

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Impact of major depression on cardiovascular outcomes for individuals with hypertension: prospective survival analysis in UK Biobank.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024433
Article Type:	Research
Date Submitted by the Author:	25-May-2018
Complete List of Authors:	Graham, Nicholas; University of Glasgow Institute of Health and Wellbeing, Gartnavel Royal Hospital 1055 Great Western Road Glasgow, UK G12 0XH Ward, Joey; University of Glasgow Institute of Health and Wellbeing Mackay, Daniel; University of Glasgow Institute of Health and Wellbeing Pell, J. P.; University of Glasgow Institute of Health and Wellbeing Cavanagh, Jonathan; University of Glasgow Institute of Health and Wellbeing Padmanabhan, Sandosh; University of Glasgow, Institute of Cardiovascular and Medical Sciences, British Heart Foundation Glasgow Cardiovascular Research Centre Smith, Daniel; University of Glasgow, Institute of Health and Wellbeing
Keywords:	EPIDEMIOLOGY, mortality, cardiovascular disease, morbidity, depression, Hypertension < CARDIOLOGY

SCHOLARONE™
Manuscripts

1
2
3 **1 Impact of major depression on cardiovascular outcomes for individuals with hypertension:**
4
5 **2 prospective survival analysis in UK Biobank.**
6

7
8 **3 Short title: Outcomes of Hypertension plus Depression**
9

10
11 4 Nicholas A GRAHAM*^a, Clinical Research Fellow
12

13
14 5 Joey WARD^a, Research Fellow
15

16
17 6 Daniel MACKAY^b, Reader in Public Health
18

19
20 7 Jill PELL^b, Professor of Public Health
21

22
23 8 Jonathan CAVANAGH^c, Professor of Psychiatry
24

25
26 9 Sandosh PADMANABHAN^d, Professor of Cardiovascular Genomics and Therapeutics
27

28
29 10 Daniel J. SMITH^a, Professor of Psychiatry.
30

31
32 11 Number of Supplementary files: 1
33

34
35 12 Word count of Manuscript: 3,873 (exc. Tables, references, abstract summary and Author
36
37 13 contribution statements)
38

39
40 14 Word count of Supplementary file: 1,451 (exc. tables)
41

42
43 15 Number of tables and figures: 18 tables (including 12 in supplementary digital content) and 3 figures
44

45
46 16 ^aInstitute of Health and Wellbeing, University of Glasgow, Gartnavel Royal Hospital, 1055 Great
47

48
49 17 Western Road, Glasgow G12 OXH. ^bInstitute of Health and Wellbeing, University of Glasgow, Public
50

51
52 18 Health, 1 Lilybank Gardens, Glasgow G12 8RZ. ^cInstitute of Health and Wellbeing, Centre for
53

54
55 19 Immunobiology, Sir Graeme Davies Building College of Medical, Veterinary and Life Sciences
56

57
58 20 University of Glasgow. ^dInstitute of Cardiovascular and Medical Sciences, British Heart Foundation
59

60
61 21 Glasgow Cardiovascular Research centre, University of Glasgow, Glasgow G12 8TA.
62

1
2
3 22 *corresponding author: nicholas.graham@glasgow.ac.uk, phone: +44 0141 211 3918,
4
5

6 23 **CONFLICTS OF INTEREST:** None.
7

8
9 24
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

25 **ABSTRACT**

26 **Objectives:** To assess whether a history of MDD in middle-aged individuals with hypertension
27 impacts on medium-term cardiovascular disease outcomes.

28 **Design:** Prospective cohort survival analysis using Cox proportional hazards regression with a median
29 follow-up of 63 months (702,902 person-years). Four mutually exclusive groups were compared:
30 hypertension only (n=56,035), MDD only (n=15,098), comorbid hypertension plus MDD (n=12,929),
31 and an unaffected (no hypertension, no MDD) comparison group (n=50,798).

32 **Setting:** UK Biobank

33 **Participants:** UK Biobank participants without cardiovascular disease aged 37–73 who completed
34 additional psychiatric questions at baseline interview in 2006–2010 (n=134,860).

35 **Primary and Secondary outcome measures:** First time adverse cardiovascular outcomes leading to
36 hospital admission or death (ICD-10 codes I20-I259, I60-69 and G45- G46) adjusted in a stepwise
37 manner for sociodemographic, health and lifestyle features. Secondary analyses were performed
38 looking specifically at stroke outcomes (ICD-10 codes I60-69 and G45- G46) and in models separated
39 by gender.

40 **Results:** Relative to controls, adjusted hazard ratios (HRs) for adverse cardiovascular outcomes were
41 increased for the hypertension only group (HR=1.36, 95%CI 1.22-1.52) and were higher still for the
42 comorbid hypertension plus MDD group (HR=1.66, 95%CI 1.45-1.9). HRs for the comorbid
43 hypertension plus MDD group were significantly raised compared to hypertension alone (HR=1.22,
44 95%CI 1.1-1.35).

45 **Conclusions:** Comorbid hypertension and depression conferred greater hazard than hypertension
46 alone for adverse cardiovascular outcomes, although evidence of an additive interaction is
47 inconsistent. Future cardiovascular risk prediction tools may benefit from the inclusion of questions
48 about prior history of depressive disorders.

49 Word count of Abstract: 239

1
2
3 50 **Key words:** epidemiology, mortality, morbidity, depression; hypertension, cardiovascular disease
4
5
6

7 51

8 52 Article Summary

9 53 **STRENGTHS AND LIMITATIONS**

- 10
11 54 • There were methodological advantages over similar studies including a very large sample
12 size, adjustment for a more comprehensive range of confounders and inclusion of non-fatal
13 adverse cardiovascular events from hospital admission data, along with death registry data.
14
15 56
16
17 57 • Definition of prior MDD history was based on ICD-10 diagnostic criteria as opposed to a
18 score on a questionnaire and our composite definition of hypertension incorporated past
19 history, current medication and objective blood pressure measurements.
20
21 58
22
23 59
24 60 • Sample was adjusted for a broad range of baseline factors such as smoking status, BMI,
25 psychotropic medication use and diabetes status amongst others, we were unable to see
26 how these factors changed over the course of follow-up, or assess adherence to medication.
27
28 62
29
30 63 • Although trained nurses interviewed participants to obtain medical information for group
31 assignment, as well as medication information, the self-reported nature may limit the
32 accuracy of information.
33
34 65
35
36 66 • UK Biobank does have some issues with selection bias, as such those with more severe
37 depression may be less likely to attend an assessment centre
38
39 67
40
41 68
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

69 INTRODUCTION

70 By 2030 major depressive disorder (MDD) and cardiovascular disease (CVD) will be the two leading
71 causes of disability worldwide¹. It is established that individuals with MDD are at increased risk of
72 developing CVD and that they experience worse long-term outcomes, with higher mortality². To
73 date, studies investigating the association between MDD and CVD have tended to focus only on
74 ischaemic heart disease, with the possibility of a specific association between MDD and
75 hypertension relatively under-investigated³.

76 Hypertension is extremely common (affecting 1 billion people worldwide)⁴ and is responsible for
77 50% of all stroke and 50% of all ischaemic heart disease cases⁵. It is commonly comorbid with MDD,
78 particularly in older age-groups^{6,7}. Furthermore, a biological link between hypertension and MDD is
79 supported by genome-wide association studies which have found that variants in calcium-channel
80 genes, important in blood pressure control and hypertension⁸, also act to increase risk for mood
81 disorders such as MDD^{9,10} and bipolar disorder^{11,12}.

82 Here we make use of prospective data from the UK Biobank cohort¹³ to test the hypothesis that a
83 history of MDD in individuals with hypertension (and no previous history of CVD) impacts adversely
84 on cardiovascular outcomes. Given the very high global prevalence of MDD and hypertension¹⁴, this
85 is an important question for public health which could inform future treatment approaches for both
86 hypertension and MDD.

87

88 METHODS

89 Study design

90 This was population cohort study using data from UK Biobank. Four mutually exclusive groups
91 (hypertension only, MDD only, hypertension plus MDD, and a comparison group) were compared for
92 adverse CVD outcomes, as well as stroke outcomes

93 **Sample description**

94 UK Biobank is a large population cohort of 502,655 participants recruited between April 2007 and
95 July 2010 from 21 assessment centres located across Great Britain¹³. At baseline assessment
96 participants completed a series of detailed assessments relating to lifestyle, current and past
97 medical history and a range of physical health measurements, including body mass index (BMI) and
98 blood pressure. UK Biobank was approved by the North West NHS Multi-Centre Research Ethics
99 Committee and all participants provided written informed consent to participate. This analysis is
100 part of UK Biobank approved application number 7155.

101 During the last two years of recruitment, questions relating to mood disorder features were added
102 to the baseline assessment schedule. From the 172,729 participants who were assessed in this way,
103 134,860 provided sufficient responses to be included in our analysis. We excluded participants from
104 our analyses based on the following *a priori* criteria: a history of bipolar disorder (n=1,831) or
105 schizophrenia (n=262); where there were insufficient data provided by participants to clearly rule
106 out MDD (n= 25,520) or hypertension (n=1,080); and where there were coding errors for date
107 and/or time of death (n=4). Participants were further excluded from the adverse cardiovascular
108 outcome if they had a record of CVD prior to recruitment (self-reported angina, myocardial
109 infarction (MI) or stroke, or evidence of previous hospital admission for angina, MI or stroke) (n=
110 9,172). For the stroke outcome this exclusion was limited to a record of only stroke prior to
111 admission (self-report or evidence of previous hospital admission for stroke) (n=2,280).

112 **Classification of hypertension and MDD**

113 Participants were defined as having hypertension if either: *a*) mean blood pressure at baseline was
114 greater than clinically-defined criteria over two measurements (systolic blood pressure greater than
115 or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg. Where only
116 one reading was available this was used); or *b*) self-reported 'hypertension diagnosed by a doctor'

1
2
3 117 plus self-report of currently taking antihypertensive medication. This composite classification was
4
5 118 used to ensure that undiagnosed hypertensive participants were not omitted from analyses and is in
6
7 119 line with similar epidemiological studies¹⁵⁻¹⁷. According to these criteria, n=68,964 participants
8
9 120 (51.1% of the sample) had hypertension for the adverse cardiovascular outcomes analysis and
10
11 121 n=73,671 participants (52% of the sample) had hypertension in the stroke outcome analysis.

12
13
14 122 A past history of MDD was defined according to the criteria for mood disorders used in several
15
16 123 previous studies with UK Biobank data^{18 19}. Participants were classified as MDD if they reported at
17
18 124 least one episode which comprised depression and/or anhedonia, lasting at least two weeks, plus
19
20 125 had consulted with a general practitioner or psychiatrist for mental ill-health (n=28,027 adverse
21
22 126 cardiovascular outcomes; n =29,528 stroke outcomes)¹⁸.

23
24
25 127 For the adverse cardiovascular outcomes, the remainder of the sample, with no history of CVD,
26
27 128 hypertension or MDD (n=50,798) were classified as a comparator group. The three mutually
28
29 129 exclusive diagnostic groups for this study were therefore: hypertension only (n=56,035); MDD only
30
31 130 (n=15,098) and hypertension plus MDD (n= 12,929). For the stroke outcomes, the remainder of the
32
33 131 sample, with no history of stroke, hypertension or MDD (n=52,502) were classified as a comparator
34
35 132 group. The three mutually exclusive diagnostic groups for this study were therefore: hypertension
36
37 133 only (n=59,724); MDD only (n=15,581) and hypertension plus MDD (n= 13,947)

38 39 40 41 134 **Outcomes**

42
43
44 135 The primary outcome was defined as a new-onset cardiovascular event leading to hospital admission
45
46 136 or death, specifically angina, MI, or chronic ischaemic heart disease (ICD-10 codes I20-I259), and
47
48 137 transient ischaemic attack (TIA) or stroke (ICD-10 codes I60-69 and G45- G46). A secondary outcome
49
50 138 was defined as stroke leading to hospital admission or death (ICD-10 codes I60-69 and G45- G46)
51
52 139 ²⁰due to the strength of relationship hypertension has with this outcome in particular⁵. Hospital
53
54 140 admission data were obtained from Hospital Episode Statistics in England, Patient Episode Database

1
2
3 141 for Wales and Scottish Morbidity Records in Scotland. Mortality outcomes were obtained from the
4
5 142 National Health Service (NHS) Information Centre for England and Wales and from the NHS Central
6
7 143 Register for Scotland. Individuals who died from a non-cardiovascular cause/stroke were censored
8
9 144 at the time of death but not recorded as having an event. Admission data were available for
10
11 145 Scottish, English and Welsh participants until 31 August 2014, 31 March 2015 and 28 February 2015
12
13 146 respectively. End of follow up was classified as these dates unless preceded by the date of death or
14
15 147 the date of first cardiovascular admission. In total 3,685 (2.73%) participants had a new-onset
16
17 148 cardiovascular event during the follow-up period and 910 (0.64%) participants had a new stroke
18
19 149 event.

150 **Confounding variables**

151 Information on potential confounding factors was available for age, sex, socioeconomic status
152 (Townsend score)²¹, self-reported ethnicity, age of leaving full-time education, history of diabetes,
153 body mass index (BMI), systolic blood pressure, history of hypercholesterolemia, alcohol use,
154 smoking history, sedentary behaviour (number of hours each day spent sitting at a computer,
155 television or driving), physical activity levels²² and psychotropic medication use. Specific details on
156 these variables are provided in supplementary digital content.

157 **Analyses**

158 Baseline characteristics were compared between groups using Chi-squared tests for categorical
159 variables and Kruskal Wallis for continuous variables. Confounding variables were assessed for
160 differences in adverse cardiovascular outcomes using log rank sums. For the four groups of interest
161 (comparator group, hypertension only group, MDD only group and hypertension plus MDD group)
162 we assessed associations with adverse cardiovascular outcomes using Cox proportional hazard
163 regression and the Efron method for ties²³. Models were applied in a staged process. Our findings
164 are reported as unadjusted (model one), partially adjusted (model two) and fully adjusted (model

1
2
3 165 three). Model two adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving
4
5 166 full time education and ethnicity) and model three additionally adjusted for health and lifestyle
6
7 167 factors (history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use,
8
9 168 systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use).
10
11 169 The assumption of proportionality of hazard was assessed for the four groups and each study
12
13 170 covariate using Schoenfeld residuals²⁴.

14
15
16 171 We also assessed for evidence of an interaction between hypertension and MDD. The relative
17
18 172 excess risk due to interaction (RERI)²⁵ was calculated to assess for additivity in the risk at each month
19
20 173 where the proportionality assumption for the variables of interest was not met. All analyses were
21
22 174 performed with Stata statistical software, version 12²⁶ with the exception of RERI which was
23
24 175 calculated using the Microsoft Excel method of Andersson and colleagues, which allows for
25
26 176 comparison of adjusted outcomes²⁷.

27
28
29
30 177 Psychotropic medication use was included as a confounding variable because of reports that these
31
32 178 medications may increase risk of mortality²⁸ but we also conducted a sensitivity analysis which
33
34 179 excluded the relatively small proportion of participants who were taking psychotropic medication.
35
36 180 Sub-group analyses looking separately at hazard rates in male and female groups only was also
37
38 181 carried out to assess for any gender specific differences a priori.

41 182 ***Time-varying covariates.***

42
43
44
45 183 In the context of Schoenfeld residuals showing non-proportionality, models with time varying
46
47 184 covariates were used. In addition, log (-log) plots were carried out to find the time point at which the
48
49 185 proportionality assumption fails by viewing at which time-point the variable of interest crosses the
50
51 186 control group. Following this, the data will be stratified by time on this this time point, effectively
52
53 187 creating two separate survival analyses pre and post the failure time point.

