Title: Relationship of Depression Screening in Cardiometabolic Disease with Vascular Events and Mortality: Findings from a Large Primary Care Cohort with 4 years follow-up.

Short Title: Depression Screening in Cardiometabolic Disease.

Authors Bhautesh Dinesh Jani MRCGP[1], Charles Boachie MSc[2], Colin McCowan PhD[2], Sarah JE Barry PhD[2], Jonathan Cavanagh FRCPsych[3], Frances S Mair FRCGP[1].

Author Affiliations: 1- General Practice and Primary Care, Institute of Health and Wellbeing, College of Medical, Veterinary and Life Sciences, University of Glasgow, United Kingdom.

2- Robertson Centre for Biostatistics, Institute of Health and Well Being, College of Medical, Veterinary and Life Sciences, University of Glasgow, United Kingdom.

3- Mental Health and Wellbeing, Institute of Health and Wellbeing, College of Medical, Veterinary and Life Sciences, University of Glasgow.

Corresponding Author: Professor Frances S Mair, General Practice and Primary Care, 1 Horselethill Road, Glasgow, United Kingdom, G12 9LX. Email: frances.mair@glasgow.ac.uk Telephone: 0044-1413308317 Fax: 0044-1413308332

Abstract

Aims

Benefits of routine depression screening for cardiometabolic disease patients remain unclear. We examined the association between depression screening and all-cause mortality and vascular events in cardiometabolic disease patients.

Methods and Results

125143 patients with cardiometabolic diseases (coronary heart disease, diabetes or previous stroke) in United Kingdom participated in primary care chronic disease management in 2008/09, which included depression screening using the Hospital Anxiety and Depression Score. 10670 receiving depression treatment exempted, 35537 screened, while 78936 not screened. We studied all-cause mortality and vascular events at four years, by electronic data linkage of 124414 patients (99·4%) on primary care registers to hospital discharge and mortality records and used Cox proportional hazards on matched data using propensity score.

Mean age for the screened and not screened population was 69 years (standard deviation-SD 11·9) and 67 years (SD 14·3), respectively; 58% (20658) of the screened population were men and 65·3% (22726) were socioeconomically deprived, compared with 54·2 % (42727) and 67·4% (51686), respectively, in the not screened population. The screened population had lower all-cause mortality (Hazard Ratio-HR 0.89) and vascular events (HR0.85) in the matched data of N=21893 patients each in the screened and the unscreened groups.

Conclusion

Depression screening was associated with a reduction in all-cause mortality and vascular events in patients with cardiometabolic diseases. The uptake of screening was poor for

unknown reasons. Reverse causality and confounding by disease severity and quality of care are important possible limitations. Further research to determine reproducibility and explore underlying mechanisms is merited.

Key Words: Depression; Coronary Heart Disease; Diabetes Mellitus; Stroke; Cardiovascular Complications.

Introduction

Patients with cardiometabolic diseases such as coronary heart disease (CHD), diabetes and stroke, depression prevalence is estimated to be 15-25% (1–3). Co-morbid depression in patients with cardiometabolic disease is associated with increased mortality, worse cardiovascular outcomes and poor functional outcomes (2,4,5).

Considering the increased prevalence and associated complications, the American Heart Association Science Advisory panel has recommended routine depression screening for all patients with CHD since 2008 (6). However, there is no evidence to date that routine depression screening for patients with cardiometabolic disease leads to any improvement in depression or cardiac outcomes (7,8). Two recently published systematic reviews did not find a single randomized trial evaluating the efficacy of depression screening as a standalone intervention in patients with cardiometabolic disease (7,8). Most of the evidence in this area has come from trials evaluating the benefits of depression screening as a part of a wider intervention, which also involved management of depressive symptoms (7,8). These trials have not found any evidence of improvements in mortality or cardiovascular outcomes with comprehensive interventions involving depressions screening and its management in patients with cardiometabolic disease (7,8). There is some evidence to suggest that collaborative care models, which usually include depression screening and comprehensive patient management, lead to improvement in depressive symptoms and glycaemic control (in patients with diabetes) but no evidence of reduction in cardiovascular outcomes (9,10).

In the UK, NICE (National Institute for Health and Care Excellence) recommends that depression screening or 'case finding' in patients with chronic disease should only be targeted towards those who are believed to be 'high risk' (11). The UK Quality and

Outcomes Framework (QOF), an annual reward and incentive programme for primary care, offered financial incentives to primary care practitioners for routine depression screening for all patients with coronary heart disease and diabetes, between 2006/07 and 2013/14 (12). These financial incentives have been withdrawn from the QOF programme since 2013/14 (13). However the potential role of standalone depression screening for all patients with cardiometabolic disease, as an intervention to identify those patients with depression but without specific management interventions, in reducing adverse outcomes related to physical health remains unclear. The aim of this project was to study the association, if any, between depression screening in patients with three cardiometabolic conditions, namely, stroke, diabetes and CHD and the rates of general hospital admissions, mental health unit admissions, cardiovascular outcomes and mortality at the end of four years follow-up .

Methods

Study Design and Setting

The data reported in this paper came from two different health boards in the West of Scotland who serve a population of circa 1.8 million. We received approval from the National Research Ethics Service (NRES), NHS Scotland Privacy Advisory Committee (PAC) NHS Greater Glasgow and Clyde Enhanced Services data group to undertake this work. The work involved retrospective analysis of a large routinely collected dataset which was completely annonymised and the research team did not have access to patient identifiers, hence individual patient consent was not obtained.

The local health boards oversaw a programme of incentivised depression screening in chronic disease as part of a wider chronic disease management programme of 'Local Enhanced Services' (LES). These are contractual arrangements at a local health board level with family practices designed to augment the basic QOF specification by incentivising additional indicators that are deemed to be particularly important for the local setting. There were no penalties for non-adherence. General practices in the health boards studied were paid under the LES scheme to carry out a comprehensive annual health assessment, which included depression screening, for all patients with one of the three common cardiometabolic conditions, CHD, diabetes and stroke. The annual health assessment was usually carried out by a practice nurse and lasted approximately one hour. Depression screening was part of the health assessment for all patients apart from those recognised to be 'under treatment' for depression at the time of their health assessment. Patients who were found to have a positive result on depression screening were offered treatment based on routine care for management of depressive symptoms based on national guidelines.

Participants

We restricted our analysis to adults aged from 18 to 90 who had a health assessment recorded for at least one of the three conditions between 01/04/2008 to 31/03/2009. A total of 125,143 patients were listed as having CHD, diabetes or stroke in the year 2008-09, the "DepChron" dataset, all of these patients underwent a comprehensive health assessment as part of LES (14,15). The definition of cardiometabolic condition (diabetes, stroke and CHD) and patient eligibility were based on the respective general practice register for these conditions. The general practice register did not take disease duration in to account while considering eligibility. Patients were labelled as 'under treatment' for depression and exempt from depression screening if they were noted to be on antidepressants (excluding amitriptyline) based on their prescription record (14,15). This strategy was used for defining patients under treatment for depression as opposed to diagnostic codes as the use of diagnostic codes for recording depression by GPs in the UK has been reported to be low (16).

