesity			1.73***	[1.60,1.87]	1.73***	[1.60,1.87]			1.45***	[1.25,1.68]	1.45***	[1.25,1.68]
Anxiety					1.08	[0.94,1.24]					1.06	[0.81,1.38]

* Columns display hazard ratio, and 95% confidence interval, *p<0.05 **p<0.01 ***p<0.0001, all models account for clustering by general practice.

Table 4. Age at first presentation of MI and Stroke

		Difference in age at presentation (years)		
MI		Coefficient	CI95%	p.va;
	Anxiety	-3.6	-5.0 – -2.1	<0.001
	Depression	-1.0	-2.5 – 0.5	0.203
Stroke				
	Anxiety	0.5	-2.7 – 3.7	0.736
	Depression	-4.1	-7.1 – -1.1	0.008

**All models adjusted for gender and ethnic group, and clustering by general practice

Highlights

• The study finds strong evidence for an independent association between depression and cardiovascular events, and weaker evidence for an association with anxiety.

• Mean age at first MI is lower in those with anxiety compared to those without anxiety, while mean age at first stroke is lower in those with depression compared to those without depression.

• The study shows an independent effect of antidepressant prescribing on risk of MI, but not stroke.

• The findings highlight that that control of traditional risk factors is the cornerstone of cardiovascular disease prevention in populations with psychiatric conditions.

• Targeting intensive management of classical cardiovascular risk factors and evaluating the benefit risk ratio of antidepressant prescribing should be prioritized amongst primary care teams.

Conflict of Interest

None

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Author contributions

Contributions	RM	MPP	QFB	SA	LA
Conceived & designed research	x	x	x	x	x
Acquired the data	x				x
Performed statistical analysis	x				x
Interpreted the data	x	x	x	x	x
Drafted the manuscript	x				X
Made critical revisions	X	x	x	x	x

Data sharing statement

The data used for this study are drawn from the anonymised clinical records of patients in the east London Database and are not available for sharing.

Depression: Read Term	Freq.	Anxiety: Read Term	Freq.
CONSULTATION:Depression	1	AGORAPHOBIA	1
Chronic depression	1,522	ANXIETY REACTION	1
DEPRESSION	41	ANXIETY STATE	1
Depressed Mood	1	Acrophobia	2
Depression	5,085	Acute Anxiety State	16
Depression NOS	1,163	Agoraphobia	90
Depression NOS tearful and low mood pre	1	Agoraphobia - no panic attacks	1
Depressive disorder	6	Agoraphobia - no panic attacks (GMS)	1
Depressive disorder NEC	7,132	Agoraphobia with panic attacks	290
Mild depression	31	Agoraphobia without mention of panic att	24
Mild depression (GMS)	2	Animal phobia	39
Moderate depression	54	Anxiety & Depression	4
Moderate major depression	1	Anxiety State	3
Postviral depression	8	Anxiety Symptoms	197
Premenstrual dysphoric disorder	8	Anxiety Symptoms Related To Bomb	12
Query Depressive disorder NEC	1	Anxiety disorder	4
Query [X]Moderate depressive episode	1	Anxiety state	2,676
Recurrent major depressive episodes, sev	186	Anxiety state NOS	2,321
Severe depression	40	Anxiety state unspecified	647
Single major depressive episode, severe,	2	Anxiety states	14,274
[X] Reactive depression NOS	1,288	Anxiety with depression	18,338
[X]Antenatal depression	1	Cancer phobia	68
[X]Atypical depression	8	Chronic Anxiety State	9
[X]Depression NOS	17,170	Chronic anxiety	799
[X]Depressive disorder NOS	111	Claustrophobia	401
[X]Depressive episode	1,910	Dental phobia	69
[X]Depressive episode, unspecf	15	Fear of crowds	2
[X]Depressive episode, unspecf (GMS)	184	Fear of death	9
[X]Depressive episode, unspecified	1,226	Fear of flying	1,241
[X]Endogen depress no psychot	4	Fear of pregnancy	36
[X]Endogen depress+psychot	1	Flying Fear /Ox	1
[X]Endogenous depression with psychotic	21	Generalised anxiety disorder	812
[X]Endogenous depression without psychot	3	Mixed anxiety and depressive disorder	30
[X]Major depression, mild	3	Mixed anxiety and depressive disorder (G	4
[X]Major depression, moderately severe	36	Needle Phobia	1
[X]Major depression, recurrent without p	5	Other Phobias	12
[X]Major depression, severe with psychot	47	Other phobias	58
[X]Major depression, severe without psyc	15	PANIC ATTACK (S)	2
[X]Manic-dep,depress+psychotic	1	PANIC ATTACK(S)	7
[X]Manic-depress psychosis,depressd,no p	1	PHOBIA	1
[X]Manic-depress psychosis,depressed typ	2	Panic Attacks	27
[X]Mild depression	409	Panic Disorder	2
[X]Mild depressive episode	1,736	Panic attack	6,058
[X]Moderate depressive episode	4,195	Panic disorder	1,219