56 188 **Patient involvement**

1
2
3 189 Although patients were not directly involved with the design of the specific research questions in
4
5 190 this study, the hypotheses tested were developed in the context of experience from clinical practice
6
7 191 that depression and hypertension may interact to impact on cardiovascular outcomes. UK Biobank
8
9 192 has an active and ongoing programme of participant involvement:
10
11 193 www.ukbiobank.ac.uk/participants/. The outcome measures used were those provided by the UK
12
13 194 Biobank data collection protocol, the design of which had input from participants. UK Biobank also
14
15 195 has a website and social media streams to disseminate research findings and they host an annual
16
17 196 scientific meeting which includes cohort participants.
18
19
20
21 197
22
23

24 198 **RESULTS**

25
26
27 199 The final sample for adverse cardiovascular outcome included 134,860 participants followed for a
28
29 200 median duration of 63 months (702,901.6 person-years follow-up). Table 1 describes the baseline
30
31 201 characteristics of the four groups. In general, the hypertension only and comorbid hypertension plus
32
33 202 MDD groups were older, had higher BMI and were more likely to have diabetes and
34
35 203 hypercholesterolemia. The depression only and comorbid hypertension plus MDD groups had a
36
37 204 higher proportion of women and were more likely to be current smokers (table 1). Gender-
38
39 205 separated descriptive tables are shown in the supplementary digital content.
40
41

42 206 The sample for stroke-specific outcomes included 141,754 participants followed for a median
43
44 207 duration of 63 months (735247.7 person-years follow-up). Table 2 describes the baseline
45
46 208 characteristics of the four groups which display similar characteristics to the adverse cardiovascular
47
48 209 outcome groups.
49

50 51 210 **Adverse cardiovascular outcomes**

52
53
54
55
56
57
58
59
60

211 Within the main analysis and the female only subgroup analysis, MDD failed the proportional
212 hazards assumption as tested by Schoenfeld residuals. Table 3 presents unadjusted and multivariate-
213 adjusted HRs for adverse cardiovascular outcomes across the groups. In the fully adjusted model,
214 relative to the comparator group, the HR for adverse cardiovascular outcomes was significantly
215 raised for the hypertension only group (HR=1.36, 95%CI 1.22-1.52) and was higher still for the
216 comorbid hypertension plus MDD group (HR=1.66, 95%CI 1.46-1.9) (sensitivity analysis HR=1.43,
217 95%CI 1.27-1.62; HR=1.72, 95%CI 1.49-1.999 respectively). Table 4 presents unadjusted and
218 multivariate-adjusted HRs for adverse cardiovascular outcomes across the groups with the
219 hypertension only group as comparator. In the fully adjusted model, relative to the hypertension
220 group, the HR for adverse cardiovascular outcomes was significantly raised for the comorbid
221 hypertension plus MDD group (HR=1.22, 95%CI 1.1-1.35). These findings were also robust to
222 sensitivity analysis (HR= 1.20, 95%CI 1.08-1.34). An adjusted survival plot is shown in fig 1 and a
223 survival analysis stratified by time is described and included within the supplementary digital
224 content (table 9 in the supplementary digital content).

225 Within the sub-analysis, the model containing only the males showed a significant increase in hazard
226 ratio for hypertension (male HR 1.29, 95% CI 1.13-1.47) (table 5 of the supplementary digital
227 content) and comorbid MDD and hypertension (male HR 1.47, 95%CI 1.24-1.74). However, the
228 difference between comorbid disease and hypertension only was not statistically significant (male
229 HR 1.14, 95%CI 0.995-1.3). The female only sub-analysis showed an increase in hazard ratio for
230 hypertension (female HR 1.64, 95%CI 1.33-2.02) and a greater increase in comorbid MDD and
231 hypertension (female HR 2.18, 95%CI 1.82-2.92). The difference between comorbid disease and
232 hypertension only was also statistically significant (female HR 1.33, 95%CI 1.14- 1.56). Sensitivity
233 analysis supported these findings.

234 ***Relative excess risk due to interaction***

235 There was evidence of an additive interaction between hypertension and MDD at baseline for the
236 overall analysis before the 22.5 month time point (RERI=0.563, 95%CI 0.189 - 0.938). However after
237 this time point there was no evidence of interaction. Table 11 in the supplementary digital content
238 shows the full results for this analysis.

239 **Stroke Outcomes**

240 None of the independent variables for stroke outcome failed the proportionality assumption. Table 5
241 presents unadjusted and multivariate-adjusted HRs for stroke outcomes across the groups. In the
242 fully adjusted model, relative to the comparator group, the HR for stroke was insignificantly raised
243 for the hypertension only group (HR=1.21, 95%CI 0.97-1.51) and the depression only group
244 (HR=1.20, 95%CI 0.89-1.63) but significantly raised for the comorbid hypertension plus MDD group
245 (HR=1.37, 95%CI 1.04-1.79). In the hypertension comparator group, no group was significantly
246 different from the hypertension only group (table 6). Similar trends were shown in the gender
247 subset analysis but mainly not reaching significance. (Tables 7-8 in supplementary digital content)
248 An adjusted survival plot is shown in figure 3. Again, all results were supported by sensitivity
249 analysis.

250 **DISCUSSION**

251 In this large population cohort of middle-aged adults without CVD (adjusted for a broad range of
252 confounders), individuals with co-morbid hypertension and MDD were at increased risk of an
253 adverse cardiovascular event over time when compared to those with hypertension alone,
254 depression alone and neither condition. There was some evidence of an additive effect between
255 hypertension and MDD at baseline, but not throughout follow-up or within subgroup analyses.
256 Differences between co-morbid hypertension and depression were more marked in females. For
257 stroke outcomes, comorbid depression and hypertension was the only group that showed
258 significantly increased hazard ratios.

259 Previous research

260 Our findings expand upon previous research from UK Biobank looking at cardiovascular diseases in
261 those with bipolar disorder and MDD¹⁹. It was found that there were significantly increased odds of
262 having 'any cardiovascular disease' (fully adjusted OR 1.15 CI 1.12–1.19) or hypertension (fully
263 adjusted OR 1.15 CI 1.13–1.18) if depressed, with an even higher odds for stroke (fully adjusted OR
264 1.26 CI 1.13–1.40). There are distinct differences between our current paper and the previous
265 publication. Follow-up data within UK-Biobank has been released to allow meaningful prospective
266 studies be conducted. Thus, the current paper has the benefits of using hospital records and death
267 certification for outcomes, rather than self-reported data. Within our current study we were able to
268 exclude those with previous self-declared and cardiovascular disease requiring hospital admission, as
269 previous studies show depression may result from cardiovascular disease^{29 30} and worsen prognosis
270³⁰. As such, we are able to make inferences about the direction of effect. In addition, we have
271 incorporated hypertension to assess for some form of interaction.

272 Other survival analyses in hypertension/MDD comorbidity have focussed primarily on mortality
273 outcomes. Using data from the National Health and Nutrition Epidemiologic Follow-up Study in the
274 United States and the Taiwanese Survey of Health and Living Status, it has been found that
275 individuals with self-reported hypertension plus depressive symptoms (compared to a reference
276 group with neither) had increased all-cause mortality (HR=1.39, 95%CI 1.14-1.69, HR=1.54, 95%CI
277 1.29-1.83, respectively)^{31 32} with the former also showing increased ischaemic heart disease –
278 specific mortality (HR=1.59, 95%CI 1.08-2.34)³¹. Similarly, Hamer and colleagues have reported a
279 prospective analysis of common mental disorder on mortality outcomes in individuals with
280 hypertension versus those without hypertension in participants from the Health Survey for England
281 and the Scottish Health Survey (1994–2004), finding that risk of CVD death was highest in the group
282 with comorbid hypertension and common mental disorder¹⁵.

283 Strengths

1
2
3 284 These observations are broadly consistent with our results but our study has a number of
4
5 285 methodological advantages, including a very large sample size, adjustment of analyses for a more
6
7 286 comprehensive range of confounders, and a focus on new-onset non-fatal and fatal adverse
8
9 287 cardiovascular events. We also used a definition of prior MDD history which was based on
10
11 288 diagnostic criteria within ICD-10 (rather than a threshold score on a depressive symptoms or general
12
13 289 wellbeing scale) and our composite definition of hypertension incorporated past history, baseline
14
15 290 medication and blood pressure measurements.

18 291 **Limitations**

21 292 However, some limitations are acknowledged. Recruitment criteria for UK Biobank may lead to
22
23 293 selection bias for this form of study. Specifically, age-restrictions may lead to underrepresentation of
24
25 294 early-onset hypertension and those with more severe forms of MDD may be less inclined to attend
26
27 295 for assessment. We also acknowledge limitations with our classifications of MDD and hypertension,
28
29 296 which were primarily self-report rather than formal diagnostic assessments. Although we have
30
31 297 excluded prior cardiovascular events where possible, the MDD plus hypertension sub-type may
32
33 298 capture older individuals with a degree of vascular depression, which has an established association
34
35 299 with raised blood pressure³³. In addition, although we adjust for a host of risk factors at baseline
36
37 300 such as smoking status, BMI and psychotropic medication, we are limited by the lack of follow-up
38
39 301 data which could show change and modification of said risk factors over time. Similarly we were
40
41 302 unable to assess for medication adherence and transitions from one investigatory group to another.
42
43 303 Such modifications could explain the non-proportional nature of the depression group, which may in
44
45 304 itself be a predictor of poor medication adherence³⁴. Although adherence to medication was not
46
47 305 formally assessed, the number and duration of antihypertensive medications used in the
48
49 306 hypertension plus MDD group was the same as for the hypertension only group (supplementary
50
51 307 digital content, table 12). As such, worse outcomes in the MDD plus hypertension group are
52
53 308 not explained by less intensive antihypertensive treatment at baseline. The amelioration of the
54
55
56
57
58
59
60

1
2
3 309 Hazard ratios in the adjusted models suggests other covariates contribute considerably to the risk.
4
5 310 This is important in the context of increased rates of diabetes, hypercholesterolemia and obesity
6
7 311 along with lower socio-economic status in the hypertension only and comorbid groups and as such it
8
9 312 is possible we may be seeing the summation of CV risk factors. Finally, the overall recruitment rate
10
11 313 to UK Biobank was low (at around 6%), however, the large final cohort size, the depth and diversity
12
13 314 of phenotype data collected at baseline and the wide sociodemographic representation of
14
15 315 participants all make our findings highly relevant to UK primary care settings. While UK Biobank
16
17 316 participants cannot be used to provide representative disease prevalence and incidence rates, valid
18
19 317 assessment of exposure-disease relationships are nonetheless widely generalizable and do not
20
21 318 require participants to be representative of the UK population at large³⁵, although findings will not
22
23 319 be generalizable to other countries.

26 320 **Possible mechanisms**

27
28
29 321 Our finding that a history of MDD, in the context of a current diagnosis of hypertension, increased
30
31 322 the risk of new-onset CVD could be explained by shared genetic and environmental risk factors³⁶.
32
33 323 Several genetic studies have found an association between the *CACNA1c* gene and MDD^{10 37-39}.
34
35 324 *CACNA1c* codes for a calcium channel which is integral to heart contraction and important for the
36
37 325 normal functioning of the autonomic nervous system; cortisol release and immune function⁴⁰⁻⁴²,
38
39 326 systems that are central to the pathophysiology of both hypertension and depression⁴³⁻⁴⁹. Indeed,
40
41 327 new evidence has emerged that subgroups of depression may have increased rates of genes related
42
43 328 to cardiovascular risk factors such as cholesterol and raised blood pressure⁵⁰. MDD could also
44
45 329 increase cardiovascular disease risk via several mechanisms that may interact with blood pressure
46
47 330 control³⁶. For example, significant life events are stressors linked to depression by causing elevated
48
49 331 cortisol leading to reduced serotonin and dopamine and increased sympathetic stimulation. This can
50
51 332 lead to cardiac ischaemia via heart rate, blood pressure and vasoconstrictive changes, plaque
52
53 333 formation due to endothelial injury, and impaired healing and thrombus formation via platelet
54
55
56
57
58
59
60

1
2
3 334 activation and haemostatic changes^{36 51 52}. Individuals with hypertension or depression already have
4
5 335 increased sympathetic activity which may be further increased in comorbid states⁵¹. Furthermore,
6
7 336 MDD is also commonly associated with unhealthy lifestyle factors such as smoking, sedentary
8
9 337 behaviour and poor diet and increased weight¹⁹ and cardiovascular side effects of medications have
10
11 338 been commonly reported. Given the finding that comorbid disease and hypertension lead to
12
13 339 increased cardiovascular events, it would be useful to assess how treatment of these conditions
14
15 340 influences outcome.

16
17
18 341 Potential menopausal effects are tempting explanations for the variation with time in the female
19
20 342 only and overall analysis, especially given the age range of the cohort. It is widely accepted that
21
22 343 oestrogen has a protective impact on the heart which may be lost at menopause⁵³. Furthermore,
23
24 344 increases in blood pressure are also noted at menopause⁵⁴ and depression may have a second
25
26 345 incidence peak around this time too.^{55 56} Due to the MDD only group generally being younger and
27
28 346 having more females than the other groups, it may capture more of the menopausal change in
29
30 347 cardiovascular hazard during follow up than other groups leading to disproportionate hazards.
31
32 348 However, such findings are found in the female only analysis where age is similar between the
33
34 349 comparator group and the MDD only group.

35
36
37
38 350 The disproportional hazards in the MDD only group leads to a trend of lowered hazard ratios at the
39
40 351 start of follow up and a significantly increased hazard at the end of follow up. This lowered trend
41
42 352 initially leads to a significant RERI finding which is not maintained. Of note, MDD correlates highly
43
44 353 with neuroticism which has been shown to be inconsistent in regards to whether it is a risk factor or
45
46 354 protective, including in UK Biobank.⁵⁷ It is thought that conscientiousness and poor self-reported
47
48 355 health interact with neuroticism for better outcomes, it may be that premenopausal or
49
50 356 perimenopausal states may influence survival positively in women⁵⁸. Of further investigatory interest
51
52 357 may be to assess if those with depression are more likely to develop hypertension during
53
54
55
56
57
58
59
60

1
2
3 358 menopause or indeed whether neuroticism and/or depression interacts with menopause to
4
5 359 influence survival.
6
7

8 360 **CONCLUSIONS**
9

10 361 Overall, our findings may have important implications for routine clinical practice, particularly within
11
12 362 primary care settings. Although evidence of an additive interaction is inconsistent, we found that
13
14 363 comorbid hypertension and depression conferred greater hazard than hypertension alone for
15
16 364 adverse cardiovascular outcomes. This significant finding remained after adjustment for factors such
17
18 365 as BMI, smoking status and diabetes and was robust to sensitivity analysis excluding those on
19
20 366 psychotropic medication. One possible implication is that clinicians should be more aware of the
21
22 367 negative long-term impact on CVD outcomes caused by a history of MDD in the context of
23
24 368 hypertension, particularly patients with no previous history of CVD. Although this work awaits
25
26 369 replication and testing in other cohorts and settings, it may be that future iterations of CVD risk
27
28 370 prediction tools, such as ASSIGN⁵⁹, would benefit from the addition of a question on whether
29
30 371 individuals have a past history of MDD, so that they can be offered more intensive support to
31
32 372 prevent CVD⁶⁰.
33
34
35

36
37 373
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 374 **ACKNOWLEDGEMENTS**
4
5

6 375 We are grateful to all participants of the UK Biobank cohort. UK Biobank was established by the
7
8 376 Wellcome Trust, the Medical Research Council, Department of Health, Scottish Government and the
9
10 377 Northwest Regional Development Agency. It has also had funding from the Welsh Assembly
11
12 378 Government and the British Heart Foundation. UK Biobank is hosted by the University of Manchester
13
14 379 and supported by the National Health Service (NHS). NG is supported by the Aitchison Family Clinical
15
16 380 Research Fellowship at the University of Glasgow and DJS is supported by a Lister Institute Prize
17
18 381 Fellowship. JC is supported by the Sackler Trust and the Wellcome Trust
19
20

21
22 382 **Footnotes**
23
24

25 383 **Authors Statement:** Contributors NG, JW, JP, JC, DS, SP and DM, contributed to study design and
26
27 384 writing of the manuscript. JP and DM contributed to data acquisition. NG conducted data processing
28
29 385 and statistical analyses.
30
31

32 386 **Funding:** Authors declare no support from any organisation for the submitted work;
33
34

35 387 **Competing interests:** All authors have completed the ICMJE uniform disclosure form at
36
37 388 http://www.icmje.org/coi_disclosure.pdf and no financial relationships with any organisations that
38
39 389 might have an interest in the submitted work in the previous three years; no other relationships or
40
41 390 activities that could appear to have influenced the submitted work.
42
43
44

45 391 **Ethics approval:** This study has been conducted using UK Biobank data. UK Biobank has received
46
47 392 ethics approval from the UK Biobank Research Ethics Committee (ref. 11/NW/0382).
48
49

50 393 **Data sharing statement:** The data used in this study are available via a direct application to UK
51
52 394 Biobank.
53
54
55
56
57
58
59
60

1
2
3 395 **Transparency statement:** The lead author affirms that this manuscript is an honest, accurate and
4
5 396 transparent account of the study being reported; that no important aspects of the study have been
6
7 397 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have
8
9 398 been explained.

10
11
12 399

13
14
15 400 **COMPETING INTERESTS STATEMENTS**

16
17
18 401 All authors have completed the ICMJE uniform disclosure form at
19
20 402 http://www.icmje.org/coi_disclosure.pdf and no financial relationships with any organisations that
21
22 403 might have an interest in the submitted work in the previous three years; no other relationships or
23
24 404 activities that could appear to have influenced the submitted work.