Measurement of Clinical Variables

The exposure of depressions screening was defined on the basis of recording of depressive subscale of Hospital Anxiety and Depression Scale (HADS-D) (17). The HADS-D gives a total score of 0 to 21 (17), and a threshold of >7 was used to define the presence of depressive symptoms, as endorsed by national guidelines (18). The area based Scottish Index of Multiple Deprivations (SIMD) was used as a measure of socioeconomic status with patients categorised into deciles of deprivation relevant to the Scottish population (19). Smoking status was divided into current non-smokers and smokers; alcohol status was classified into moderate (< 21 units men, <14 units women), hazardous (21-50 units men, 14-35 units women) and harmful (>50 units men, >35 units women) based on their weekly units consumption (20). We checked for a new prescription of antidepressants for the duration of

the observation period for the not screened patients and for six months after the date of screening for the screened patients; we excluded amitriptyline as it is often used in the management of chronic pain in primary care. No reliable information was available on the number of patients who were referred for psychological therapies following their depression screening.

Measurement of Outcome Variables

We electronically linked the health records for patients on primary care registers with hospitalization and mortality records held by the Information Services Division (ISD), Scotland from April 2009 to March 2013. We studied six different outcomes for using the International System of Disease Classification- 10th Edition (ICD-10) codes for diagnostic accuracy (21). The outcomes studied included all-cause mortality, all-cause hospital admissions, cardiovascular disease (CVD) related mortality, CVD related hospital admissions, psychiatry unit admissions and new vascular events (myocardial infarction-MI and stroke incidence).

Statistical Analysis

Time to event analysis was performed to compare the six adverse clinical outcomes between the screened and the not screened population. Kaplan-Meier style plots were used to initially visualise the results for each clinical outcome, unadjusted for covariates, to evaluate the benefits of depression screening with the not screened group as the reference category.

We performed a propensity score matching analysis to assess the impact of depression screening when accounting for factors that influenced whether a patient was screened. A propensity score is the probability that an individual would be assigned to a group, given a set

of covariates. We used stepwise selection logistic regression to produce the predicted probability (propensity score) that an individual belongs to the screened or non-screened group base The method of matching patients in the screened and un-screened groups was based on matching on an allowable absolute difference between exact propensity scores. This score was obtained from a logistic regression model for the probability that a patient would have been screened. The screened and un-screened patients were matched 1:1 where the absolute difference between their scores was +/- 0.01. All the individual predictors included in the model were forced to stay in whether significant or not. See Supplement 1 for the SAS output from the logistic regression model.

We included the following predictors and their pairwise interaction in the logistic regression models: sex, age, SIMD (quintiles), antidepressant initiation, number of co-morbidities, alcohol consumption, history of diabetes, body mass index group, smoking status, ethnicity, systolic blood pressure (BP), diastolic BP, cholesterol, fasting glucose, random glucose, pulse rate, estimated glomerular filtration rate, Hba1c and serum creatinine. The continuous variables were centred on their mean and missing values replaced with zero. For each continuous variable, with the exception of age which has very low missing, we included a dummy variable with missing yes or no. The resulting matched data was used to produce the Cox's proportional hazards regression stratified by the matched pairs and the hazard ratios from the matched data was compared between the depression screened and the unscreened group.

We also performed univariable and multivariable analysis to compare the rate of adverse clinical outcomes between patients with depression screen positive (HADS-D>7) and those with depression screen negative. The multivariable analysis was adjusted for the covariates

age, sex, SIMD, multimorbidity and the initiation of antidepressants. Age (18-29, 30-49, 50-69, 70-89), sex (male and female) socio-economic status (SIMD quintiles 1-5) and initiation of antidepressants (yes/no) were entered into all of the models as binary variables. Number of comorbid conditions (range 1-3, representing a combination of one or more of the three cardiometabolic disease under investigations: CHD, stroke or diabetes) was entered into all regression models as an ordinal variable. Smoking status and alcohol consumption variables were excluded from regression models due to high missing values.

Analysis was carried out using the R statistical software, version 3.0.2 and SAS, version 9.3 by SAS Institute Inc., Cary, NC, USA.

Sensitivity analysis

We performed a sub-group analysis to measure the interaction effect of different demographic and clinical variables with depression screening. We compared the rate of the six adverse clinical outcomes between the screened and non-screened patients in five different sub-groups based on age, sex, socioeconomic status, number of cardiometabolic comorbidities and initiation of antidepressants. These results were visualised using a forest plot.

We also performed an additional sensitivity analysis in patients who had results of both smoking and alcohol consumption recorded, and compared outcomes between the depression screened and the non-screened groups.

Results

Sample Size, Characteristics and Clinical Outcomes

A total of 125,143 patients were recorded to have at least one of the three cardiometabolic diseases, CHD, diabetes and previous stroke, and they all underwent comprehensive health assessment. Of the total sample, 10670 (8.5%) patients were 'under treatment' for depression and were thus exempt from screening. The remaining 114473 (91.5% of total sample size) patients were all eligible for depression screening. However, depression screening was only recorded in 35537 (31.1% of those eligible) of those undergoing the annual health assessment and 78936 (68.9%) of those assessed were not screened for depression (see Figure 1). 6.3% (4989/78936) of the not screened population were started on new antidepressants during the observation period (with no clear explanation recorded), whereas 3.6% (1268/35537) of the screened population were started on new antidepressants within six months of depression screening. Electronic data linkage between primary care disease registers and hospital discharge and mortality records was successful for 99.4% (124414/125143) of patients. The demographic features, distribution of clinical variables and the absolute number of adverse clinical outcomes for the screened and not screened population are compared in Table 1.

Among the patients who had recorded results of depression screening, 7080/35537 (19.9%) were identified as screen positives based on HADS-D >7 (see Figure 1). New antidepressants were initiated for 2.4% (696/28457) of patients with HADS-D negative and 8.1% (572/7080) of patients with HADS-D positive within six months of depression screening. The median duration of follow-up was 210 weeks. At the end of 4 years follow-up period, the overall mortality rate was 16.2% (18590/114473). Table 2 compares the demographic features, clinical variables distribution and the absolute number of adverse clinical outcomes for HADS-D positive and HADS-D negative patients.

Comparison of Clinical Outcomes between Depression Screened and Not Screened Patients

Figure 2 shows a panel of Kaplan-Meier plots for all of the six adverse clinical outcomes studied for the two patient groups. As shown in the figure, the screened group did better in all clinical outcomes apart from all-cause hospital admissions, which were similar for both the groups.