[X]Moderate depressve episode (GMS)	18	Panic disorder without agoraphobia	2
[X]Monopolar depression NOS	1	Phobia unspecified	170
[X]Other depressive episodes	34	Phobic Anxiety	33
[X]Other recurrent depressive disorders	7	Phobic State	1
[X]Prolonged single episode of reactive	6	Phobic anxiety	303
[X]Rec psychogen dep psychosis	1	Phobic disorder NOS	24
[X]Recur epis/psychogen depres	1	Phobic disorders	41
[X]Recur epis/react depression	1	Phobic state	3
[X]Recur,major dep+psychotic	1	Query Generalised anxiety disorder	1
[X]Recurr dep now sever+psych	1	Query Panic attack	3
[X]Recurr dep now sever+psych (GMS)	2	Query Panic disorder	1
[X]Recurr depress disorder cur epi sever	6	Recurrent anxiety	331
[X]Recurr major depr ep, severe with psy	45	School Phobia	1
[X]Recurr severe episodes/major depressi	4	Social phobia (GMS)	1
[X]Recurrent depress disorder cur epi se	10	Social phobia, fear of public speaking	29
[X]Recurrent depressive disord (GMS)	4	Social phobia-eating in public (GMS)	1
[X]Recurrent depressive disorder	504	Social phobic disorders	62
[X]Recurrent depressive disorder, curren	10	Stress - acute reaction	2
[X]Recurrent depressive disorder, curren	19	Test request: Anxiety with depression	1
[X]Recurrent depressive disorder, curren	10	Weight fixation	3
[X]Recurrent depressive disorder, unspec	26	[X]Agoraphob no hist/panic dis	21
[X]Recurrent episodes of depressive reac	1	[X]Agoraphobia	273
[X]Recurrent episodes of psychogenic dep	3	[X]Agrophob no hist/panic dis	3
[X]Recurrent episodes of reactive depres	4	[X]Animal phobias	5
[X]Recurrent psychotic depress	30	[X]Anxiety NOS	2,742
[X]Recurrent severe episodes of psychoti	4	[X]Anxiety disord unspecified (GMS)	1
[X]Recurrent severe episodes/reactive de	1	[X]Anxiety disorder, unspecified	202
[X]SAD - Seasonal affective disorder	21	[X]Anxiety hysteria	8
[X]SAD-Seasonl affectiv disord	15	[X]Anxiety neurosis	236
[X]Seasonal depressive disorder	3	[X]Anxiety reaction	275
[X]Seasonal depressive disordr	4	[X]Anxiety state	514
[X]Severe depressiv no psychot (GMS)	5	[X]Claustrophobia	15
[X]Severe depressive + psychot	1	[X]Generalized anxiety disord	1
[X]Severe depressive + psychot (GMS)	7	[X]Generalized anxiety disord (GMS)	11
[X]Severe depressive episode with psycho	215	[X]Generalized anxiety disorder	151
[X]Severe depressive episode without psy	1,215	[X]Mild anxiety depression	144
[X]Sgl epi,maj depres+psyc sym	3	[X]Mixed anxiety and depressive disorder	486
[X]Single epis/depress react	1	[X]Mixed anxiety/depressve dis (GMS)	1
[X]Single epis/psychog depress	1	[X]Needle phobia	210
[X]Single episode agitated depressn w'ou	1	[X]Other anxiety disorders	58
[X]Single episode major depression w'out	7	[X]Other mixed anxiety disord (GMS)	1
[X]Single episode of depressive reaction	1	[X]Other mixed anxiety disorders	3
[X]Single episode of major depression an	2	[X]Other phobic anxiety disord	1
[X]Single episode of masked depression N	1	[X]Other phobic anxiety disorders	3
[X]Single episode of psychogenic depress	1	[X]Other specif anxiety disord (GMS)	1
[X]Single episode of psychogenic depress	1	[X]Other specified anxiety disorders	6

[X]Single episode of psychotic depressio	10	[X]Panic attack	98
[X]Single episode of reactive depression	15	[X]Panic disorder [episodic paroxysmal a	57
[X]Single episode of reactive depressive	2	[X]Panic disorder with agoraphobia	19
[X]Single major depr ep, severe with psy	1	[X]Panic disorder with agrophobia	1
[X]Sngl episd/reactive depresn	3	[X]Panic disorder+agoraphobia	54
[X]Sngl episod/psychot depress	1	[X]Panic disorder+agrophobia	2
depression	3	[X]Panic episodic paroxysm anx (GMS)	5
depression, MNW, NFD	1	[X]Panic state	38
		[X]Phobia NOS	49
		[X]Phobic anxiety disorder, unspecified	7
		[X]Phobic anxiety disorders	32
		[X]Phobic anxiety disordr unsp (GMS)	4
		[X]Phobic state NOS	6
		[X]Simple phobia	16
		[X]Social neurosis	3
		[X]Social phobias	118
		[X]Specific (isolated) phobia	2
		[X]Specific (isolated) phobia (GMS)	1
		[X]Specific (isolated) phobias	75
		anxiety /ox	2
		anxiety autonomic situational /ox	19
		flying fear /ox	1
		phobia against flying recent going on	1
		pregnancy fear /ox	1