25
26
27 405
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

406 **References**

407

- 408 1. Organization. WH. The global burden of disease: 2004 update. Geneva, Switzerland.: WHO press.
409 2008.
- 410 2. Hare DL, Toukhsati SR, Johansson P, et al. Depression and cardiovascular disease: a clinical review.
411 *Eur Heart J* 2014;35(21):1365-72. doi: 10.1093/eurheartj/eh462
- 412 3. Cohen BE, Edmondson D, Kronish IM. State of the Art Review: Depression, Stress, Anxiety, and
413 Cardiovascular Disease. *Am J Hypertens* 2015;28(11):1295-302. doi: 10.1093/ajh/hpv047
- 414 4. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide
415 data. *Lancet* 2005;365(9455):217-23. doi: 10.1016/S0140-6736(05)17741-1
- 416 5. Lawes CM, Vander Hoorn S, Rodgers A, et al. Global burden of blood-pressure-related disease,
417 2001. *Lancet* 2008;371(9623):1513-8. doi: 10.1016/S0140-6736(08)60655-8
- 418 6. Meng L, Chen D, Yang Y, et al. Depression increases the risk of hypertension incidence: a meta-
419 analysis of prospective cohort studies. *J Hypertens* 2012;30:842 - 51.
- 420 7. Wu EL, Chien IC, Lin CH, et al. Increased risk of hypertension in patients with major depressive
421 disorder: a population-based study. *J Psychosom Res* 2012;73(3):169-74. doi:
422 10.1016/j.jpsychores.2012.07.002
- 423 8. Johnson AD, Newton-Cheh C, Chasman DI, et al. Association of hypertension drug target genes
424 with blood pressure and hypertension in 86,588 individuals. *Hypertension* 2011;57(5):903-
425 10. doi: 10.1161/HYPERTENSIONAHA.110.158667
- 426 9. Casamassima F HJ, Fava M, Sachs GS, Smoller JW, Cassano GB, Lattanzi L, Fagerness J, Stange JP,
427 Perlis RH. Phenotypic effects of a bipolar liability gene among individuals with major
428 depressive disorder. *Am J Med Genet B Neuropsychiatr Genet* 2010;153B:303-09.
- 429 10. Green EK, Grozeva D, Jones I, et al. The bipolar disorder risk allele at CACNA1C also confers risk
430 of recurrent major depression and of schizophrenia. *Molecular Psychiatry* 2010;15(10):1016-
431 22. doi: 10.1038/mp.2009.49
- 432 11. Ferreira MA, O'Donovan MC, Meng YA, et al. Collaborative genome-wide association analysis
433 supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat Genet* 2008;40(9):1056-8.
434 doi: 10.1038/ng.209
- 435 12. Consortium WTCC. Identification of risk loci with shared effects on five major psychiatric
436 disorders: a genome-wide analysis. *The Lancet* 2013;381(9875):1371-79.
- 437 13. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the
438 causes of a wide range of complex diseases of middle and old age. *PLoS Med*
439 2015;12(3):e1001779. doi: 10.1371/journal.pmed.1001779
- 440 14. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age,
441 and year: findings from the global burden of disease study 2010. *PLoS Med*
442 2013;10(11):e1001547. doi: 10.1371/journal.pmed.1001547
- 443 15. Hamer M, Batty GD, Stamatakis E, et al. The combined influence of hypertension and common
444 mental disorder on all-cause and cardiovascular disease mortality. *J Hypertens*
445 2010;28(12):2401-6. doi: 10.1097/HJH.0b013e32833e9d7c
- 446 16. Ong KL, Cheung BM, Man YB, et al. Prevalence, awareness, treatment, and control of
447 hypertension among United States adults 1999-2004. *Hypertension* 2007;49(1):69-75. doi:
448 10.1161/01.hyp.0000252676.46043.18 [published Online First: 2006/12/13]
- 449 17. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of
450 hypertension, 1988-2008. *Jama* 2010;303(20):2043-50. doi: 10.1001/jama.2010.650
451 [published Online First: 2010/05/27]
- 452 18. Smith DJ, Nicholl BI, Cullen B, et al. Prevalence and characteristics of probable major depression
453 and bipolar disorder within UK biobank: cross-sectional study of 172,751 participants. *PLoS*
454 *One* 2013;8(11):e75362. doi: 10.1371/journal.pone.0075362

- 1
2
3 455 19. Martin DJ, Ul-Haq Z, Nicholl BI, et al. Cardiometabolic disease and features of depression and
4 456 bipolar disorder: population-based, cross-sectional study. *Br J Psychiatry* 2016;208(4):343-
5 457 51. doi: 10.1192/bjp.bp.114.157784
- 6 458 20. Woodfield R, Grant I, Group UKBSO, et al. Accuracy of Electronic Health Record Data for
7 459 Identifying Stroke Cases in Large-Scale Epidemiological Studies: A Systematic Review from
8 460 the UK Biobank Stroke Outcomes Group. *PLOS ONE* 2015;10(10):e0140533. doi:
9 461 10.1371/journal.pone.0140533
- 10 462 21. Townsend P. Deprivation. *Journal of Social Policy* 2009;16(02):125. doi:
11 463 10.1017/s0047279400020341
- 12 464 22. Guo W, Bradbury KE, Reeves GK, et al. Physical activity in relation to body size and composition
13 465 in women in UK Biobank. *Annals of Epidemiology* 2015;25(6):406-13.e6. doi:
14 466 <http://dx.doi.org/10.1016/j.annepidem.2015.01.015>
- 15 467 23. Efron B. The Efficiency of Cox's Likelihood Function for Censored Data. *Journal of the American*
16 468 *Statistical Association*, 1977;72(359):557-65.
- 17 469 24. Schoenfeld D. Partial Residuals for the Proportional Hazards Regression-Model. *Biometrika*
18 470 1982;69(1):239-41. doi: Doi 10.2307/2335876
- 19 471 25. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology*
20 472 (*Cambridge, Mass*) 1992;3(5):452-6. [published Online First: 1992/09/01]
- 21 473 26. Stata Statistical Software, version 12 [program]. College station, Texas.
- 22 474 27. Andersson T, Alfredsson L, Kallberg H, et al. Calculating measures of biological interaction.
23 475 *European journal of epidemiology* 2005;20(7):575-9. [published Online First: 2005/08/27]
- 24 476 28. Weich S, Pearce HL, Croft P, et al. Effect of anxiolytic and hypnotic drug prescriptions on
25 477 mortality hazards: retrospective cohort study. *BMJ* 2014;348:g1996. doi: 10.1136/bmj.g1996
- 26 478 29. Kang HJ, Stewart R, Bae KY, et al. Predictive value of homocysteine for depression after acute
27 479 coronary syndrome. *Oncotarget* 2016;7(42):69032-40. doi: 10.18632/oncotarget.11966
- 28 480 30. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis
29 481 among patients with acute coronary syndrome: systematic review and recommendations: a
30 482 scientific statement from the American Heart Association. *Circulation* 2014;129(12):1350-69.
31 483 doi: 10.1161/CIR.0000000000000019
- 32 484 31. Axon RN, Zhao Y, Egede LE. Association of depressive symptoms with all-cause and ischemic
33 485 heart disease mortality in adults with self-reported hypertension. *Am J Hypertens*
34 486 2010;23(1):30-7. doi: 10.1038/ajh.2009.199
- 35 487 32. Kuo PL, Pu C. The contribution of depression to mortality among elderly with self-reported
36 488 hypertension: analysis using a national representative longitudinal survey. *J Hypertens*
37 489 2011;29(11):2084-90. doi: 10.1097/HJH.0b013e32834b59ad [published Online First:
38 490 2011/09/22]
- 39 491 33. Aizenstein HJ, Baskys A, Boldrini M, et al. Vascular depression consensus report – a critical
40 492 update. *BMC Medicine* 2016;14(1):161. doi: 10.1186/s12916-016-0720-5
- 41 493 34. Goldstein CM, Gathright EC, Garcia S. Relationship between depression and medication
42 494 adherence in cardiovascular disease: the perfect challenge for the integrated care team.
43 495 *Patient preference and adherence* 2017;11:547-59. doi: 10.2147/PPA.S127277
- 44 496 35. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related
45 497 Characteristics of UK Biobank Participants With Those of the General Population. *American*
46 498 *journal of epidemiology* 2017;186(9):1026-34. doi: 10.1093/aje/kwx246 [published Online
47 499 First: 2017/06/24]
- 48 500 36. Nemeroff CB, Goldschmidt-Clermont PJ. Heartache and heartbreak - the link between depression
49 501 and cardiovascular disease. *Nat Rev Cardiol* 2012;9(9):526-39.
- 50 502 37. He K, An Z, Wang Q, et al. CACNA1C, schizophrenia and major depressive disorder in the Han
51 503 Chinese population. *British Journal of Psychiatry* 2014;204(1):36-39. doi:
52 504 10.1192/bjp.bp.113.126979

- 1
2
3 505 38. Liu Y, Blackwood DH, Caesar S, et al. Meta-Analysis of Genome-Wide Association Data of Bipolar
4 506 Disorder and Major Depressive Disorder. *Molecular psychiatry*
5 507 2011;16(1):10.1038/mp.2009.107. doi: 10.1038/mp.2009.107
6 508 39. Sullivan PF, De Geus EJC, Willemsen G, et al. Genome-wide association for major depressive
7 509 disorder: A possible role for the presynaptic protein piccolo. *Molecular Psychiatry*
8 510 2009;14(4):359-75. doi: 10.1038/mp.2008.125
9 511 40. Robert V, Triffaux E, Savignac M, et al. Singularities of calcium signaling in effector T-
10 512 lymphocytes. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*
11 513 2013;1833(7):1595-602. doi: <http://dx.doi.org/10.1016/j.bbamcr.2012.12.001>
12 514 41. Nohara LL, Stanwood SR, Omilusik KD, et al. Tweeters, Woofers and Horns: The Complex
13 515 Orchestration of Calcium Currents in T Lymphocytes. *Frontiers in immunology* 2015;6:234.
14 516 doi: 10.3389/fimmu.2015.00234 [published Online First: 2015/06/09]
15 517 42. Loechner KJ, Salmon WC, Fu J, et al. Cell Cycle-Dependent Localization of Voltage-Dependent
16 518 Calcium Channels and the Mitotic Apparatus in a Neuroendocrine Cell Line(AT-20). *Int J Cell*
17 519 *Biol* 2009;2009:487959. doi: 10.1155/2009/487959
18 520 43. Dantzer R, O'Connor JC, Freund GG, et al. From inflammation to sickness and depression: when
19 521 the immune system subjugates the brain. *Nat Rev Neurosci* 2008;9(1):46-56. doi:
20 522 10.1038/nrn2297
21 523 44. Abboud FM, Harwani SC, Chapleau MW. Autonomic neural regulation of the immune system:
22 524 implications for hypertension and cardiovascular disease. *Hypertension* 2012;59(4):755-62.
23 525 doi: 10.1161/HYPERTENSIONAHA.111.186833
24 526 45. Schiffrin EL. The immune system: role in hypertension. *The Canadian journal of cardiology*
25 527 2013;29(5):543-8. doi: 10.1016/j.cjca.2012.06.009 [published Online First: 2012/08/21]
26 528 46. Mancia G, Grassi G. The autonomic nervous system and hypertension. *Circ Res*
27 529 2014;114(11):1804-14. doi: 10.1161/CIRCRESAHA.114.302524
28 530 47. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary
29 531 heart disease. *Psychosomatic medicine* 2005;67 Suppl 1:S29-33. doi:
30 532 10.1097/01.psy.0000162254.61556.d5 [published Online First: 2005/06/15]
31 533 48. Baune BT, Stuart M, Gilmour A, et al. The relationship between subtypes of depression and
32 534 cardiovascular disease: a systematic review of biological models. *Transl Psychiatry*
33 535 2012;2(3):e92. doi: 10.1038/tp.2012.18
34 536 49. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new
35 537 developments. *Trends Neurosci* 2008;31(9):464-8. doi: 10.1016/j.tins.2008.06.006
36 538 50. Howard DM, Clarke T-K, Adams MJ, et al. The Stratification Of Major Depressive Disorder Into
37 539 Genetic Subgroups. *bioRxiv* 2017 doi: 10.1101/134601
38 540 51. Barton DA, Dawood T, Lambert EA, et al. Sympathetic activity in major depressive disorder:
39 541 identifying those at increased cardiac risk? *J Hypertens* 2007;25(10):2117-24. doi:
40 542 10.1097/HJH.0b013e32829baae7 [published Online First: 2007/09/22]
41 543 52. Gouin J-P, Kiecolt-Glaser JK. The Impact of Psychological Stress on Wound Healing: Methods and
42 544 Mechanisms. *Immunology and allergy clinics of North America* 2011;31(1):81-93. doi:
43 545 10.1016/j.iac.2010.09.010
44 546 53. Rosano GM, Panina G. Oestrogens and the heart. *Therapie* 1999;54(3):381-5. [published Online
45 547 First: 1999/09/29]
46 548 54. Zanchetti A, Facchetti R, Cesana GC, et al. Menopause-related blood pressure increase and its
47 549 relationship to age and body mass index: the SIMONA epidemiological study. *J Hypertens*
48 550 2005;23(12):2269-76. [published Online First: 2005/11/05]
49 551 55. Eaton WW, Anthony JC, Gallo J, et al. Natural history of diagnostic interview schedule/ dsm-iv
50 552 major depression: The baltimore epidemiologic catchment area follow-up. *Archives of*
51 553 *General Psychiatry* 1997;54(11):993-99. doi: 10.1001/archpsyc.1997.01830230023003
52
53
54
55
56
57
58
59
60

- 1
2
3 554 56. Blazer DG, Kessler RC, McGonagle KA, et al. The prevalence and distribution of major depression
4 555 in a national community sample: the National Comorbidity Survey. *Am J Psychiatry*
5 556 1994;151(7):979-86. doi: 10.1176/ajp.151.7.979 [published Online First: 1994/07/01]
6 557 57. Gale CR, Čukić I, Batty GD, et al. When Is Higher Neuroticism Protective Against Death? Findings
7 558 From UK Biobank. *Psychological Science* 2017;28(9):1345-57. doi:
8 559 10.1177/0956797617709813
9 560 58. Ploubidis GB, Grundy E. Personality and all cause mortality: Evidence for indirect links.
10 561 *Personality and Individual Differences* 2009;47(3):203-08. doi:
11 562 <https://doi.org/10.1016/j.paid.2009.02.022>
12 563 59. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to
13 564 cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended
14 565 Cohort (SHHEC). *Heart* 2007;93(2):172-76. doi: 10.1136/hrt.2006.108167
15 566 60. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and
16 567 Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;336(7659):1475-82. doi:
17 568 10.1136/bmj.39609.449676.25

19 569
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

570 **Table 1. Baseline characteristics for adverse cardiovascular outcomes**

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 50798	N = 56035	N = 15098	N = 12929
Median age (range)*	54 (47 - 61)	61 (55 - 65)	53 (46 - 60)	60 (53 - 64)
Females, N (%)	29228 (57.54%)	25893 (46.21%)	10929 (72.39%)	7676 (59.37%)
Ethnicity, N (%)				
White	46147 (90.84%)	51249 (91.46%)	14247 (94.36%)	12272 (94.92%)
Asian/Asian British	1771 (3.49%)	1696 (3.03%)	261 (1.73%)	179 (1.38%)
Black/ Black British	1323 (2.6%)	1769 (3.16%)	219 (1.45%)	222 (1.72%)
Median Townsend score (range)*	-1.89 (-3.45 - 0.54)	-2.07 (-3.51 - 0.39)	-1.64 (-3.3 - 0.93)	-1.84 (-3.42 - 0.76)
Age at leaving full-time education, N (%)				
<16	5916 (11.65%)	12085 (21.57%)	1725 (11.43%)	2607 (20.16%)
16	10265 (20.21%)	11827 (21.11%)	3178 (21.05%)	2732 (21.13%)
>16	34090 (67.11%)	31480 (56.18%)	10090 (66.83%)	7503 (58.03%)
Total physical activity in metabolic	3.97 (1.68 - 8.03)	3.79 (1.51 - 8.03)	3.89 (1.66 - 8)	3.68 (1.49 - 7.95)
Sedentary time in hours, median (range)*	4 (3 - 6)	4.5 (3.5 - 6)	4.5 (3 - 6)	5 (3.5 - 6)

Diabetes, N (%)	1268 (2.5%)	3777 (6.74%)	380 (2.52%)	929 (7.19%)
Hypercholesterolaemia, N (%)	3011 (5.93%)	9210 (16.44%)	893 (5.91%)	2211 (17.1%)
Systolic BP in mmHg, median (range)*	125.5 (118 - 132)	149.5 (142 - 159.5)	124 (116 - 131)	147.5 (140.5 - 157.)
Body Mass Index, N (%)				
<18.5	389 (0.77%)	142 (0.25%)	103 (0.68%)	34 (0.26%)
18.5 – 25	22549 (44.39%)	13678 (24.41%)	6251 (41.4%)	2874 (22.23%)
25-30	20410 (40.18%)	25216 (45%)	5936 (39.32%)	5389 (41.68%)
>30	7450 (14.67%)	16999 (30.34%)	2808 (18.6%)	4632 (35.83%)
Smoking status, N (%)				
Never smoked	30626 (60.29%)	31503 (56.22%)	7864 (52.09%)	6454 (49.92%)
Previously smoked	15056 (29.64%)	20140 (35.94%)	5118 (33.9%)	5065 (39.18%)
Current smoker	4970 (9.78%)	4199 (7.49%)	2093 (13.86%)	1381 (10.68%)
Alcohol frequency, N (%)				
Daily or almost daily	9450 (18.6%)	12970 (23.15%)	2736 (18.12%)	2881 (22.28%)
Three or four times a week	12175 (23.97%)	13033 (23.26%)	3253 (21.55%)	2837 (21.94%)
Once or twice a week	13644 (26.86%)	13889 (24.79%)	3880 (25.7%)	2916 (22.55%)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