As a result of propensity score matching, N=21893 patients each in the depression screened and the unscreened group were matched for 19 demographic, behavioural and clinical patient characteristics (see Table 3). Cox proportional hazards regression on the matched data showed that the screened group had lower risk than the not screened group for all of the six clinical outcomes studied at the end of the four year observation period (see Table 4).

Comparison of Clinical Outcomes between Depression Screen Positive (HADS-D>7) and Screen Negative Patients

The panel of Kaplan-Meier plots in Figure 3 shows that patients with a negative depression screen did better in all six clinical outcomes under study at the end of four years.

The screen positive groups (HADS-D mild 8-10, moderate to severe 11-21) had higher risk for all adverse clinical outcomes when compared to the screen negative group in the unadjusted analyses using the Cox proportional hazards. The risk for screen positives compared to screen negatives was unmitigated after adjusting for age, sex, socioeconomic deprivation, number of cardiometabolic comorbidities and antidepressant initiation (Table 5).

Among the 1268 patients among depression screened who were treated with initiation of antidepressants, the adjusted HR for all-cause mortality was not significantly different for the

mild depression group (HR 0.89, CI 0.57- 1.37) and the moderate/severe depression group (HR 1.33, CI 0.85-2.08), when compared to the screening negative group.

Sensitivity Analysis

In the sub-group analyses for different patient groups, comparing the clinical outcomes for the depression screened and not screened patients, screened patients had better outcomes in the sub-group analyses based on age, sex and socioeconomic status (see Figure 4). For the sub-group of patients who were initiated on new antidepressants, the confidence crossed the significance line for all-cause hospital admissions, cardiovascular disease related hospital admissions and psychiatry unit admissions. This implies that there was no statistically significant difference for these three clinical outcomes between the screened and the not screened patients who were initiated on antidepressants. Similarly, for the sub-group of patients with all three cardiometabolic conditions, there was no statistically significant difference between the screened and the not screened group for all-cause hospital admissions, psychiatry unit admissions, incidence of stroke/MI and CVD related hospital admissions.

In the subset of patients who had results of smoking and alcohol consumption recorded (22068/114473), the trends in results of better clinical outcomes in the depression screened group was unchanged, after additionally adjusting for smoking and alcohol consumption (see supplement 1).

Discussion

Summary of Findings

In a large, community based sample of patients with CHD, previous stroke, or diabetes, depression screening was associated with reduced risk at four years of: all-cause mortality; CVD related mortality; CVD related hospital admissions; psychiatry unit admissions; and new vascular events, in matched data analysis using propensity score methods. Patients who had a positive result on depression screening were also significantly more likely to experience increased risk of these same adverse clinical outcomes. These associations remained significant after adjusting for demographic factors such as age, sex and socio-economic status; and clinical factors such as number of cardiometabolic conditions and initiation of antidepressants.

Patients who were not screened for depression were more likely to be initiated on new antidepressants when compared to the screened patients as a whole but less likely when compared to those who had a positive result on depression screening.

Strengths and Limitations

This study has a number of key strengths, in that the data came from a large, community based sample reflecting real life clinical practice and electronic data linkage enabled successful follow-up for the majority of patients in the cohort. There are several limitations. In this large, community based sample of patients with CHD, previous stroke, or diabetes only a minority had depression screening recorded despite incentivisation. Since only a minority of the patients were actually screened, there may be important differences between patients with known depression status and those whose depression status was unknown, which are not clearly evident from their baseline demographic data. There is a possibility that

the observed association is due to confounding as patients in this study were not randomly allocated to the screened and unscreened groups. For example, practitioners may intuitively screen patients where they are more likely to get a positive result, for instance patients with severe disease or multimorbidity. Also, there is a possibility of reverse causality with GPs reviewing a patient whom they consider to have depression and offering screening subsequently. Previously reported barriers to discussing depression (or mental health) in patients with chronic disease in primary care, such as stigma associated around the 'label' and physicians' preconception of normalizing depression in patients with chronic disease, could also be influencing factors behind low uptake of depression screening in our study (22,23). Additionally, patients with other psychiatric co-morbidities such as dementia or psychoses who are at higher risk of co-morbid depression may have been excluded from depression screening by the GP and may have been in the unscreened group. This could be one of the reasons for the higher observed rate of new antidepressants prescribing in the unscreened group as compared to the screened group.

In addition, the rate of data completion was better in the screened population than the unscreened population, which may be a marker of better quality of care received by the screened population, and in turn may have contributed to the observed difference in clinical outcomes between the two groups. For example, the information on blood pressure measurement and smoking consumption was available for 69.9% (55198/78936) and 32.3% (25554/78936) respectively for the unscreened group. In comparison, the information on blood pressure measurement and smoking consumption was available for 90.4% (32139/35537) and 42.4% (15092/35537) respectively for the depression screen group. Among those patients who did not have a diagnosis of diabetes at the time of data collection, blood glucose measurement is recommended as a screening test for diabetes (13). Blood

glucose measurement was performed for 22.6% (9187/40576) patients without diabetes in the unscreened population; while it was performed for 59.9% (10237/17084) patients without diabetes in the screened population. Among patients with diabetes, HbA1c was recorded for 57.8% (22180/38360) patients in the unscreened group as compared to 84.9% (15678/18453) patients in the depression screened group. The only exception was the results recording for alcohol consumption, which was better for the unscreened group.

Secondly, we did not have information on disease severity or disease duration for the patients in the cohort. The information on cardiac medications was missing as well. These factors are likely to have influenced the clinical outcomes considered in our study.

Thirdly, information on psychosocial treatment options offered to the patients in our cohort was not available. However, there is no evidence to date that psychosocial therapies in the treatment of depression in patients with cardiometabolic disease has any beneficial effect on cardiovascular disease related physical outcomes or mortality (24–26). The overall rate of antidepressant initiation was higher for the unscreened 6.3% (4989/78936) when compared to those who were screened for depression 3.6% (1268/35537). This may suggest a possibility of bias against depression screening in the subset of patients who were apparently treated for depression with antidepressants but not screened for depression.

Fourthly, we did not have any information on health care utilization over the observation period, such as frequency of visits to family practitioner and involvement with secondary care services such as cardiac rehabilitations team. These factors are likely to have influenced the clinical outcomes considered in this study.

Finally, the overall accuracy of depression screening in our study was reliant on HADS-D which is a self-reported measure and has various drawbacks when used for assessing depressive symptoms in patients with cardiometabolic disease in a primary care setting (18,27,28). There are some other self-reported measures for depression screening, such as the Patient Health Questionnaire (PHQ-9) and Beck's Depression Inventory (BDI), which have been found to have a better overall diagnostic accuracy in patients with cardiometabolic disease(18,27,28).