One to three times a month	6052	(11.91%)	5588	(9.97%)	2058	(13.63%)	1512	(11.69%)
Special occasions only	5534	(10.89%)	6330	(11.3%)	1904	(12.61%)	1729	(13.37%)
Never	3924	(7.72%)	4199	(7.49%)	1262	(8.36%)	1048	(8.11%)
Psychotropic medication, N (%)	1341	(2.64%)	1795	(3.2%)	2844	(18.84%)	2522	(19.51%)

571 *Data presented as N (%) except * which are median values (interquartile range). Data presented as MET-hrs (hours spent doing exercise adjusted for*
 572 *multiples of basal metabolic rate in accordance with IPAQ).*

573

Peer review only

574 Table 2 Baseline characteristics for stroke outcomes

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 52502	N = 59724	N = 15581	N = 13947
Median age (range)*	54 (47 - 61)	61 (55 - 65)	54 (47 - 61)	60 (53 - 64)
Females, N (%)	29684 (56.54%)	26937 (45.1%)	11143 (71.52%)	8090 (58.01%)
Ethnicity, N (%)				
White	47697 (90.85%)	54578 (91.38%)	14697 (94.33%)	13212 (94.73%)
Asian/Asian British	1857 (3.54%)	1889 (3.16%)	280 (1.8%)	209 (1.5%)
Black/ Black British	1355 (2.58%)	1854 (3.1%)	223 (1.43%)	246 (1.76%)
Median Townsend score (range)*	-1.89 (-3.45 - 0.55)	-2.04 (-3.49 - 0.44)	-1.56 (-3.28 - 1.15)	-1.74 (-3.4 - 0.93)
Age at leaving full-time education, N (%)				
<16	6446 (12.28%)	13396 (22.43%)	1884 (12.09%)	2945 (21.12%)
16	10590 (20.17%)	12507 (20.94%)	3270 (20.99%)	2953 (21.17%)
>16	34914 (66.5%)	33114 (55.45%)	10317 (66.22%)	7947 (56.98%)
Total physical activity in metabolic	3.96 (1.67 - 8.02)	3.75 (1.5 - 8)	4.13 (1.67 - 8.36)	3.66 (1.45 - 7.83)
Sedentary time in hours, median (range)*	4 (3 - 6)	5 (3.5 - 6)	5 (3.5 - 6.5)	5 (4 - 7)

Diabetes, N (%)	1454 (2.77%)	4502 (7.54%)	449 (2.88%)	1163 (8.34%)
Hypercholesterolaemia, N (%)	3592 (6.84%)	10768 (18.03%)	1049 (6.73%)	2620 (18.79%)
Systolic BP in mmHg, median (range)*	125.5 (118 - 132)	149.5 (142 - 159.5)	127 (120.5 - 133)	147.5 (140.5 - 156.5)
Body Mass Index, N (%)				
<18.5	395 (0.75%)	151 (0.25%)	104 (0.67%)	38 (0.27%)
18.5 – 25	22967 (43.75%)	14242 (23.85%)	6374 (40.91%)	3017 (21.63%)
25-30	21185 (40.35%)	26817 (44.9%)	6149 (39.46%)	5769 (41.36%)
>30	7953 (15.15%)	18514 (31.%)	2954 (18.96%)	5123 (36.73%)
Smoking status, N (%)				
Never smoked	31318 (59.65%)	32982 (55.22%)	8052 (51.68%)	6834 (49%)
Previously smoked	15851 (30.19%)	22019 (36.87%)	5340 (34.27%)	5560 (39.87%)
Current smoker	5170 (9.85%)	4501 (7.54%)	2163 (13.88%)	1519 (10.89%)
Alcohol frequency, N (%)				
Daily or almost daily	9760 (18.59%)	13751 (23.02%)	2817 (18.08%)	3085 (22.12%)
Three or four times a week	12563 (23.93%)	13827 (23.15%)	3335 (21.4%)	3020 (21.65%)
Once or twice a week	14089 (26.84%)	14719 (24.65%)	3993 (25.63%)	3125 (22.41%)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

One to three times a month	6220	(11.85%)	5971	(10%)	2122	(13.62%)	1627	(11.67%)
Special occasions only	5744	(10.94%)	6794	(11.38%)	1978	(12.69%)	1885	(13.52%)
Never	4102	(7.81%)	4630	(7.75%)	1330	(8.54%)	1199	(8.6%)
Psychotropic medication, N (%)	1408	(2.68%)	1996	(3.34%)	2976	(19.1%)	2778	(19.92%)

575 *Data presented as N (%) except * which are median values (interquartile range). Data presented as MET-hrs (hours spent doing exercise adjusted for*
 576 *multiples of basal metabolic rate in accordance with IPAQ).*

Peer review only

577 Table 3: Risk of adverse cardiovascular event by clinical group: unadjusted, partially adjusted and fully adjusted models.

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.60	(2.39 - 2.82)	3.31x10 ⁻¹¹³	1.72	(1.57 - 1.88)	1.99x10 ⁻³³	1.36	(1.22 - 1.52)	2.92x10 ⁻⁸
MDD only	0.69	(0.51 - 0.94)	0.02	0.82	(0.6 - 1.13)	0.23	0.75	(0.54 - 1.04)	0.08
Hypertension and MDD	2.84	(2.55 - 3.17)	6.31x10 ⁻⁷⁷	2.27	(2.02 - 2.55)	2.75x10 ⁻⁴⁴	1.66	(1.45 - 1.9)	7.48x10 ⁻¹⁴
Time varying Variables									
MDD only	1.01	(1.004 - 1.02)	2.38x10 ⁻³	1.01	(1.004 - 1.02)	3.19x10 ⁻³	1.01	(1.004 - 1.02)	3.03x10 ⁻³

578

579 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity. †Additionally adjusted for history of
 580 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
 581 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, C.I. = Confidence interval.

582

583 Table 4: Risk of adverse cardiovascular event by clinical group: unadjusted, partially adjusted and fully adjusted models with hypertension as the
584 comparator

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value
<i>Hypertension only</i>	1(ref)			1(ref)			1(ref)		
<i>No Hypertension - No MDD</i>	0.38	(0.35 - 0.42)	3.31x10 ⁻¹¹³	0.58	(0.53 - 0.63)	1.99x10 ⁻³³	0.73	(0.66 - 0.82)	2.92x10 ⁻⁸
<i>MDD only</i>	0.27	(0.2 - 0.36)	1.14x10 ⁻¹⁷	0.48	(0.35 - 0.66)	4.91x10 ⁻⁶	0.55	(0.4 - 0.76)	3.23x10 ⁻⁴
<i>Hypertension and MDD</i>	1.09	(0.996 - 1.2)	0.06	1.32	(1.2 - 1.46)	3.07x10 ⁻⁸	1.22	(1.1 - 1.35)	1.30x10 ⁻⁴
Time varying Variables									
<i>MDD only</i>	1.01	(1.004 - 1.02)	0.002	1.01	(1.004 - 1.02)	3.19x10 ⁻³	1.01	(1.004 - 1.02)	3.03x10 ⁻³

585 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity. †Additionally adjusted for history of
586 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
587 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, C.I. = Confidence interval.

588

589 Table 5: Risk of stroke event by clinical group: unadjusted, partially adjusted and fully adjusted models.

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value
No Hypertension- No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.55	(2.16 - 3.02)	3.84x10 ⁻²⁸	1.64	(1.38 - 1.96)	3.35x10 ⁻⁸	1.21	(0.97 - 1.51)	0.09
MDD only	1.14	(0.86 - 1.52)	0.37	1.37	(1.02 - 1.84)	0.037	1.20	(0.89 - 1.63)	0.24
Hypertension and MDD	2.67	(2.13 - 3.34)	9.79x10 ⁻¹⁸	2.05	(1.63 - 2.58)	1.08x10 ⁻⁹	1.37	(1.04 - 1.79)	0.02

590 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity. †Additionally adjusted for history of
 591 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
 592 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, C.I. = Confidence interval.

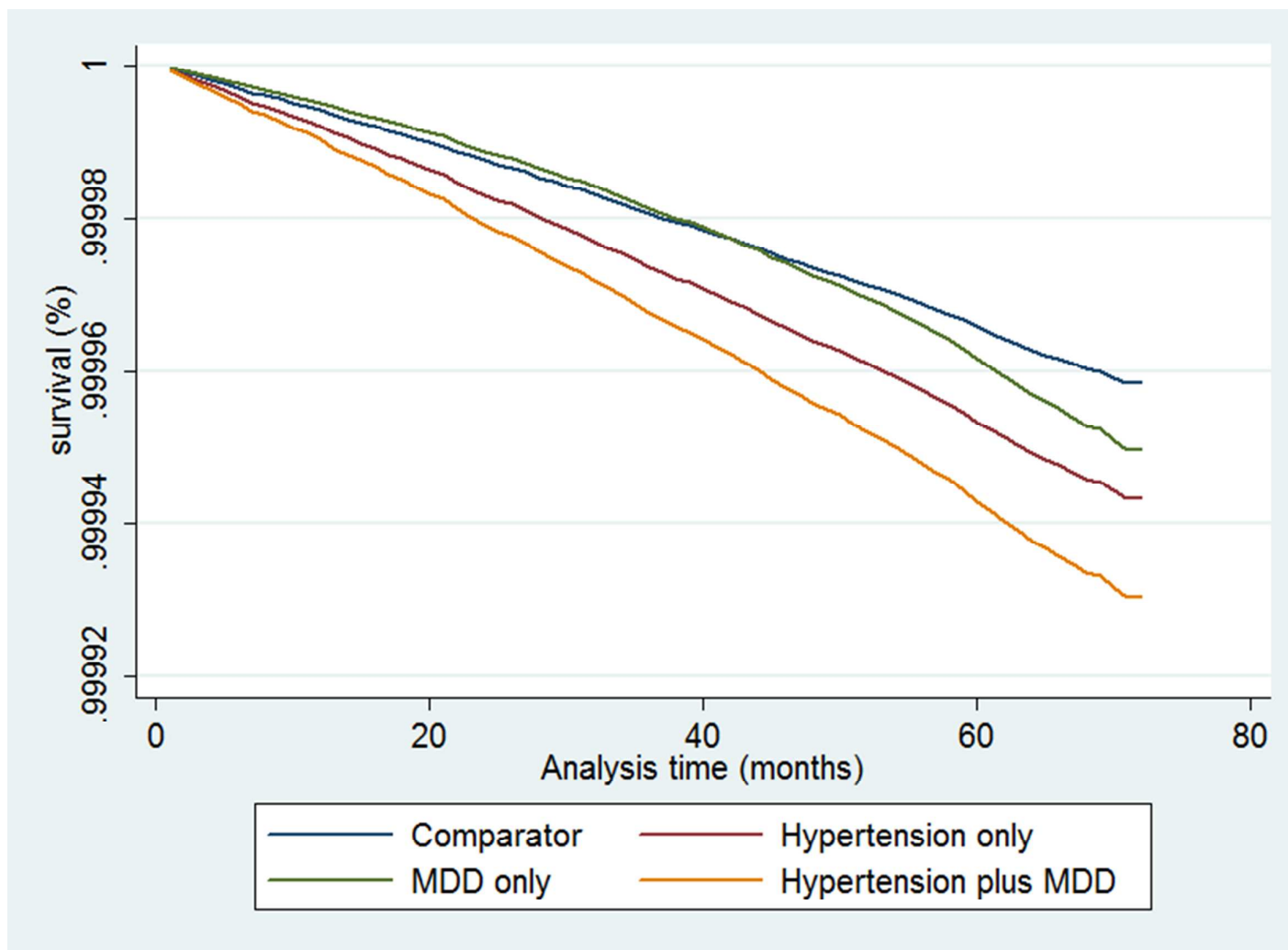
595 Table 6: Risk of stroke event by clinical group: unadjusted, partially adjusted and fully adjusted models with hypertension as the comparator

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value
<i>Hypertension only</i>	1(ref)			1(ref)			1(ref)		
<i>No Hypertension - No MDD</i>	0.39	(0.33 - 0.46)	3.84x10 ⁻²⁸	0.61	(0.51 - 0.73)	3.35x10 ⁻⁸	0.82	(0.66 - 1.03)	0.09
<i>MDD only</i>	0.45	(0.34 - 0.58)	1.43x10 ⁻⁹	0.83	(0.63 - 1.1)	0.19	0.99	(0.73 - 1.35)	0.95
<i>Hypertension and MDD</i>	1.05	(0.86 - 1.27)	0.64	1.25	(1.03 - 1.52)	0.03	1.13	(0.92 - 1.39)	0.26

596 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of
597 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
598 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, C.I. = Confidence interval.