Comparison with existing literature

The rate of positive screens identified as a result of depression screening in our study of routine practice was 19.9% which is within the range of rates of 6-22% reported in clinical trials (7) and rates of 2 to 20% in epidemiological studies (29,30). In our study, patients with positive depression screening were more likely to have adverse outcomes, this is consistent with previous evidence which shows increased risk of mortality and cardiovascular related outcomes in patients with depression co-morbid with CHD (31), diabetes(32) and history of previous stroke (33). The potential influence of antidepressant prescribing on the findings of our study remains unclear. The Cochrane reviews on patients with CHD (24) and diabetes (25) have found no benefits of treating depressive symptoms with antidepressants on reducing all-cause mortality and cardiovascular related complications. For stroke patients, the evidence is very little with only one trial in patients with post stroke depression finding improvement in all-cause mortality for up to 9 years of follow-up with 8 weeks of antidepressants treatment compared against placebo (34).

Implication of Findings

The American Heart Association has issued a scientific statement in 2014 suggesting that depression should be considered a risk factor for poor prognosis in patients with acute coronary syndrome; however clinical implications for detecting and managing co-morbid depression in patients with cardiometabolic disease remains unclear (35). In patients with cardiometabolic diseases, to date, there has been no evidence that depression screening offered as a part of a wider intervention in randomized controlled trials evaluating depression management, leads to improvements in all-cause mortality and cardiovascular related outcomes. If the observed association between depression screening and improvement in cardiovascular outcomes, mortality and all cause admissions is true, it has important implications for the management of cardiometabolic disease. There may be potential benefits from depression screening in cardiometabolic disease, especially in patients at high risk, and further research is needed in this area.

Conclusion

In a general practice sample of patients with CHD, stroke, or diabetes, depression screening was associated with improvements in all-cause mortality, cardiovascular related outcomes and psychiatry unit admissions at four years. There is a possibility that these results could be explained by residual confounding from unknown differences in disease severity, quality of care and health care utilization. Further research is necessary to determine whether these results are replicable using other datasets; to investigate the nature of the observed relationship; and increase understanding of the mechanisms underpinning these effects.

Source of Funding

The study was funded by BUPA Foundation TBF-MR11-041F.

Conflict of Interests

The authors declare that they have no conflict of interests.

Supplement 1

Propensity score matching results and sensitivity analysis results for patients with smoking and alcohol records

References

1. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *DiabetMed*. 2006;**23**:1165–1173.
2. Hadidi N, Treat-Jacobson DJ, Lindquist R. Poststroke depression and functional outcome: a critical review of literature. *Hear Lung*. 2009;**38**:151–162.
3. Whooley MA, De JP, Vittinghoff E, Otte C, Moos R, Carney RM, Ali S, Dowray S, Na B, Feldman MD, Schiller NB, Browner WS. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA*. 2008;**300**:2379–2388.
4. Katon WJ, Rutter C, Simon G, Lin EH, Ludman E, Ciechanowski P, Kinder L, Young B, Von KM. The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care*. 2005;**28**:2668–2672.
5. Pozuelo L, Tesar G, Zhang J, Penn M, Franco K, Jiang W. Depression and heart disease: what do we know, and where are we headed? *CleveClinJMed*. 2009;**76**:59–70.
6. Lichtman JH, Bigger JT, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lespérance F, Mark DB, Sheps DS, Taylor CB, Froelicher ES. Depression and coronary heart disease: recommendations for screening, referral, and treatment. *Circulation*. 2008;**118**:1768–1775.
7. Thombs BD, Roseman M, Coyne JC, Jonge P de, Delisle VC, Arthurs E, Levis B, Ziegelstein RC. Does Evidence Support the American Heart Association's Recommendation to Screen Patients for Depression in Cardiovascular Care? An Updated Systematic Review. *PLoS One*. 2013;**8**:e52654.
8. Ontario HQ. Screening and management of depression for adults with chronic diseases: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2013;**13**:1–45.
9. Atlantis E, Fahey P, Foster J. Collaborative care for comorbid depression and diabetes: a systematic review and meta-analysis. *BMJ Open*. 2014;**4**:e004706.
10. Tully PJ, Baumeister H. Collaborative care for comorbid depression and coronary heart disease: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2015;**5**:e009128.
11. NICE. Depression in adults with a chronic physical health problem: Treatment and management. NICE guidelines [CG91]. 2009.
12. HSCIC. Quality Outcomes Framework [Internet]. 2012. Available from: http://www.hscic.gov.uk/qof
13. NHS Employers. Quality Outcomes Framework 2013/14. 2013. 2013.
14. Jani BD, Purves D, Barry S, Cavanagh J, McLean G, Mair FS. Challenges and Implications of Routine Depression Screening for Depression in Chronic Disease and Multimorbidity: A Cross Sectional Study. *PLoS One*. 2013;**8**:e74610.
15. Jani BD, Cavanagh J, Barry SJE, Der G, Sattar N, Mair FS. Revisiting the J shaped curve, exploring the association between cardiovascular risk factors and concurrent depressive symptoms in patients with cardiometabolic disease: Findings from a large cross-sectional study. *BMC Cardiovasc Disord*. 2014;**14**:139.

16. Rait G, Walters K, Griffin M, Buszewicz M, Petersen I, Nazareth I. Recent trends in the incidence of recorded depression in primary care. *Br J Psychiatry*. The Royal College of Psychiatrists; 2009;**195**:520–524.

17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta PsychiatrScand*. 1983;**67**:361–370.

18. NICE. Depression in Adults (update) (CG90). Natl. Inst. Heal. Clin. Excell. 2009.

19. Information Services Division. Scottish Index of Multiple Deprivation (SIMD)http://simd.scotland.gov.uk/publication-2012/ [Internet]. 2012. 2012. Available from: http://www.scotland.gov.uk/Topics/Statistics/SIMD

20. Survey TSH. The Scottish Health Survey [Internet]. 2010. Available from: http://www.scotland.gov.uk/Resource/Doc/358842/0121284.pdf

21. WHO. International Statistical Classification of Diseases and Related Health Problems (International Classification of Diseases)(ICD) 10th Revision - Version:2010 [Internet]. Occup. Health (Auckl). 2010. Available from: http://apps.who.int/classifications/icd10/browse/2010/en

22. Coventry PA, Hays R, Dickens C, Bundy C, Garrett C, Cherrington A, Chew-Graham C. Talking about depression: a qualitative study of barriers to managing depression in people with long term conditions in primary care. *BMC Fam Pract*. 2011;**12**:10.

23. Karasz A, Dowrick C, Byng R, Buszewicz M, Ferri L, Olde Hartman TC, Van DS, Weel-Baumgarten E van, Reeve J. What we talk about when we talk about depression: doctor-patient conversations and treatment decision outcomes. *BrJGenPract*. 2012;**62**:e55–e63.

24. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database Syst Rev*. 2011;**9**:CD008012.

25. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. *Cochrane Database Syst Rev*. John Wiley & Sons, Ltd; 2012;**12**:CD008381.

26. Hackett ML, Anderson CS, House AO. Management of depression after stroke: a systematic review of pharmacological therapies. *Stroke*. 2005;**36**:1098–1103.

27. Meader N, Mitchell AJ, Chew-Graham C, Goldberg D, Rizzo M, Bird V, Kessler D, Packham J, Haddad M, Pilling S. Case identification of depression in patients with chronic physical health problems: a diagnostic accuracy meta-analysis of 113 studies. *BrJGenPract*. 2011;**61**:e808–e820.

28. Haddad M, Walters P, Phillips R, Tsakok J, Williams P, Mann A, Tylee A. Detecting Depression in Patients with Coronary Heart Disease: A Diagnostic Evaluation of the PHQ-9 and HADS-D in Primary Care, Findings From the UPBEAT-UK Study. *PLoS One*. 2013;**8**:e78493.

29. Yano EM, Chaney EF, Campbell DG, Klap R, Simon BF, Bonner LM, Lanto AB, Rubenstein L V. Yield of practice-based depression screening in VA primary care settings. *J Gen Intern Med*. 2012;**27**:331–338.

30. Burton C, Simpson C, Anderson N. Diagnosis and treatment of depression following routine screening in patients with coronary heart disease or diabetes: a database cohort

study. *PsycholMed*. 2013;**43**:529–537.

31. Meijer A, Conradi HJ, Bos EH, Thombs BD, Melle JP van, Jonge P de. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. *Gen Hosp Psychiatry*. 2011;**33**:203–216.

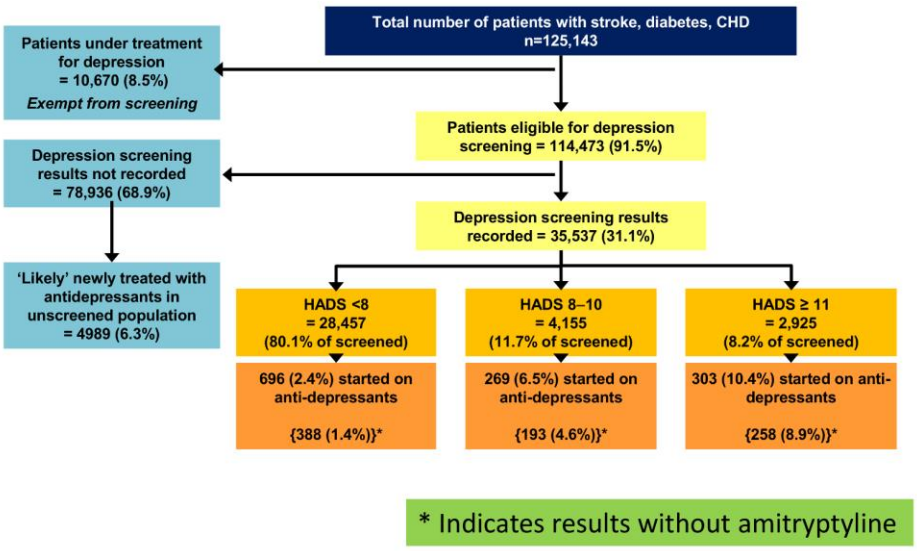
32. Egede LE, Nietert PJ, Zheng D. Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. *Diabetes Care*. 2005;**28**:1339–1345.

33. Bartoli F, Lillia N, Lax A, Crocamo C, Mantero V, Carrà G, Agostoni E, Clerici M. Depression after stroke and risk of mortality: a systematic review and meta-analysis. *Stroke Res Treat*. 2013;**2013**:862978.

34. Jorge RE, Robinson RG, Arndt S, Starkstein S. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. *Am J Psychiatry*. 2003;**160**:1823–1829.

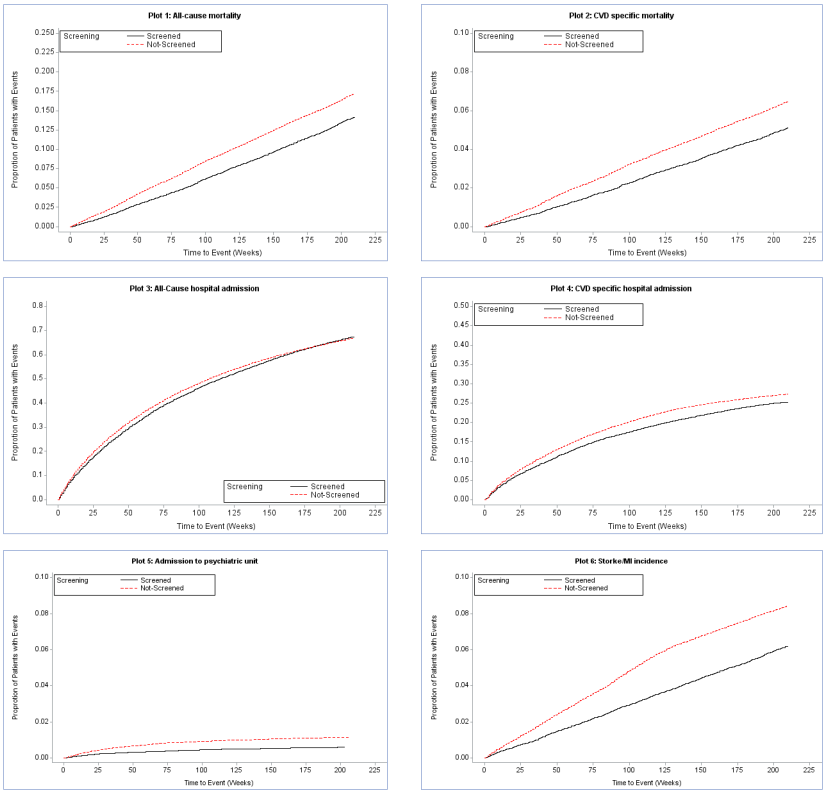
35. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering L V, Frasure-Smith N, Freedland KE, Jaffe AS, Leifheit-Limson EC, Sheps DS, Vaccarino V, Wulsin L. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation*. 2014;**129**:1350–1369.

Figure 1 Title: Study sample size and recruitment.