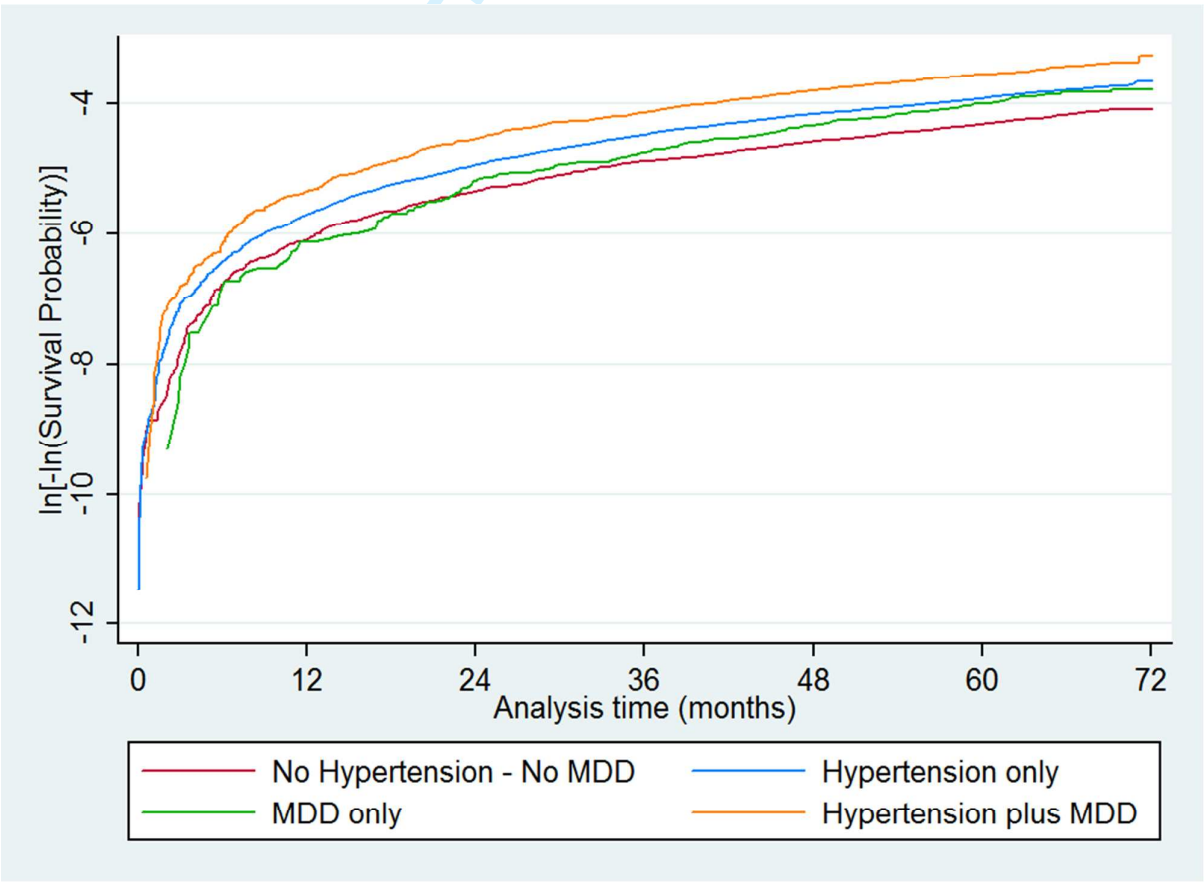
599

1 **Fig1. Adjusted survival analysis graph for adverse cardiovascular outcome.**



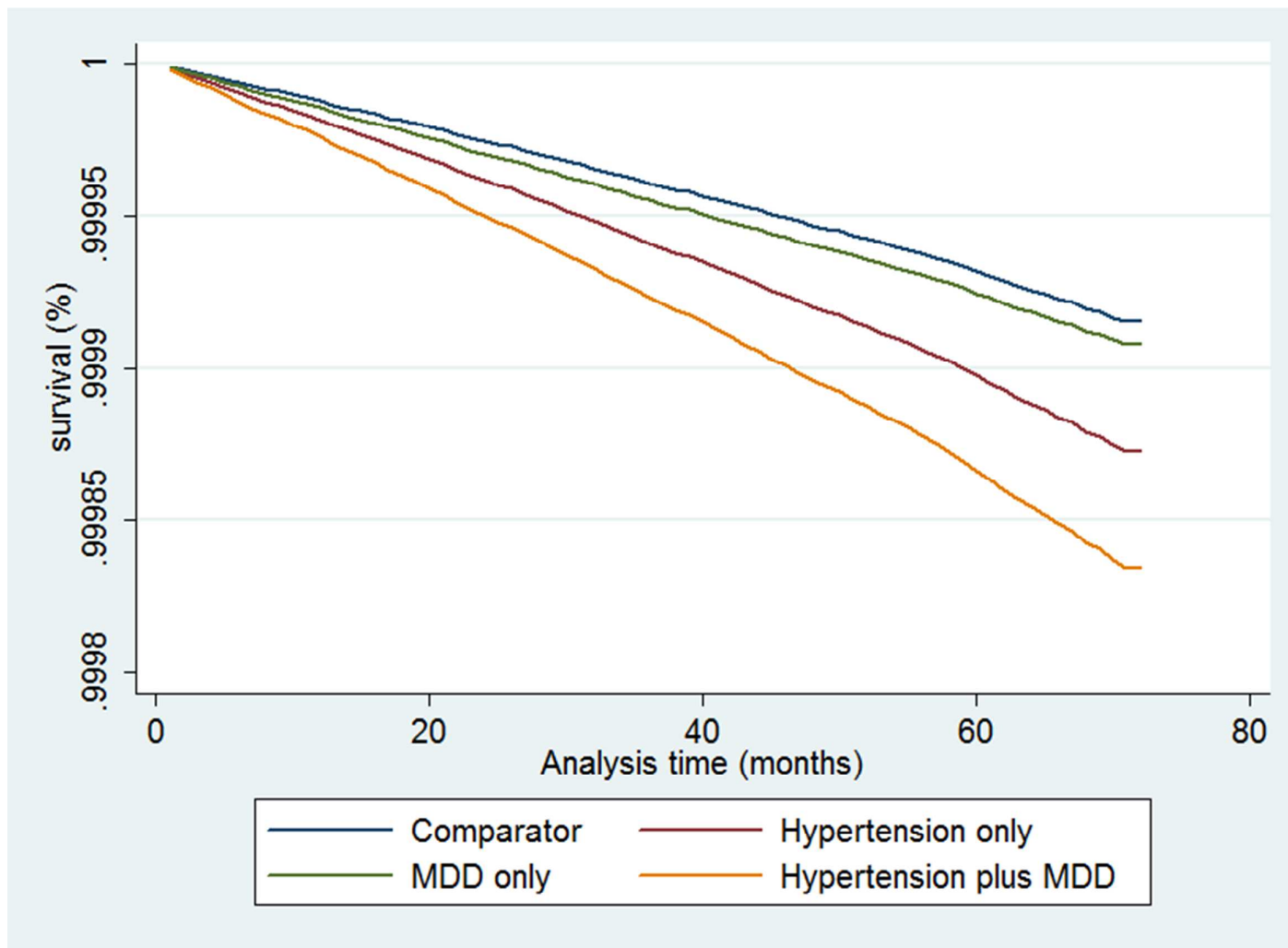
3

4 Fig 2. Log (-log) plot showing non-proportionality of MDD only survival over time. Paths between the comparator group and the MDD group appear to
5 cross at the 22.5 month mark.



6

7 **Fig 3. Adjusted survival analysis graph for stroke outcomes.**



8

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

9 Supplemental Digital Content 1.doc

10

For peer review only

Supplementary information for Impact of major depression on cardiovascular outcomes for individuals with hypertension: prospective study in UK Biobank. Graham et al

METHODS

New-onset cardiovascular outcomes

Date and cause of death were obtained from death certificates held by the National Health Service (NHS) Information Centre for participants from England and Wales and the NHS Central Register Scotland for participants from Scotland. Date and cause of hospital admissions were identified via record linkage to Health Episode Statistics (HES) records for England, the Patient Episode Database for Wales (PEDW) and to the Scottish Morbidity Records (SMR) for Scotland. Detailed information about the record linkage procedure is available online ^{1 2}. At the time of analysis, mortality data were available up to 31st January 2016 for England and Wales and 11th November 2015 for Scotland. Hospital admission data were available for the Scottish, English and Welsh participants until the 31st August 2014, 31st March 2015, and 28th February 2015 respectively. Therefore, for new cardiovascular events, end of follow up was classified as the hospital admission dates unless preceded by the date of death or the date of first cardiovascular event. New onset cardiovascular events were defined as an ICD 10 code of G45, G46, I20- I25, or I6 recorded on a death certificate or hospital admission. Deaths that predated the assessment date were excluded from analysis as presumed errors as were those in which data had only recorded a death date but no cause of death or a cause of death but no death date. Participants that had hospital admissions prior to the assessment date due to the aforementioned ICD10 codes were excluded as were not first episode. In addition, ICD-9 codes 430-438, 410-414, 429 and

1
2
3 429.2 were also excluded. hospital records are not available for the entire lifetime of study
4
5 individuals, potentially missing some early cardiovascular events, as such those with self-
6
7 declared prior cardiovascular disease at baseline were also excluded.
8
9

10 **Blood Pressure**

11
12
13 Blood pressure was measured in a sitting position partway through the interview and at the
14
15 end of the interview using a digital blood pressure monitor (Omron HEM-7015IT.). Full
16
17 protocol is available online <https://biobank.ctsu.ox.ac.uk/crystal/docs/Bloodpressure.pdf>
18
19
20
21
22

23 **Physical activity**

24
25
26 Physical activity was based on self-report, utilising the short form International Physical
27
28 Activity Questionnaire (IPAQ). Participants reported the frequency and duration of
29
30 moderate and vigorous activity along with walking undertaken in a typical week³. Data were
31
32 analysed in accordance with the IPAQ scoring protocol⁴ and total physical activity was
33
34 computed as the sum of walking, moderate and vigorous activity, measured as metabolic
35
36 equivalents (MET-hours/week). Physical activity was used in analyses as a continuous
37
38 variable. Participants who reported greater than 24 hours a day doing all activity were
39
40 classified as missing.
41
42
43
44

45 **Sedentary behaviour**

46
47
48 Sedentary behaviour duration was derived from the sum of self-reported time spent driving,
49
50 using computer and watching television. Those stating that they had performed “less than
51
52 an hour” of sedentary activities were coded as 0.5hrs to allow use of a continuous variable.
53
54
55
56
57
58
59
60

1
2
3 Participants who reported greater than 24 hours a day doing all activity were classified as
4
5 missing.
6

7 **Socio-demographic and other covariates**

8
9
10 Self-report on taking antihypertensive medication was taken from a question specific to
11
12 cardiovascular medications, where antihypertensive medication was an option to respond.
13
14 Area-based socioeconomic status was derived from postcode of residence, utilising the
15
16 census-derived Townsend deprivation index scored on housing, employment, social class
17
18 and car availability where a negative score represents greater affluence^{5 6}. Age was
19
20 calculated from dates of birth and baseline assessment date. Smoking status was
21
22 categorised into never, former and current smoking based on self-report, those who wished
23
24 not to answer were coded as missing. Drink frequency was categorised into daily, three or
25
26 four times a week, once or twice a week, one to three times a month, special occasions
27
28 only, and never based on self-report. Those who wished not to answer were coded as
29
30 missing. Medical history of diabetes and high cholesterol was collected from the self-
31
32 completed, baseline assessment questionnaire of medical conditions. Ethnicity was
33
34 categorised as Caucasian, black/mixed and Asian/mixed based on self-report. Other
35
36 ethnicities coded as missing due to small numbers. Age at completing full-time education
37
38 was categorised as (<16, 16, >16). Height and body weight were measured by trained nurses
39
40 during the initial assessment centre visit. Body mass index (BMI) was calculated as
41
42 $(\text{weight}/\text{height}^2)$ and the WHO criteria⁷ to classify BMI into: underweight <18.5, normal
43
44 weight 18.5-24.9, overweight 25.0-29.9 and obese $\geq 30.0 \text{ kg.m}^{-2}$. Psychotropic medication
45
46 use was defined by the presence of pharmaceuticals from British National Formulary (BNF)
47
48 chapters 4.1.1 to 4.3.4⁸ on self-report medication lists at baseline. Duration of hypertension
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 was calculated utilising age and age of hypertension diagnosis. Antihypertensive medication
4
5 count was calculated as the absolute number of ACE inhibitors, angiotensin II receptor
6
7 antagonists, calcium channel blockers, beta-blockers and thiazide diuretics prescribed to an
8
9 individual. Generic medication names were sought and cross-referenced with the BNF
10
11 chapters 2.2.1, 2.4, 2.5.5 and 2.6.2⁸.
12
13

14 15 16 17 **Statistical analysis:** 18

19
20 A best-fit multivariable regression spline model (stata command “mvr”) was used to find
21
22 the best model to adjust for non-linear covariates. For the adverse cardiovascular outcomes,
23
24 A single knot was fitted for age at age 50 and two knots were fitted for total physical activity
25
26 at 1.65 and 8.062 metabolic equivalent hours. In the male subgroup analysis two knots were
27
28 fitted for total physical activity at 1.7 and 8.507 metabolic equivalent hours, in the female
29
30 subgroup two knots were fitted for total physical activity at 1.57 and 3.75 and two knots
31
32 were fitted at systolic blood pressure 121.5 and 147.5. No bends were noted in any models
33
34 for the stroke outcomes.
35
36
37

38 39 **Model selection and covariate adjustment** 40

41
42 Two continuous variables, age and total physical activity, expressed non-linearity within the main
43
44 analysis and male subgroup analysis for cardiovascular outcomes and as such regression splines
45
46 were used with two and three knots respectively. Two knots were included within the female
47
48 subgroup analysis for physical activity. For stroke outcome there were no bends in the main or sex-
49
50 specific models. Further detail on this is provided in the supplementary digital content.
51
52
53
54
55
56

1
2
3 Within the main analysis for cardiovascular outcomes, the groups of depression only, Asian/Asian
4 British ethnicity and BMI<18.5 covariates failed the proportionality assumption and as such, were
5
6 incorporated into the model as a time varying coefficients. Within the sex specific models depression
7
8 only failed the PH test within the female only analysis and ethnicity and BMI failed within the male
9
10 only analysis. For the stroke outcomes gender and BMI class failed the proportionality assumption
11
12 within the main analysis, with no failures within the sex-specific analysis. Analysis was repeated with
13
14 the hypertension only as the comparator group to assess for any significant difference between the
15
16 co-morbid group and the hypertension only group.
17
18

19 20 **Time varying covariates**

21
22
23 Due to the finding of MDD failing the proportionality assumption in the cardiovascular outcome in
24
25 the primary analysis a series of further analyses have been performed to find when the assumption
26
27 was not met. A log (-log) plot (fig 2) showed the proportionality assumption was broken at 22.5
28
29 months in the fully adjusted model in the primary analysis. As such, separate models were
30
31 performed prior to and after these points. Prior to 22.5months the HR for MDD shows a trend that is
32
33 reduced but insignificant (HR 0.82, 95%CI 0.6 - 1.13), becoming significantly increased after the 22.5
34
35 time point. (HR 1.27, 95%CI 1.06 - 1.52) (Table 9 supplementary digital content). Both stratified
36
37 models passed the proportionality assumption using Schoenfeld residuals. Similar to the major
38
39 analysis, the female model showed the MDD only group failing the proportionality assumption,
40
41 although this was at the 29 month time point. (tables 6 and 10 of the supplementary digital
42
43 content).
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

References

1. Palmer LJ. UK Biobank: bank on it. *Lancet* 2007;369(9578):1980-2. doi: 10.1016/S0140-6736(07)60924-6
2. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *Plos Medicine* 2015;12(3) doi: 10.1371/journal.pmed.1001779
3. Guo W, Bradbury KE, Reeves GK, et al. Physical activity in relation to body size and composition in women in UK Biobank. *Annals of Epidemiology* 2015;25(6):406-13.e6. doi: <http://dx.doi.org/10.1016/j.annepidem.2015.01.015>
4. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Medicine and science in sports and exercise* 2003;35(8):1381-95. doi: 10.1249/01.mss.0000078924.61453.fb [published Online First: 2003/08/06]
5. Townsend P. Deprivation. *Journal of Social Policy* 2009;16(02):125. doi: 10.1017/s0047279400020341
6. Townsend P, Phillimore M, Beattie A. Health and Deprivation: Inequality and the North. London: Croom Helm Ltd 1988.
7. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;894:i-xii, 1-253.
8. COMMITTEE. JF. British National Formulary. 67 ed. London: BMJ Group and Pharmaceutical Press 2014.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

For peer review only

Supplementary Tables and figures

Supplementary Table1: Descriptive analysis for adverse cardiovascular outcome – males only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N= 21570	N = 30142	N = 4169	N = 5253
Median age (range)*	54 (47 - 61)	61 (54 - 65)	53 (46 - 60)	59 (52 - 64)
Ethnicity, N (%)				
<i>White</i>	19562 (90.69%)	27808 (92.26%)	3923 (94.1%)	5001 (95.2%)
<i>Asian/Asian British</i>	863 (4.%)	969 (3.21%)	87 (2.09%)	86 (1.64%)
<i>Black/ Black British</i>	559 (2.59%)	780 (2.59%)	52 (1.25%)	54 (1.03%)
Median Townsend score (range)*	-1.87 (-3.47 - 0.59)	-2.08 (-3.53 - 0.41)	-1.58 (-3.3 - 1.07)	-1.81 (-3.44 - 0.78)
Age at leaving full-time education, N (%)				
<16	2517 (11.67%)	6328 (20.99%)	464 (11.13%)	1005 (19.13%)
16	4473 (20.74%)	6235 (20.69%)	859 (20.6%)	1096 (20.86%)
>16	14344 (66.5%)	17257 (57.25%)	2807 (67.33%)	3118 (59.36%)
Total physical activity in metabolic	4.15 (1.75 - 8.51)	3.99 (1.65 - 8.51)	4.15 (1.7 - 8.36)	3.76 (1.54 - 7.97)

Sedentary time in hours, median (range)*	4.5 (3.5 - 6)	5 (3.5 - 6.5)	5 (3.5 - 6.5)	5 (4 - 7)
Diabetes, N (%)	721 (3.34%)	2401 (7.97%)	159 (3.81%)	477 (9.08%)
Hypercholesterolaemia, N (%)	1614 (7.48%)	5585 (18.53%)	363 (8.71%)	1056 (20.1%)
Systolic BP in mmHg, median (range)*	128 (121.5 - 133.5)	149.5 (142 - 159)	127.5 (120.5 - 133)	148 (141 - 157)
Body Mass Index, N (%)				
<18.5	74 (0.34%)	35 (0.12%)	22 (0.53%)	12 (0.23%)
18.5 – 25	7607 (35.27%)	5842 (19.38%)	1394 (33.44%)	890 (16.94%)
25-30	10594 (49.11%)	15114 (50.14%)	2019 (48.43%)	2532 (48.2%)
>30	3295 (15.28%)	9151 (30.36%)	734 (17.61%)	1819 (34.63%)
Smoking status, N (%)				
Never smoked	12038 (55.81%)	15145 (50.25%)	1999 (47.95%)	2268 (43.18%)
Previously smoked	6777 (31.42%)	12125 (40.23%)	1447 (34.71%)	2295 (43.69%)
Current smoker	2688 (12.46%)	2776 (9.21%)	716 (17.17%)	686 (13.06%)
Alcohol frequency, N (%)				
Daily or almost daily	4822 (22.36%)	8653 (28.71%)	969 (23.24%)	1503 (28.61%)
Three or four times a week	5718 (26.51%)	7913 (26.25%)	1022 (24.51%)	1323 (25.19%)

Once or twice a week	5932 (27.5%)	7546 (25.03%)	1063 (25.5%)	1178 (22.43%)
One to three times a month	2193 (10.17%)	2392 (7.94%)	440 (10.55%)	479 (9.12%)
Special occasions only	1554 (7.2%)	2154 (7.15%)	328 (7.87%)	423 (8.05%)
Never	1343 (6.23%)	1473 (4.89%)	345 (8.28%)	345 (6.57%)
Psychotropic medication, N (%)	398 (1.85%)	670 (2.22%)	678 (16.26%)	879 (16.73%)

Data presented as N (%) except * which are median values (interquartile range). Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ).