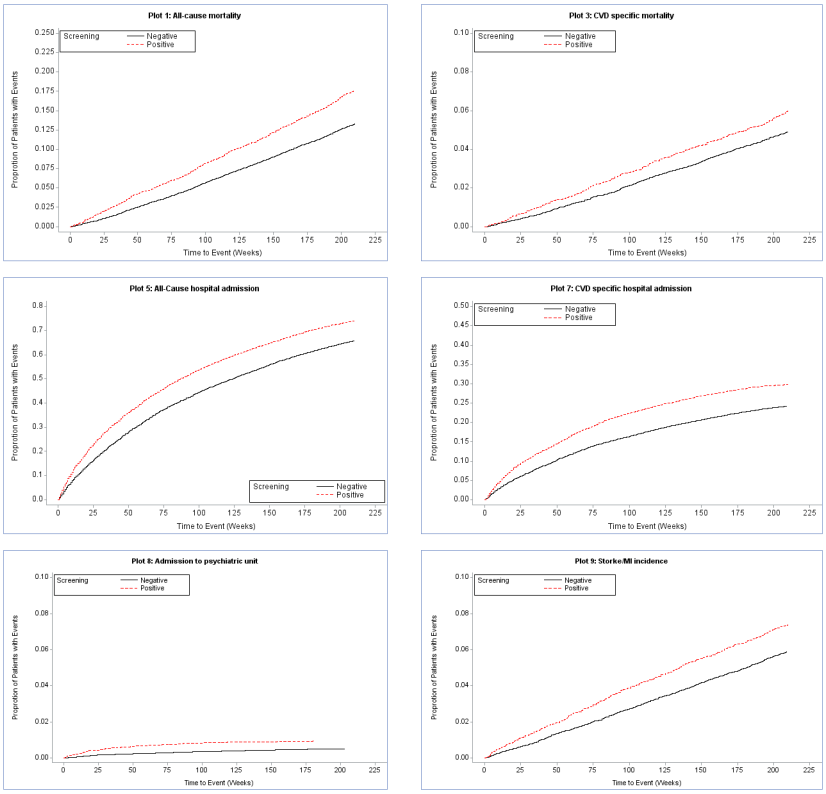
Legend: HADS=Hospital Anxiety and Depression Score.

Figure 2 Title: Kaplan-Meier plots comparing clinical outcomes between depression screened and the not screened patient groups in existing cardiometabolic disease.



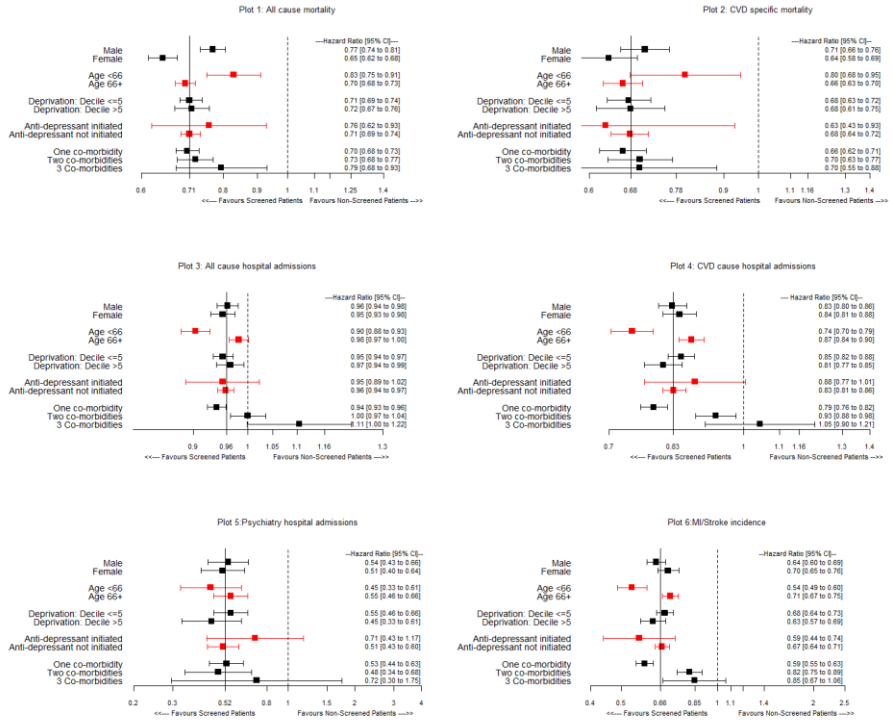
Legend: A panel of six plots for six different clinical outcomes comparing cumulative incidence for the depression screened and the not screened patient groups.

Figure 3 Title: Kaplan-Meier plots comparing clinical outcomes between HADS-D positive and HADS-D negative patient groups in existing cardiometabolic disease.



Legend: A panel of six plots for six different clinical outcomes comparing cumulative incidence for the depression screened and the not screened patient groups.

Figure 4 Title: Subgroup analyses for clinical outcomes for depression screened and the not screened patient groups in existing cardiometabolic disease.



Legend: A panel of six forest plots for six different clinical outcomes. If a line for an individual patient subgroup crosses the line of significance (1), it implies that the difference in outcome is not statistically significant for that particular subgroup of patients.

Table 1 Title: Comparison of depression screened and the not screened patient groups in existing cardiometabolic disease.

	Depression Screened N= 35537	Not Screened N=78936	p-value
Age(years) - mean (SD), n	69.0 (11.9), 35526	67.0 (14.3), 78905	<0.001
White ethnicity-n/N (%)	30693/33214 (92.4)	53343/59043 (90.3)	<0.001
Male sex - n/N (%)	20658/35519 (58.2)	42727/78889 (54.2)	<0.001
Deprived socio-economic status SIMD deciles<=5 -n/N (%)	22726/34805 (65.3)	51686/76740 (67.4)	<0.001
Alcohol consumption - n/N (%)			
Moderate Hazardous Harmful	30367/31471 (96.5) 988/31471 (3.1) 116/31471 (0.4)	19469/20338 (95.7) 724/20338 (3.6) 145/20338 (0.7)	<0.001
Smoking Status - n/N (%)			
Non-smokers Current smokers	9907/15092 (65.6) 5185/15092 (34.4)	15510/25554 (60.7) 10044/25554 (39.3)	<0.001
Number of co-morbidities - n/N (%)			
One Two Three	27356/35537 (77.0) 7410/35537 (20.9) 771/35537 (2.2)	65417/78936 (82.9) 12265/78936 (15.5) 1254/78936 (1.6)	<0.001
Antidepressant initiation -n/N (%)	1268/35537(3.5)	4989/78936 (6.3)	<0.001
All-cause mortality -n/N (%)	5021/35537 (14.1)	13569/78936 (17.2)	<0.001
New vascular events (Stroke/MI incidence) -n/N (%)	2068/35537 (5.8)	6193/78936 (7.8)	<0.001
All-cause hospital admissions -n/N (%)	23717/35537 (66.7)	52089/78936 (66.0)	0.013
Cardiovascular disease related hospital admissions -n/N (%)	6701/35537 (18.9)	16278/78936 (20.6)	<0.001
Psychiatry unit admissions -n/N (%)	203/35537 (0.6)	866/78936 (1.1)	<0.001
Cardiovascular disease related mortality- n/N (%)	1734/35537 (4.8%)	4823/78936 (6.1%)	<0.001

Legend: SIMD=Scottish Index of Multiple Deprivation SD= Standard Deviation.