Supplementary Table 2: Descriptive analysis for adverse cardiovascular outcome – females only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 29228	N = 25893	N = 10929	N = 7676
Median age (range)*	54 (47 - 61)	61 (55 - 65)	53 (47 - 60)	60 (53 - 64)
Ethnicity, N (%)				
White	26585 (90.96%)	23441 (90.53%)	10324 (94.46%)	7271 (94.72%)
Asian/Asian British	908 (3.11%)	727 (2.81%)	174 (1.59%)	93 (1.21%)
Black/ Black British	764 (2.61%)	989 (3.82%)	167 (1.53%)	168 (2.19%)
Median Townsend score (range)*	-1.90 (-3.44 - 0.51)	-2.06 (-3.5 - 0.38)	-1.66 (-3.3 - 0.84)	-1.87 (-3.4 - 0.74)
Age at leaving full-time education, N (%)				
<16	3399 (11.63%)	5757 (22.23%)	1261 (11.54%)	1602 (20.87%)
16	5792 (19.82%)	5592 (21.6%)	2319 (21.22%)	1636 (21.31%)
>16	19746 (67.56%)	14223 (54.93%)	7283 (66.64%)	4385 (57.13%)
Total physical activity in metabolic	3.87 (1.65 - 7.71)	3.51 (1.37 - 7.59)	3.79 (1.65 - 7.91)	3.65 (1.45 - 7.93)
Sedentary time in hours, median (range)*	4 (3 - 5)	4 (3 - 5.5)	4 (3 - 5.5)	4.5 (3 - 6)

Diabetes, N (%)	547 (1.87%)	1376 (5.31%)	221 (2.02%)	452 (5.89%)
Hypercholesterolaemia, N (%)	1397 (4.78%)	3625 (14.%)	530 (4.85%)	1155 (15.05%)
Systolic BP in mmHg, median (range)*	123.5 (115.5 - 130.5)	149.5 (142 - 160)	122.5 (114.5 - 130)	147.5 (140.5 - 157)
Body Mass Index, N (%)				
<18.5	315 (1.08%)	107 (0.41%)	81 (0.74%)	22 (0.29%)
18.5 – 25	14942 (51.12%)	7836 (30.26%)	4857 (44.44%)	1984 (25.85%)
25-30	9816 (33.58%)	10102 (39.01%)	3917 (35.84%)	2857 (37.22%)
>30	4155 (14.22%)	7848 (30.31%)	2074 (18.98%)	2813 (36.65%)
Smoking status, N (%)				
Never smoked	18588 (63.6%)	16358 (63.18%)	5865 (53.66%)	4186 (54.53%)
Previously smoked	8279 (28.33%)	8015 (30.95%)	3671 (33.59%)	2770 (36.09%)
Current smoker	2282 (7.81%)	1423 (5.5%)	1377 (12.6%)	695 (9.05%)
Alcohol frequency, N (%)				
Daily or almost daily	4628 (15.83%)	4317 (16.67%)	1767 (16.17%)	1378 (17.95%)
Three or four times a week	6457 (22.09%)	5120 (19.77%)	2231 (20.41%)	1514 (19.72%)
Once or twice a week	7712 (26.39%)	6343 (24.5%)	2817 (25.78%)	1738 (22.64%)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

One to three times a month	3859 (13.2%)	3196 (12.34%)	1618 (14.8%)	1033 (13.46%)
Special occasions only	3980 (13.62%)	4176 (16.13%)	1576 (14.42%)	1306 (17.01%)
Never	2581 (8.83%)	2726 (10.53%)	917 (8.39%)	703 (9.16%)
Psychotropic medication, N (%)	943 (3.23%)	1125 (4.34%)	2166 (19.82%)	1643 (21.4%)

Data presented as N (%) except * which are median values (interquartile range). Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ).

Peer review only

Supplementary Table 3: Descriptive analysis for stroke outcome – males only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 22816	N = 32787	N = 4438	N = 5857
Median age (range)*	55 (47 - 62.)	61 (54 - 65)	54 (47 - 61)	60 (53 - 64)
Ethnicity, N (%)				
<i>White</i>	20699 (90.72%)	30219 (92.17%)	4173 (94.03%)	5569 (95.08%)
<i>Asian/Asian British</i>	932 (4.08%)	1116 (3.4%)	102 (2.3%)	105 (1.79%)
<i>Black/ Black British</i>	576 (2.52%)	820 (2.5%)	53 (1.19%)	59 (1.01%)
Median Townsend score (range)*	-1.88 (-3.47 - 0.59)	-2.05 (-3.5 - 0.46)	-1.56 (-3.28 - 1.15)	-1.74 (-3.4 - 0.93)
Age at leaving full-time education, N (%)				
<16	2900 (12.71%)	7256 (22.13%)	558 (12.57%)	1193 (20.37%)
16	4702 (20.61%)	6704 (20.45%)	909 (20.48%)	1222 (20.86%)
>16	14960 (65.57%)	18471 (56.34%)	2930 (66.02%)	3397 (58.%)
Total physical activity in metabolic	4.12 (1.74 - 8.48)	3.96 (1.65 - 8.44)	4.13 (1.67 - 8.36)	3.66 (1.45 - 7.83)
Sedentary time in hours, median (range)*	5 (3.5 - 6)	5 (4 - 7)	5 (3.5 - 6.5)	5 (4 - 7)

Diabetes, N (%)	873 (3.83%)	2951 (9.%)	208 (4.69%)	635 (10.84%)
Hypercholesterolaemia, N (%)	2045 (8.96%)	6736 (20.54%)	457 (10.3%)	1293 (22.08%)
Systolic BP in mmHg, median (range)*	128 (121.5 - 133.5)	149 (142 - 159)	127 (120.5 - 133)	147.5 (140.5 - 156.5)
Body Mass Index, N (%)				
<18.5	79 (0.35%)	39 (0.12%)	22 (0.5%)	12 (0.2%)
18.5 – 25	7867 (34.48%)	6215 (18.96%)	1452 (32.72%)	960 (16.39%)
25-30	11203 (49.1%)	16341 (49.84%)	2142 (48.26%)	2780 (47.46%)
>30	3667 (16.07%)	10192 (31.09%)	822 (18.52%)	2105 (35.94%)
Smoking status, N (%)				
Never smoked	12502 (54.79%)	16054 (48.96%)	2094 (47.18%)	2469 (42.15%)
Previously smoked	7399 (32.43%)	13603 (41.49%)	1582 (35.65%)	2610 (44.56%)
Current smoker	2836 (12.43%)	3013 (9.19%)	754 (16.99%)	770 (13.15%)
Alcohol frequency, N (%)				
Daily or almost daily	5085 (22.29%)	9309 (28.39%)	1021 (23.01%)	1645 (28.09%)
Three or four times a week	6039 (26.47%)	8556 (26.1%)	1077 (24.27%)	1450 (24.76%)
Once or twice a week	6264 (27.45%)	8161 (24.89%)	1121 (25.26%)	1305 (22.28%)

One to three times a month	2307 (10.11%)	2642 (8.06%)	478 (10.77%)	538 (9.19%)
Special occasions only	1666 (7.3%)	2394 (7.3%)	355 (8.%)	503 (8.59%)
Never	1444 (6.33%)	1711 (5.22%)	383 (8.63%)	414 (7.07%)
Psychotropic medication, N (%)	429 (1.88%)	793 (2.42%)	735 (16.56%)	1025 (17.5%)

Data presented as N (%) except * which are median values (interquartile range). Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ).

Supplementary Table 4: Descriptive analysis for stroke outcome – females only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 29684	N = 26937	N = 11143	N = 8090
Median age (range)*	54 (47 - 61)	61 (56 - 65)	53 (47 - 60)	60 (54 - 64)
Ethnicity, N (%)				
White	26998 (90.95%)	24359 (90.43%)	10524 (94.44%)	7643 (94.47%)
Asian/Asian British	925 (3.12%)	773 (2.87%)	178 (1.6%)	104 (1.29%)
Black/ Black British	779 (2.62%)	1034 (3.84%)	170.00 (1.53%)	187 (2.31%)
Median Townsend score (range)*	-1.90 (-3.44 - 0.52)	-2.03 (-3.48 - 0.43)	-1.66 (-3.29 - 0.86)	-1.83 (-3.38 - 0.85)
Age at leaving full-time education, N (%)				
<16	3546 (11.95%)	6140 (22.79%)	1326 (11.9%)	1752 (21.66%)
16	5888 (19.84%)	5803 (21.54%)	2361 (21.19%)	1731 (21.4%)
>16	19954 (67.22%)	14643 (54.36%)	7387 (66.29%)	4550 (56.24%)
Total physical activity in metabolic	3.85 (1.65 - 7.7)	3.49 (1.35 - 7.57)	3.79 (1.65 - 7.89)	3.61 (1.41 - 7.87)

Sedentary time in hours, median (range)*	4.0 (3 - 5)	4.0 (3 - 5.5)	4.0 (3 - 5.5)	4.5 (3 - 6)
Diabetes, N (%)	581 (1.96%)	1551 (5.76%)	241 (2.16%)	528 (6.53%)
Hypercholesterolaemia, N (%)	1547 (5.21%)	4032 (14.97%)	592 (5.31%)	1327 (16.4%)
Systolic BP in mmHg, median (range)*	123.5 (115.5 - 131)	149.5 (142 - 160)	122.5 (114.5 - 130)	147.0 (140.5 - 157)
Body Mass Index, N (%)				
<18.5	316 (1.06%)	112 (0.42%)	82 (0.74%)	26 (0.32%)
18.5 – 25	15100 (50.87%)	8027 (29.8%)	4922 (44.17%)	2057 (25.43%)
25-30	9982 (33.63%)	10476 (38.89%)	4007 (35.96%)	2989 (36.95%)
>30	4286 (14.44%)	8322 (30.89%)	2132 (19.13%)	3018 (37.31%)
Smoking status, N (%)				
Never smoked	18816 (63.39%)	16928 (62.84%)	5958 (53.47%)	4365 (53.96%)
Previously smoked	8452 (28.47%)	8416 (31.24%)	3758 (33.73%)	2950 (36.46%)
Current smoker	2334 (7.86%)	1488 (5.52%)	1409 (12.64%)	749 (9.26%)
Alcohol frequency, N (%)				

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Daily or almost daily	4675	(15.75%)	4442	(16.49%)	1796	(16.12%)	1440	(17.8%)
Three or four times a week	6524	(21.98%)	5271	(19.57%)	2258	(20.26%)	1570	(19.41%)
Once or twice a week	7825	(26.36%)	6558	(24.35%)	2872	(25.77%)	1820	(22.5%)
One to three times a month	3913	(13.18%)	3329	(12.36%)	1644	(14.75%)	1089	(13.46%)
Special occasions only	4078	(13.74%)	4400	(16.33%)	1623	(14.57%)	1382	(17.08%)
Never	2658	(8.95%)	2919	(10.84%)	947	(8.5%)	785	(9.7%)
Psychotropic medication, N (%)	979	(3.3%)	1203	(4.47%)	2241	(20.11%)	1753	(21.67%)

Data presented as N (%) except * which are median values (interquartile range). Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ).

review only

Supplementary Table 5: Risk of adverse cardiovascular event by clinical group, in males only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value
No Hypertension- No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.21	(2.00-2.45)	2.28x10⁻⁵³	1.62	(1.46-1.83)	5.80x10⁻¹⁹	1.29	(1.13-1.47)	1.35x10⁻⁴
MDD only	1.17	(0.95-1.56)	0.12	1.18	(0.95-1.46)	0.12	1.12	(0.9-1.39)	0.3
Hypertension and MDD	2.46	(2.13-2.84)	3.12x10⁻³⁴	1.95	(1.68-2.27)	2.81x10⁻¹⁸	1.47	(1.24-1.74)	8.71x10⁻⁶

*Adjusted for sociodemographic factors (age, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, H.R. =Hazard ratio, C.I.= Confidence interval

Supplementary Table 6: Risk of adverse cardiovascular event by clinical group, in females only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.75	(2.38 - 3.18)	6.16x10⁻⁴³	1.86	(1.6-2.17)	1.43x10⁻¹⁵	1.64	(1.33-2.02)	4.36x10⁻⁶
MDD only	0.67	(0.42-1.08)	0.10	0.72	(0.45-1.17)	0.19	0.68	(0.42-1.1)	0.12
Hypertension and MDD	3.68	(3.1-4.38)	5.62x10⁻⁴⁹	2.78	(1.58-3.29)	4.62x10⁻²⁹	2.18	(1.82-2.92)	4.76x10⁻¹¹
Time varying Variables									
MDD only	1.02	(1.006-1.03)	2.45x10⁻³	1.02	(1.005-1.03)	4.00x10⁻³	1.02	(1.004-1.03)	6.19x10⁻³

*Adjusted for sociodemographic factors (age, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, H.R. =Hazard ratio, C.I.= Confidence interval

Supplementary Table 7: Risk of stroke event by clinical group, in males only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.43	(1.95 - 3.03)	1.92x10⁻¹⁵	1.74	(1.38 - 2.19)	2.58x10⁻⁶	1.19	(0.9 - 1.58)	0.22
MDD only	1.45	(0.96 - 2.2)	0.07	1.65	(1.09 - 2.5)	0.02	1.49	(0.97 - 2.29)	0.07
Hypertension and MDD	2.39	(1.74 - 3.27)	7.34x10⁻⁸	1.87	(1.35 - 2.6)	1.55x10⁻⁴	1.20	(0.83 - 1.74)	0.33

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, H.R. =Hazard ratio, C.I.= Confidence interval

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Supplementary Table 8: Risk of stroke event by clinical group, in females only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.38	(1.84 - 3.09)	6.50x10⁻¹¹	1.51	(1.14 - 1.99)	3.63x10⁻³	1.25	(0.88 - 1.79)	0.21
MDD only	1.09	(0.73 - 1.62)	0.67	1.15	(0.76 - 1.75)	0.51	0.99	(0.64 - 1.53)	0.98
Hypertension and MDD	3.05	(2.22 - 4.21)	8.71x10⁻¹²	2.22	(1.59 - 3.08)	2.27x10⁻⁶	1.62	(1.08 - 2.42)	0.02

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, H.R. =Hazard ratio, C.I.= Confidence interval

Supplementary Table 9: Time stratified analysis by moment of proportional hazards failure for adverse cardiovascular outcomes (stratified at 22.5 months)

Group	Fully adjusted* model pre-22.5 months			Fully adjusted* model post-22.5 months		
	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.36	(1.12 - 1.66)	0.002	1.36	(1.19 - 1.55)	5.06x10⁻⁶
MDD only	0.82	(0.60 - 1.13)	0.22	1.27	(1.06 - 1.52)	0.01
Hypertension and MDD	1.75	(1.39 - 2.21)	2.62x10⁻⁶	1.62	(1.38 - 1.90)	5.72x10⁻⁹

**Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.*

MDD = Major depressive disorder, H.R. =Hazard ratio, C.I.= Confidence interval

Supplementary Table 10: Time stratified analysis by moment of proportional hazards failure for adverse cardiovascular outcomes (females only - stratified at 29 months)

Group	Fully adjusted* model pre-29 months			Fully adjusted* model post-29 months		
	H.R.	95% C.I.	p-value	H.R.	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.49	(1.06 - 2.08)	0.02	1.75	(1.33 - 2.30)	5.56x10 ⁻⁵
MDD only	0.73	(0.48 - 1.10)	0.13	1.58	(1.19 - 2.09)	0.002
Hypertension and MDD	1.80	(1.24 - 2.62)	0.002	2.47	(1.83 - 3.33)	2.89x10 ⁻⁹

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.

MDD = Major depressive disorder, H.R. =Hazard ratio, C.I.= Confidence interval

Supplementary Table 11: Relative excess risk due to interaction results on fully adjusted* models

Analysis	RERI	95% C.I.
Adverse cardiovascular outcome before 22.5 months	0.563	(0.189 - 0.938)
Adverse cardiovascular outcome after 22.5 months	-0.009	(-0.293 - 0.275)
Adverse cardiovascular outcome (males only)	0.058	(-0.240 - 0.357)
Adverse cardiovascular outcome (females only)before 29 months	0.588	(0.074 - 1.103)
Adverse cardiovascular outcome (females only)after 29 months	0.142	(-0.447 - 0.732)
Stroke outcome	-0.047	(-0.485 - 0.391)
Stroke outcome (males only)	-0.480	(-1.195 - 0.234)
Stroke outcome (females only)	0.372	(-0.216 - 0.959)

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.

RERI = Relative excess risk due to interaction, C.I.= Confidence interval

Supplementary Table 12: Comparison of additional hypertension factors (medication and diagnosis duration) across groups

	No Hypertension – No MDD		Hypertension only		MDD only		Hypertension and MDD	
Antihypertensive medication prescription, N (%)	1,265	(2.49)	19,045	(33.99)	476	(3.04)	5,037	(37.34)
Number of antihypertensive medications, N (range)*	1	(1-1)	1	(1-2)	1	(1-1)	1	(1-2)
Reported a duration of hypertension, N (%)	1,376	(2.71)	16,709	(29.82)	678	(4.32)	4,525	(33.55)
Duration of hypertension in years, median (range)*	6	(2-14)	8	(4-13)	6	(3-14)	8	(4 - 14)

*Median quantity of antihypertensive medications and median duration of hypertensive diagnosis presented for those on antihypertensive medications and supplied an age of hypertension diagnosis, respectively. MDD = Major Depressive disorder

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7

1		#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
2				
3				
4	Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
5				
6				
7				
8				
9				
10	Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-8
11				
12				
13				
14				
15				
16				
17				
18	Bias	#9	Describe any efforts to address potential sources of bias	6
19				
20	Study size	#10	Explain how the study size was arrived at	6
21				
22				
23	Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	See note 1
24				
25				
26				
27				
28	Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8-9
29				
30				
31				
32		#12b	Describe any methods used to examine subgroups and interactions	See note 2
33				
34				
35				
36		#12c	Explain how missing data were addressed	6-7
37				
38		#12d	If applicable, explain how loss to follow-up was addressed	1
39				
40				
41		#12e	Describe any sensitivity analyses	9
42				
43	Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	10
44				
45				
46				
47				
48				
49				
50				
51		#13b	Give reasons for non-participation at each stage	6,7
52				
53		#13c	Consider use of a flow diagram	n/a
54				
55				
56	Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	10
57				
58				
59				
60				

		confounders. Give information separately for exposed and unexposed groups if applicable.	
	#14b	Indicate number of participants with missing data for each variable of interest	See note 3
	#14c	Summarise follow-up time (eg, average and total amount)	10
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	6
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
	#16b	Report category boundaries when continuous variables were categorized	n/a
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	See note 4
Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

Author notes

1. 6,7,8,9, supplementary

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

- 1 2. 8-9, supplementary
- 2
- 3 3. n/a (supplementary)
- 4
- 5 4. 11-12, supplemental
- 6

7 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License
8 CC-BY. This checklist was completed on 25. May 2018 using <http://www.goodreports.org/>, a tool
9 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

BMJ Open

Impact of major depression on cardiovascular outcomes for individuals with hypertension: prospective survival analysis in UK Biobank.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024433.R1
Article Type:	Original research
Date Submitted by the Author:	11-Dec-2018
Complete List of Authors:	Graham, Nicholas; University of Glasgow Institute of Health and Wellbeing, Gartnavel Royal Hospital 1055 Great Western Road Glasgow, UK G12 0XH Ward, Joey; University of Glasgow Institute of Health and Wellbeing Mackay, Daniel; University of Glasgow Institute of Health and Wellbeing Pell, J. P.; University of Glasgow Institute of Health and Wellbeing Cavanagh, Jonathan; University of Glasgow Institute of Health and Wellbeing Padmanabhan, Sandosh; University of Glasgow, Institute of Cardiovascular and Medical Sciences, British Heart Foundation Glasgow Cardiovascular Research Centre Smith, Daniel; University of Glasgow, Institute of Health and Wellbeing
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Cardiovascular medicine
Keywords:	EPIDEMIOLOGY, mortality, cardiovascular disease, morbidity, depression, Hypertension < CARDIOLOGY

SCHOLARONE™
Manuscripts

1
2
3 1 **Impact of major depression on cardiovascular outcomes for individuals with hypertension:**
4
5 2 **prospective survival analysis in UK Biobank.**
6
7

8 3 **Short title: Outcomes of Hypertension plus Depression**
9

10
11 4 Nicholas A GRAHAM^{*a}, Clinical Research Fellow
12

13
14 5 Joey WARD^a, Research Fellow
15

16
17 6 Daniel MACKAY^b, Reader in Public Health
18

19
20 7 Jill PELL^b, Professor of Public Health
21

22
23 8 Jonathan CAVANAGH^c, Professor of Psychiatry
24

25
26 9 Sandosh PADMANABHAN^d, Professor of Cardiovascular Genomics and Therapeutics
27

28
29 10 Daniel J. SMITH^a, Professor of Psychiatry.
30

31
32 11 Number of Supplementary files: 1
33

34
35 12 Word count of Manuscript: 3,836 (exc. Tables, references, abstract, summary and Author contribution
36
37 13 statements)
38

39
40 14 Word count of Supplementary file: 1,455 (exc. tables)
41

42
43 15 Number of tables and figures: 18 tables (including 12 in supplementary digital content) and 3 figures
44

45
46 16 ^aInstitute of Health and Wellbeing, University of Glasgow, Gartnavel Royal Hospital, 1055 Great
47

48
49 17 Western Road, Glasgow G12 OXH. ^bInstitute of Health and Wellbeing, University of Glasgow, Public
50

51
52 18 Health, 1 Lilybank Gardens, Glasgow G12 8RZ. ^cInstitute of Health and Wellbeing, Centre for
53

54
55 19 Immunobiology, Sir Graeme Davies Building College of Medical, Veterinary and Life Sciences
56

57
58 20 University of Glasgow. ^dInstitute of Cardiovascular and Medical Sciences, British Heart Foundation
59

60
21 Glasgow Cardiovascular Research centre, University of Glasgow, Glasgow G12 8TA.

1
2
3 22 *corresponding author: nicholas.graham@glasgow.ac.uk, phone: +44 0141 211 3918,
4
5

6 23 **CONFLICTS OF INTEREST:** None.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3 25 **ABSTRACT**
4
5

6 26 **Objectives:** To assess whether a history of major depressive disorder (MDD) in middle-aged
7
8 27 individuals with hypertension influences first-onset cardiovascular disease outcomes.

10 28 **Design:** Prospective cohort survival analysis using Cox proportional hazards regression with a median
11
12 29 follow-up of 63 months (702,902 person-years). Four mutually exclusive groups were compared:
13
14 30 hypertension only (n=56,035), MDD only (n=15,098), comorbid hypertension plus MDD (n=12,929),
15
16 31 and an unaffected (no hypertension, no MDD) comparison group (n=50,798).
17
18

19 32 **Setting:** UK Biobank

21 33 **Participants:** UK Biobank participants without cardiovascular disease aged 37–73 who completed
22
23 34 psychiatric questions relating ICD-10 diagnostic criteria on a touchscreen questionnaire at baseline
24
25 35 interview in 2006–2010 (n=134,860).
26
27

28 36 **Primary and Secondary outcome measures:** First-onset adverse cardiovascular outcomes leading to
29
30 37 hospital admission or death (ICD-10 codes I20-I259, I60-69 and G45- G46), adjusted in a stepwise
31
32 38 manner for sociodemographic, health and lifestyle features. Secondary analyses were performed
33
34 39 looking specifically at stroke outcomes (ICD-10 codes I60-69 and G45- G46) and in models separated
35
36 40 by gender.
37
38

39 41 **Results:** Relative to controls, adjusted hazard ratios (HRs) for adverse cardiovascular outcomes were
40
41 42 increased for the hypertension only group (HR=1.36, 95%CI 1.22-1.52) and were higher still for the
42
43 43 comorbid hypertension plus MDD group (HR=1.66, 95%CI 1.45-1.9). HRs for the comorbid
44
45 44 hypertension plus MDD group were significantly raised compared to hypertension alone (HR=1.22,
46
47 45 95%CI 1.1-1.35). An additive interaction measured using relative excess risk due to interaction
48
49 46 (RERI) was identified at baseline (RERI=0.563, 95%CI 0.189 - 0.938) but not maintained during follow-
50
51 47 up.
52
53

54 48 **Limitations:** Possible selection bias in UK Biobank and inability to assess for levels of medication
55
56 49 adherence.
57
58
59
60

1
2
3 50 **Conclusions:** Comorbid hypertension and MDD conferred greater hazard than hypertension alone
4
5 51 for adverse cardiovascular outcomes, although evidence of an additive interaction between
6
7 52 hypertension and MDD was inconsistent over time. Future cardiovascular risk prediction tools may
8
9 53 benefit from the inclusion of questions about prior history of depressive disorders.
10
11

12 54 Word count of Abstract: 297
13
14

15 55 **Key words:** epidemiology, mortality, morbidity, depression; hypertension, cardiovascular disease
16
17 56

18
19
20 57 Article Summary
21

22 58 **STRENGTHS AND LIMITATIONS**

- 23
24 59 • Methodological advantages over previous studies, including a very large sample size,
25
26 60 adjustment for a more comprehensive range of confounders, and the inclusion of non-fatal
27
28 61 adverse cardiovascular events from hospital admission data and death registry data.
29
30 62 • Definition of prior MDD history was based on ICD-10 diagnostic criteria (rather than a score
31
32 63 on a symptoms questionnaire) and our composite definition of hypertension incorporated
33
34 64 past history, current medication and objective blood pressure measurements.
35
36 65 • Although analyses were adjusted for a broad range of baseline factors (such as smoking
37
38 66 status, BMI, psychotropic medication use and diabetes), we were unable to account for how
39
40 67 these factors may have changed over the course of follow-up, or assess adherence to
41
42 68 cardiovascular medications.
43
44 69 • Trained nurses interviewed UK Biobank participants, but the self-report nature of some of
45
46 70 these data may represent a limitation.
47
48 71 • UK Biobank may have issues with respect to selection biases. For example, individuals with
49
50 72 more severe MDD may have been less likely to volunteer.
51
52
53
54
55
56
57
58
59
60

74 INTRODUCTION

75 By 2030 major depressive disorder (MDD) and cardiovascular disease (CVD) will be the two leading
76 causes of disability worldwide¹. It is established that individuals with MDD are at increased risk of
77 developing CVD and that they experience worse long-term outcomes². To date, studies looking at
78 the interaction between hypertension and MDD have focussed on all-cause death³⁻⁵ cardiovascular
79 death⁵ or incorporated individuals with previous CVD³⁻⁶, and suggested a possible additive
80 interaction between hypertension and MDD on survival^{5 6}. MDD is well known to worsen post-
81 cardiovascular event survival^{6 7}. The risk to first onset cardiovascular is not known. Within this study
82 we look specifically at first onset events, irrespective of whether they lead to death or not.

83 Hypertension is extremely common (affecting 1 billion people worldwide)⁸ and is responsible for
84 50% of all cardiovascular disease⁹. It is commonly comorbid with MDD^{10 11}, with recent meta-analysis
85 showing 27% of individuals with hypertension having MDD¹² and population-based studies showing
86 a hypertension prevalence of 21% in those with MDD¹¹. A biological link has been found by genome-
87 wide association studies, showing calcium-channel genes, important in blood pressure (BP) control
88 and hypertension¹³, also act to increase risk for MDD^{14 15} and bipolar disorder^{16 17}. The sympathetic
89 nervous system (SNS), Renin-angiotensin system, the immune system and the cortisol stress
90 response system are all also implicated in both conditions¹⁸. Medication management of both
91 conditions are also thought to impact one another with side effects of psychotropic medications
92 including raised BP and vice versa¹⁹⁻²¹, although there is contrary evidence suggesting either
93 medication or MDD may in actual fact be protective of hypertension^{20 22}.

94 Here we make use of prospective data from the UK Biobank cohort²³ to test the hypothesis that a
95 lifetime history of MDD in individuals with hypertension (but no previous history of CVD) impacts
96 adversely on first-episode cardiovascular events. We also assess whether MDD exacerbates the
97 effects of hypertension as a risk factor for cardiovascular events. Given the high global prevalence of

1
2
3 98 MDD and hypertension²⁴, this is an important question for public health, which could inform future
4
5 99 treatment approaches for both conditions.
6
7

8 100 **METHODS**

101 **Study design**

102 This was population cohort study using data from UK Biobank. Four mutually exclusive groups
103 (hypertension only, MDD only, hypertension plus MDD, and a comparison group) were compared for
104 adverse CVD outcomes, as well as stroke outcomes

105 **Sample description**

106 UK Biobank is a large population cohort of 502,655 participants recruited between April 2007 and
107 July 2010 from 21 assessment centres located across Great Britain²³. Participants aged 40-69 were
108 invited to take participate if registered with the NHS and lived within a reasonable distance of an
109 assessment centre. At baseline assessment participants completed a series of detailed assessments
110 relating to lifestyle and medical history on touchscreen questionnaire and have a range of physical
111 health measurements, including body mass index (BMI) and BP taken by a nurse. UK Biobank was
112 approved by the North West NHS Multi-Centre Research Ethics Committee and all participants
113 provided written informed consent to participate. This analysis is part of UK Biobank approved
114 application number 7155.

115 During the last two years of recruitment, questions relating to mood disorder features were added
116 to the baseline assessment schedule questionnaire. From the 172,729 participants asked these
117 questions, 134,860 provided sufficient responses to be included in our analysis. We excluded
118 participants from our analyses based on the following *a priori* criteria: a history of bipolar disorder
119 (n=1,831) or schizophrenia (n=262); where there were insufficient data provided by participants to
120 clearly rule out MDD (n= 25,520) or hypertension (n=1,080); and where there were coding errors for
121 date and/or time of death (n=4). These exclusions were based on self-report and criteria from Smith

1
2
3 122 et al. for the psychiatric outcomes where available, or where they responded “don’t know” or
4
5 123 “prefer not to answer” to questions or data was missing that would limit our ability to exclude the
6
7 124 presence of hypertension or MDD. Participants were further excluded from the adverse CVD
8
9 125 outcome if they had a record of CVD prior to recruitment (self-reported angina, myocardial
10
11 126 infarction (MI) or stroke, or previous hospital admission for angina, MI or stroke) (n= 9,172). For the
12
13 127 stroke outcome this exclusion was limited to a record of stroke prior to baseline assessment (self-
14
15 128 report or previous hospital admission for stroke) (n=2,280).

19 129 **Classification of hypertension and MDD**

20
21
22
23 130 Participants were defined as having hypertension if either: *a*) mean BP at baseline was greater than
24
25 131 clinically-defined criteria over two measurements (systolic BP greater than or equal to 140 mmHg or
26
27 132 diastolic BP greater than or equal to 90 mmHg. Where only one reading was available this was used
28
29 133 (n=1,571)); or *b*) self-reported ‘hypertension diagnosed by a doctor’ plus self-report of currently
30
31 134 taking antihypertensive medication. This composite classification was used to ensure that
32
33 135 undiagnosed hypertensive participants were not misclassified and is in line with similar
34
35 136 epidemiological studies^{5 25 26}. The requirement for antihypertensive use in the context of a history of
36
37 137 hypertension was incorporated to limit those on beta-blockers for anxiety. According to these
38
39 138 criteria, n=68,964 participants (51.1% of the sample) had hypertension for the adverse
40
41 139 cardiovascular outcomes analysis and n=73,671 participants (52% of the sample) had hypertension
42
43 140 in the stroke outcome analysis.

44
45
46
47
48 141 A history of lifetime MDD was defined according to the criteria for mood disorders developed by
49
50 142 Smith et al^{27 28} and has been used in further papers²⁸⁻³². (n=28,027 adverse cardiovascular outcomes;
51
52 143 n =29,528 stroke outcomes). This is described in more detail within the supplementary content.
53
54
55 144 For the adverse cardiovascular outcomes, the remainder of the sample, with no history of
56
57
58 145 hypertension or MDD (n=50,798) were classified as a comparator group. The three mutually
59
60

1
2
3 146 exclusive diagnostic groups for this study were therefore: hypertension only (n=56,035); MDD only
4
5 147 (n=15,098) and hypertension plus MDD (n= 12,929). For the stroke outcomes, the mutually exclusive
6
7 148 groups were hypertension only (n=59,724); MDD only (n=15,581) and hypertension plus MDD (n=
8
9 149 13,947) and no hypertension – no MDD (n=52,502).

13 150 **Outcomes**

16 151 The primary outcome was defined as a first-episode cardiovascular event leading to hospital
17
18 152 admission or death, specifically angina, MI, or chronic ischaemic heart disease (ICD-10 codes I20-
19
20 153 I259), and transient ischaemic attack (TIA) or stroke (ICD-10 codes I60-69 and G45- G46). A
21
22 154 secondary outcome was defined as stroke leading to hospital admission or death (ICD-10 codes I60-
23
24 155 69 and G45- G46)³³ due to the strength of relationship hypertension has with this outcome in
25
26 156 particular⁹. Admission data were obtained from Hospital Episode Statistics in England, Patient
27
28 157 Episode Database for Wales and Scottish Morbidity Records in Scotland. Mortality outcomes were
29
30 158 obtained from the National Health Service (NHS) Information Centre for England and Wales and
31
32 159 from the NHS Central Register for Scotland. Individuals who died from a non-cardiovascular
33
34 160 cause/stroke were censored at the time of death but not recorded as having an event. Admission
35
36 161 data were available for Scottish, English and Welsh participants until 31 August 2014, 31 March 2015
37
38 162 and 28 February 2015 respectively. End of follow-up was classified as these dates unless preceded by
39
40 163 date of death or the date of first cardiovascular admission. In total 3,685 (2.73%) participants had a
41
42 164 first-episode cardiovascular event during the follow-up period (total number of all deaths plus non-
43
44 165 fatal cardiovascular events = 5,788) and 910 (0.64%) participants had a first-episode stroke event
45
46 166 (total number of all deaths plus non-fatal stroke events = 7,317).

53 167 **Confounding variables**

54
55 168 Information on potential confounding factors was available for age, sex, socioeconomic status
56
57 169 (Townsend score)³⁴, self-reported ethnicity, age of leaving full-time education, diabetes, body mass
58
59
60

1
2
3 170 index (BMI), systolic BP, hypercholesterolemia, alcohol use, smoking history, sedentary behaviour
4
5 171 (number of hours each day spent sitting at a computer, television or driving), physical activity levels³⁵
6
7 172 and psychotropic medication use. Specific details on these variables are provided in supplementary
8
9
10 173 content.