Table 2 Title: Comparison of HADS-D positive and HADS-D negative patient groups in existing cardiometabolic disease.

	HADS-D Positive N= 7080	HADS-D Negative N=28457	p-value
Age(years) - mean (SD), n	66.89 (12.36), 7077	69.56 (11.72), 28449	<0.001
White ethnicity-n/N (%)	5953/6534 (91.1)	24740/26680 (92.7)	<0.001
Male sex - n/N (%)	3900/7072 (55.1)	16758/28447 (58.9)	<0.001
Deprived socio-economic status SIMD deciles<=5 -n/N (%)	5332/6917 (77.1)	17394/27888 (62.4)	<0.001
Alcohol consumption - n/N (%)			
Moderate	5628/5853 (96.2)	24739/25618 (96.6)	<0.001
Hazardous	184/5853 (3.1)	804/25618 (3.1)	
Harmful	41/5853 (0.7)	75/25618 (0.3)	
Smoking Status - n/N (%)			
Non-smokers	1901/3582 (53.1)	8005/11510 (69.5)	<0.001
Current smokers	1680/3582 (46.9)	3505/11510 (30.5)	
Number of co-morbidities - n/N (%)			
One	5095/7080 (72.0)	22261/28457 (78.2)	<0.001
Two	1781/7080 (25.2)	5629/28457 (19.8)	
Three	204/7080 (2.9)	567/28457 (2.0)	
Antidepressant initiation -n/N (%)	572/7080 (8.1)	696/28457 (2.4)	<0.001
All-cause death -n/N (%)	1244/7080 (17.6)	3777/28457 (13.3)	<0.001
New vascular events (Stroke/MI incidence) -n/N (%)	486/7080 (6.9)	1582/28457 (5.6)	<0.001
All-cause hospital admissions -n/N (%)	5184/7080 (73.2)	18533/28457 (65.1)	<0.001
Cardiovascular disease related hospital admissions -n/N (%)	1538/7080 (21.7)	5163/28457 (18.1)	<0.001
Psychiatry unit admissions -n/N (%)	66/7080 (0.9)	137/28457 (0.5)	<0.001
Cardiovascular disease related mortality- n/N (%)	398/7080 (5.6%)	1336/28457 (4.6%)	<0.001

Legend: HADS-D= Hospital Anxiety and Depression Score-depressive subscale HADS-D positive=HADS-D>7.SIMD=Scottish Index of Multiple Deprivation. SD= Standard Deviation.

Table 3 Title: Comparison of demographic, behavioural and cardiovascular factors in depression screened and not screened patient groups in existing cardiometabolic disease for the matched data.

Patient Characteristics		Screened - N = 21893	Non-Screened - N = 21893	p-value
Sex	Missing/Total (%)	13/21893 (0.1)	12/21893 (0.1)	0.84
	Male	12068/21880 (55.2)	12047/21881 (55.1)	
	Female	9812/21880 (44.8)	9834/21881 (44.9)	
Age (years)	Missing/Total (%)	6/21893 (0.03 %)	8/21893 (0.04 %)	0.62
	Mean (SD)	67.9 (12.4)	67.8 (12.9)	
	Median (IQR)	69.0 (60.0 to 77.0)	70.0 (59.0 to 78.0)	
	Min - Max	18.0 - 90.0	18.0 - 90.0	
Body mass index (kg/m2)	Missing/Total (%)	4603/21893 (21.02 %)	4652/21893 (21.25 %)	0.09
	Mean (SD)	29.0 (6.1)	29.0 (6.2)	
	Median (IQR)	28.1 (24.9 to 32.1)	28.3 (24.9 to 32.2)	
	Min - Max	5.9 - 96.0	12.5 - 99.0	
BMI missing	Yes	4603/21893 (21.0)	4652/21893 (21.2)	0.57
	No	17290/21893 (79.0)	17241/21893 (78.8)	
SIMD (quintiles)	No	470/21893 (2.1)	492/21893 (2.2)	0.89
	1 = Most deprived	9271/21423 (43.3)	9256/21401 (43.3)	
	2	4087/21423 (19.1)	4062/21401 (19.0)	
	3	2614/21423 (12.2)	2617/21401 (12.2)	
	4	2383/21423 (11.1)	2403/21401 (11.2)	
	5 = Least deprived	3068/21423 (14.3)	3063/21401 (14.3)	
Antidepressant initiation	Yes	1222/21893 (5.6)	1244/21893 (5.7)	0.65
	No	20671/21893 (94.4)	20649/21893 (94.3)	
Number of co-morbidities	One	16972/21893 (77.5)	16939/21893 (77.4)	0.45
	Two	4450/21893 (20.3)	4444/21893 (20.3)	
	Three	471/21893 (2.2)	510/21893 (2.3)	
History of	Yes	11938/21893 (54.5)	11967/21893 (54.7)	0.78

Diabetes				
	No	9955/21893 (45.5)	9926/21893 (45.3)	
Smoking Status	No	12994/21893 (59.4)	13079/21893 (59.7)	0.89
	Ex-smoker	5307/8899 (59.6)	5287/8814 (60.0)	
	Current Smoker	3507/8899 (39.4)	3442/8814 (39.1)	
	Non-smoker	85/8899 (1.0)	85/8814 (1.0)	
Systolic BP (mmHg)	Missing/Total (%)	1984/21893 (9.06 %)	2073/21893 (9.47 %)	0.99
	Mean (SD)	133.7 (17.9)	133.7 (18.2)	
	Median (IQR)	132.0 (121.0 to 143.0)	132.0 (120.0 to 142.0)	
	Min - Max	60.0 - 228.0	55.0 - 244.0	
SBP Missing	Yes	1984/21893 (9.1)	2073/21893 (9.5)	0.14
	No	19909/21893 (90.9)	19820/21893 (90.5)	
Diastolic BP (mmHg)	Missing/Total (%)	1984/21893 (9.06 %)	2073/21893 (9.47 %)	0.12
	Mean (SD)	75.3 (10.5)	75.3 (10.5)	
	Median (IQR)	76.0 (70.0 to 80.0)	76.0 (70.0 to 80.0)	
	Min - Max	30.0 - 131.0	38.0 - 135.0	
Cholesterol (mmol/l)	Missing/Total (%)	2913/21893 (13.31 %)	2917/21893 (13.32 %)	0.86
	Mean (SD)	4.4 (1.1)	4.4 (1.1)	
	Median (IQR)	4.2 (3.7 to 4.9)	4.2 (3.6 to 5.0)	
	Min - Max	1.1 - 14.5	1.0 - 14.2	
Cholesterol missing	Yes	2913/21893 (13.3)	2917/21893 (13.3)	0.96
	No	18980/21893 (86.7)	18976/21893 (86.7)	
Fasting glucose (mmol/l)	Missing/Total (%)	18179/21893 (83.04 %)	18170/21893 (82.99 %)	0.88
	Mean (SD)	7.4 (3.3)	7.4 (3.4)	
	Median (IQR)	6.4 (5.3 to 8.3)	6.3 (5.3 to 8.2)	
	Min - Max	1.9 - 28.9	1.0 - 30.0	
Fasting glucose missing	Yes	18179/21893 (83.0)	18170/21893 (83.0)	0.91
	No	3714/21893 (17.0)	3723/21893 (17.0)	

Random glucose (mmol/l)	Missing/Total (%)	14984/21893 (68.44 %)	14948/21893 (68.28 %)	0.64
	Mean (SD)	7.9 (4.4)	7.9 (4.3)	
	Median (IQR)	6.2 (5.2 to 9.0)	6.2 (5.2 to 8.9)	
	Min - Max	1.4 - 37.0	1.0 - 36.5	
Random glucose missing	Yes	14984/21893 (68.4)	14948/21893 (68.3)	0.71
	No	6909/21893 (31.6)	6945/21893 (31.7)	
Pulse rate/min	Missing/Total (%)	11729/21893 (53.57 %)	11758/21893 (53.71 %)	0.53
	Mean (SD)	70.5 (11.4)	70.5 (11.0)	
	Median (IQR)	70.0 (62.0 to 78.0)	70.0 (62.0 to 78.0)	
	Min - Max	30.0 - 150.0	37.0 - 150.0	
Pulse missing	Yes	11729/21893 (53.6)	11758/21893 (53.7)	0.78
	No	10164/21893 (46.4)	10135/21893 (46.3)	
EGFR (ml/min/m2)	Missing/Total (%)	13681/21893 (62.49 %)	13577/21893 (62.02 %)	0.32
	Mean (SD)	3.6 (0.7)	3.6 (0.7)	
	Median (IQR)	4.0 (3.0 to 4.0)	4.0 (3.0 to 4.0)	
	Min - Max	0.0 - 4.0	0.0 - 4.0	
EGFR missing	Yes	13681/21893 (62.5)	13577/21893 (62.0)	0.31
	No	8212/21893 (37.5)	8316/21893 (38.0)	
Hba1c (mmol/mol)	Missing/Total (%)	11957/21893 (54.62 %)	11861/21893 (54.18 %)	0.20
	Mean (SD)	7.7 (1.8)	7.7 (1.8)	
	Median (IQR)	7.2 (6.4 to 8.5)	7.2 (6.4 to 8.6)	
	Min - Max	3.9 - 16.4	2.0 - 18.1	
Hba1c missing	Yes	11957/21893 (54.6)	11861/21893 (54.2)	0.36
	No	9936/21893 (45.4)	10032/21893 (45.8)	
Creatinine (Umol/l)	Missing/Total (%)	11763/21893 (53.73 %)	11659/21893 (53.25 %)	0.63
	Mean (SD)	89.7 (29.9)	89.6 (28.9)	
	Median (IQR)	84.0 (73.0 to 98.0)	84.0 (73.0 to 98.0)	
	Min - Max	40.0 - 494.0	40.0 - 485.0	

Creatinine missing	Yes	11763/21893 (53.7)	11659/21893 (53.3)	0.32
	No	10130/21893 (46.3)	10234/21893 (46.7)	

Legend: Min=minimum Max=maximum SD=Standard Deviation IQR=Interquartile Range SIMD=Scottish Index of Multiple Deprivation BP=Blood Pressure EGFR=Estimated Glomerular Filtration Rate CI=Confidence Intervals MI=Myocardial Infarction

Table 4: Comparison of hazard ratios in depression screened and not screened patient groups in existing cardiometabolic disease for the matched data (N=21893 in each group).

Adverse Clinical Outcome	HR (with 95% CI) for the depression screened vs. not screened group (matched data from propensity score)
All-cause mortality	0.89 (0.84 - 0.93)
New vascular events (Stroke/MI incidence)	0.85 (0.78 - 0.91)
All-cause hospital admissions	0.95 (0.92 - 0.97)
Cardiovascular disease related hospital admissions	0.92 (0.88 - 0.97)
Psychiatry unit admissions	0.61 (0.48 - 0.76)
Cardiovascular disease related mortality	0.85 (0.78 - 0.93)

Legend: HR=Hazard Ratio. CI=Confidence Intervals. MI=Myocardial Depression. Hospital Anxiety and Depression Score-Depressive subscale used for depression screening.

Table 5 Title: Hazard ratios for clinical outcomes for HADS-D positive compared to the HADS-D negative patient groups in existing cardiometabolic disease.

	Clinical Outcomes	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Mild depression (HADS-D 8-10)	All-cause mortality	1.35 (1.24 - 1.46)	1.42 (1.31 - 1.54)
Moderate/severe depression (HADS-D 11-21)		1.37 (1.25-1.50)	1.67 (1.52-1.83)
Mild depression (HADS-D 8-10)	CVD related mortality	1.21 (1.05 - 1.39)	1.25 (1.08 - 1.43)
Moderate/severe depression (HADS-D 11-21)		1.25 (1.06-1.47)	1.50 (1.27-1.77)
Mild depression (HADS-D 8-10)	All-Cause hospital admissions	1.27 (1.22 - 1.32)	1.25 (1.20-1.30)
Moderate/severe depression (HADS-D 11-21)		1.31 (1.26-1.37)	1.35 (1.29-1.42)
Mild depression (HADS-D 8-10)	CVD related hospital admissions	1.34 (1.25 - 1.44)	1.28 (1.19 - 1.38)
Moderate/severe depression (HADS-D 11-21)		1.36 (1.25-1.48)	1.39 (1.28-1.52)
Mild depression (HADS-D 8-10)	Psychiatric unit admissions	1.77 (1.22 - 2.57)	1.73 (1.19 - 2.52)
Moderate/severe depression (HADS-D 11-21)		2.25 (1.52-3.32)	2.19 (1.45-3.30)

Mild depression (HADS-D 8-10) Moderate/severe depression (HADS-D 11-21)	New vascular events (Stroke/MI)	1.31 (1.16 - 1.49) 1.22 (1.05-1.41)	1.28 (1.13 - 1.45) 1.29 (1.10-1.51)

Legend: CI=Confidence Intervals CVD=Cardiovascular Disease MI=Myocardial Infarction HADS-D= Hospital Anxiety and Depression Score-Depressive Subscale HADS-D positive=HADS-D>7 Adjusted analysis=adjusted for age, sex, deprivation status, number of cardiometabolic conditions and initiation of antidepressants.