13 174 **Analyses**

16 175 Baseline characteristics were compared between groups using Chi-squared tests for categorical
17
18 176 variables and Kruskal Wallis for continuous variables. Confounding variables were assessed for
19
20 177 differences in adverse cardiovascular outcomes using log rank sums. For the four groups of interest
21
22 178 we assessed associations with adverse cardiovascular outcomes using Cox proportional hazard
23
24 179 regression and the Efron method for ties³⁶. Models were applied in a staged process in line with
25
26 180 previous studies³⁻⁵ and reported as unadjusted (model one), partially adjusted (model two) and fully
27
28 181 adjusted (model three). Model two adjusted for sociodemographic factors (age, sex, Townsend
29
30 182 score, age of leaving full time education and ethnicity) and model three additionally adjusted for
31
32 183 health and lifestyle factors (diabetes, hypercholesterolemia, BMI, smoking history, alcohol use,
33
34 184 systolic BP, sedentary hours per day, physical activity and psychotropic medication use). The
35
36 185 proportionality of hazard assumption³⁷ was assessed using Schoenfeld residuals³⁷. We compared our
37
38 186 fully adjusted models with results from competing risk analyses using the Fine and Grey approach³⁸,
39
40 187 incorporating non-cardiovascular deaths as a competing event for cardiovascular events, and non-
41
42 188 stroke deaths for stroke events. The relative excess risk due to interaction (RERI)³⁹ was calculated to
43
44 189 assess for additivity in the risk. This was done at each month where the proportionality assumption
45
46 190 for the variables of interest was not met. All analyses were performed with Stata statistical software,
47
48 191 version 12⁴⁰ with the exception of RERI which was calculated using the Microsoft Excel method of
49
50 192 Andersson and colleagues, which allows for comparison of adjusted outcomes⁴¹.
51
52
53
54
55
56
57 193 Psychotropic medication use was included as a confounding variable because of reports that they
58
59 194 may increase risk of mortality⁴² but we also conducted a sensitivity analysis which excluded

1
2
3 195 participants who were taking psychotropic medication. Sub-group analyses looking separately at
4
5 196 hazard ratios (HR) in male and female groups only was also carried out to assess for any gender
6
7 197 specific differences in light of differing rates of depression and adverse cardiovascular events in each
8
9
10 198 gender^{43 27}.

13 199 ***Time-varying coefficients.***

16 200 In the context of Schoenfeld residuals showing non-proportionality, models with time varying
17
18 201 coefficients were used. In addition, log(-log) plots were carried out to find the time point at which
19
20 202 the proportionality assumption failed. Following this, the data will be stratified by time at this time
21
22 203 point, effectively creating two separate survival analyses pre and post the failure time point.

26 204 **Patient involvement**

29
30 205 Although patients were not directly involved with the design of the specific research questions in
31
32 206 this study, the hypotheses tested were developed in the context of clinical experience that
33
34 207 depression and hypertension may interact to impact on CVD. UK Biobank has an active and ongoing
35
36 208 programme of participant involvement: www.ukbiobank.ac.uk/participants/. The outcome
37
38 209 measures used were those provided by the UK Biobank data collection protocol, the design of which
39
40 210 had input from participants. UK Biobank also has a website and social media streams to disseminate
41
42 211 research findings and hosts an annual scientific meeting, which includes cohort participants.

46 212 **RESULTS**

49
50 213 The final sample for adverse cardiovascular outcome included 134,860 participants followed for a
51
52 214 median duration of 63 months (702,901.6 person-years follow-up, mean 62.5 months). Table 1
53
54 215 describes the baseline characteristics of the four groups. In general, the hypertension only and
55
56 216 comorbid hypertension plus MDD groups were older, had higher BMI and were more likely to have
57
58 217 diabetes and hypercholesterolemia. The MDD only and comorbid hypertension plus MDD groups
59
60

1
2
3 218 had a higher proportion of women and were more likely to be current smokers (table 1). Gender-
4
5 219 separated descriptive tables are shown in the supplementary content (Supplementary tables 1 and
6
7
8 220 2).

9
10 221 The sample for stroke-specific outcomes included 141,754 participants followed for a median
11
12 222 duration of 63 months (735247.7 person-years follow-up, mean 62.2 months). Table 2 describes the
13
14 223 baseline characteristics of the four groups which display similar characteristics to the adverse CVD
15
16 224 outcome groups. Gender-separated descriptive tables are shown in the supplementary content
17
18
19 225 (Supplementary tables 3 and 4).

226 **Adverse cardiovascular outcomes**

227 Within the main analysis and the female only subgroup analysis, MDD failed the proportional
228 hazards assumption. Table 3 presents unadjusted and multivariate-adjusted Hazard ratios (aHR) for
229 adverse cardiovascular outcomes. In the fully adjusted model, relative to the comparator group, the
230 aHR for adverse cardiovascular outcomes was significantly raised for hypertension only (aHR=1.36,
231 95%CI 1.22-1.52) and higher still for comorbid hypertension plus MDD (aHR=1.66, 95%CI 1.46-1.9)
232 but reduced for MDD only (aHR=0.55, 95%CI 0.46-0.76). Although this was noted to increase over
233 time as a time-varying coefficient. With the exception of MDD, these findings were robust to
234 sensitivity-analysis excluding those on psychotropic medication (sensitivity analysis aHR=1.43, 95%CI
235 1.27-1.62; aHR=1.72, 95%CI 1.49-1.999, aHR=0.74, 95%CI 0.52-1.06 respectively). Table 4 presents
236 HRs and aHRs for adverse
237 cardiovascular outcomes using the hypertension only group as comparator. In the fully adjusted
238 model, relative to hypertension, the aHR for adverse cardiovascular outcomes was significantly
239 raised for comorbid hypertension plus MDD (aHR=1.22, 95%CI 1.1-1.35, sensitivity-analysis aHR=
240 1.20, 95%CI 1.08-1.34). An adjusted survival plot is shown in figure 1.

1
2
3 241 Within the sub-analysis, the male-only model showed a significant increase in hazard ratio for
4
5 242 hypertension (male aHR 1.29, 95% CI 1.13-1.47) (table 5 of the supplementary digital content) and
6
7 243 comorbid MDD and hypertension (male aHR 1.47, 95%CI 1.24-1.74). However, the difference
8
9 244 between comorbid disease and hypertension only was not statistically significant (aHR 1.14, 95%CI
10
11 245 0.995-1.3). The female only sub-analysis showed an increase in hazard ratio for hypertension (aHR
12
13 246 1.64, 95%CI 1.33-2.02) and a greater increase in comorbid MDD and hypertension (aHR 2.18, 95%CI
14
15 247 1.82-2.92) (table 6 of the supplementary content). The difference between comorbid disease and
16
17 248 hypertension only was also statistically significant (aHR 1.33, 95%CI 1.14- 1.56). Sensitivity analysis
18
19 249 supported these findings.
20
21
22
23

24 250 **Stroke Outcomes**

25
26
27 251 None of the independent variables for stroke outcome failed the proportionality assumption. Table 5
28
29 252 presents HRs and aHRs for stroke outcomes. In the fully adjusted model, the aHR for stroke was
30
31 253 insignificantly raised for hypertension only (aHR=1.21, 95%CI 0.97-1.51) and depression only
32
33 254 (aHR=1.20, 95%CI 0.89-1.63) but significantly raised for comorbid hypertension plus MDD (aHR=1.37,
34
35 255 95%CI 1.04-1.79). In the hypertension comparator group, no group was significantly different from
36
37 256 hypertension only (table 6). Similar trends were shown in the gender subset analysis but not
38
39 257 reaching significance (Tables 7-8 in supplementary digital content). An adjusted survival plot is
40
41 258 shown in figure 2. Again, all results were supported by sensitivity analysis excluding those on
42
43 259 psychotropic medication.
44
45
46
47

48 260 **Relative excess risk due to interaction, time stratified analysis and competing risk analysis**

49
50
51 261 Survival analysis stratified by time is described and included within the supplementary content
52
53 262 (supplementary table 9 and 10 and figure 3). There was evidence of an additive interaction between
54
55 263 hypertension and MDD at baseline for the overall analysis before the 22.5 month time point
56
57 264 (RERI=0.563, 95%CI 0.189 - 0.938). However, after this time point there was no evidence of
58
59
60

1
2
3 265 interaction. Table 11 in the supplementary digital content shows the full results for this analysis.
4
5 266 Competing risk analysis showed no significant difference from the main analyses for cardiovascular
6
7 267 outcomes or stroke outcomes (tables 7-8)
8
9

10
11 268

12 13 14 269 **DISCUSSION**

15
16
17 270 In this large population cohort of middle-aged adults without CVD (adjusted for a broad range of
18
19 271 confounders), individuals with co-morbid hypertension and MDD were at increased risk of adverse
20
21 272 cardiovascular events when compared to those with hypertension alone, MDD alone and neither
22
23 273 condition. There was some evidence of an additive effect between hypertension and MDD at
24
25 274 baseline, but not throughout follow-up or within subgroup analyses. Differences between co-
26
27 275 morbid disease and either disease alone or no disease were more marked in females. For stroke
28
29 276 outcomes, comorbid depression and hypertension was the only group that showed significantly
30
31 277 increased hazard ratios.
32
33

34 35 278 **Previous research**

36
37
38 279 Our findings expand upon previous research from UK Biobank looking at cardiovascular diseases in
39
40 280 those with bipolar disorder and MDD²⁸. It was found that there were significantly increased odds of
41
42 281 having 'any CVD' (fully adjusted OR 1.15 CI 1.12–1.19) or hypertension (fully adjusted OR 1.15 CI
43
44 282 1.13–1.18) if depressed, with even higher odds for stroke (fully adjusted OR 1.26 CI 1.13–1.40).
45
46 283 There are distinct differences between our current paper and the previous publication. Follow-up
47
48 284 data within UK-Biobank has been released to allow meaningful prospective studies be conducted.
49
50 285 Thus, the current paper has the benefits of using hospital records and death certification for
51
52 286 outcomes, rather than self-reported data. We are also able to make inferences about the direction
53
54 287 of effect regarding MDD and CVD and assess the influence of hypertension and MDD over time, both
55
56
57
58
59
60

1
2
3 288 in isolation and when comorbid, and assess for statistical interaction to inform on whether there
4
5 289 may be a biological interaction.
6
7

8 290 Other survival analyses in hypertension/MDD comorbidity have focussed primarily on mortality
9
10 291 outcomes. In the National Health and Nutrition Epidemiologic Follow-up Study in the United States³¹
11
12 292 and the Taiwanese Survey of Health and Living Status³², individuals with self-reported hypertension
13
14 293 plus depressive symptoms (compared to a reference group with neither) had increased all-cause
15
16 294 mortality (aHR=1.39, 95%CI 1.14-1.69, aHR=1.54, 95%CI 1.29-1.83, respectively)³⁴ with the former
17
18 295 also showing increased CVD specific mortality (aHR=1.59, 95%CI 1.08-2.34)⁴. Similarly, Hamer and
19
20 296 colleagues⁵ reported a prospective analysis of common mental disorder on mortality outcomes in
21
22 297 individuals with hypertension versus those without hypertension in participants from the Health
23
24 298 Survey for England and the Scottish Health Survey (1994–2004), finding that risk of CVD death was
25
26 299 highest in the group with comorbid disease.
27
28
29
30

31 **Strengths**

32
33
34 301 These observations are broadly consistent with our results but our study has a number of
35
36 302 methodological advantages, including a very large sample size, adjustment of analyses for a more
37
38 303 comprehensive range of confounders, and a focus on first-episode non-fatal and fatal adverse
39
40 304 cardiovascular events. We also used a definition of prior MDD history which was based on
41
42 305 diagnostic criteria within ICD-10 (rather than a threshold score on a depressive symptoms or general
43
44 306 wellbeing scale) and our composite definition of hypertension incorporated past history, baseline
45
46 307 medication and BP measurements. We believe our lifetime definition to be better suited as it offers
47
48 308 a view depression and depressive symptoms over the course of a lifespan as opposed the past week.
49
50 309 Also, within our current study we were able to exclude those with previous self-declared or hospital
51
52 310 admission CVD, as previous studies show depression may result from cardiovascular disease^{44 45} and
53
54 311 worsen prognosis⁴⁵
55
56
57
58
59
60

312 **Limitations**

313 However, some limitations are acknowledged. Recruitment criteria for UK Biobank may lead to
314 selection bias. Specifically, age-restrictions may lead to underrepresentation of early-onset
315 hypertension and those with more severe MDD may be less inclined to attend for assessment. We
316 also acknowledge limitations with our classifications of MDD and hypertension, which were primarily
317 self-report rather than formal diagnostic assessments. Although we have excluded prior
318 cardiovascular events where possible, the MDD plus hypertension sub-type may capture older
319 individuals with a degree of vascular depression, which has an established association with raised
320 BP⁴⁶. In addition, although we adjust for a host of risk factors at baseline such as smoking status, BMI
321 and psychotropic medication, we are limited by the lack of follow-up data, which could show change
322 and modification of said risk factors over time. Similarly, we were unable to assess for medication
323 adherence and transitions from one investigatory group to another. Such modifications could
324 explain the non-proportional nature of the depression group, which may in itself be a predictor of
325 poor medication adherence⁴⁷. Although adherence to medication was not formally assessed, the
326 number and duration of antihypertensive medications used in the hypertension plus MDD group was
327 the same as for the hypertension only group (supplementary content, table 12). As such, worse
328 outcomes in the MDD plus hypertension group are not explained by less intensive antihypertensive
329 treatment at baseline. The end-points used for stroke and cardiovascular events also require to be
330 further validated, however are in line with previous epidemiological studies⁵ and have been
331 suggested in previous papers in UK Biobank³³. Cardiovascular endpoints have not, to our knowledge,
332 been validated within UKbiobank, however we do not feel that this will bias the results towards any
333 particular group. The amelioration of the aHR suggests other covariates contribute considerably to
334 the risk. This is important in the context of increased rates of diabetes, hypercholesterolemia and
335 obesity along with lower socio-economic status in the hypertension only and comorbid groups and
336 as such it is possible we may be seeing the summation of CV risk factors. Finally, the overall
337 recruitment rate to UK Biobank was low (at around 6%); however, the large final cohort size, the

1
2
3 338 depth and diversity of phenotype data collected at baseline, and the wide sociodemographic
4
5 339 representation of participants all make our findings highly relevant to UK primary care settings.
6
7 340 While UK Biobank participants cannot be used to provide representative disease prevalence and
8
9 341 incidence rates, valid assessment of exposure-disease relationships are nonetheless widely
10
11 342 generalizable and do not require participants to be representative of the UK population at large⁴⁸,
12
13 343 although findings will not be generalizable to other countries.
14
15

16 17 344 **Possible mechanisms**

18
19
20 345 Our finding that a history of MDD, in the context of a current diagnosis of hypertension increased
21
22 346 the risk of first-episode CVD is complicated by the time varying risk that MDD conveys to CVD. Sub-
23
24 347 sample analysis show this time-varying aspect is gender-specific to females. Within our sample, the
25
26 348 MDD group has a slightly reduced BP compared to comparators. Previously, reduced BP has been
27
28 349 put forth as being causative of MDD and therefore reducing CVD risk²⁰, but findings from
29
30 350 longitudinal studies are inconsistent with regards to direction of effect^{49 50}. Potential menopausal
31
32 351 effects are also tempting explanations. Common factors for BP and mood such as neuropeptide Y^{51 52}
33
34 352 may also influence cardiovascular outcomes. Neuropeptide Y has a complex relationship with
35
36 353 oestrogen⁵³ and both have dampening effect on the SNS⁵⁴.
37
38
39
40
41 354 Personality factors may also play a role. MDD correlates highly with neuroticism which, although
42
43 355 inconsistent, may be protective of cardiovascular disease⁵⁵. Conscientiousness traits may lead to
44
45 356 better outcomes⁵⁶ and it is possible that this trait has been selected for within UK Biobank. Despite
46
47 357 this early reduced risk, due to the time varying nature of MDD, MDD has increased risk in the latter
48
49 358 aspects of the time-stratified analyses for the full and female only analyses (supplementary table 9
50
51 359 and 10). The findings from our study in this context suggest MDDs role as a risk factor for
52
53 360 cardiovascular disease and its relationship with blood pressure may be much more complex than
54
55 361 initially thought, in particular within female populations.
56
57
58
59
60

1
2
3 362 We can see in the hypertension only baseline models that comorbid hypertension and depression
4
5 363 convey a significantly greater risk than hypertension alone. Individuals with either hypertension or
6
7 364 depression may have increased sympathetic stimulation that is increased further in comorbid states
8
9
10 365 leading to worse outcomes⁵⁷.

11
12
13 36614
15 367 **CONCLUSIONS**

16
17
18 368 Overall, our findings may have important implications for routine clinical practice, particularly within
19
20 369 primary care settings and further demonstrate the complex relationship between depression and
21
22 370 hypertension. Although evidence of an additive interaction is inconsistent, we found that comorbid
23
24 371 hypertension and depression conferred greater hazard than hypertension alone for adverse
25
26 372 cardiovascular outcomes. This significant finding remained after adjustment for factors such as BMI,
27
28 373 smoking status and diabetes and was robust to sensitivity analysis excluding those on psychotropic
29
30 374 medication. One possible implication is that clinicians should be more aware of the negative long-
31
32 375 term impact on CVD outcomes caused by a history of MDD in the context of hypertension, even in
33
34 376 those with no previous history of CVD. Although this work awaits replication and testing in other
35
36 377 cohorts and settings, further work in this field may suggest that future iterations of CVD risk
37
38 378 prediction tools, such as ASSIGN⁵⁸, would benefit from the addition of a question on whether
39
40 379 individuals have a past history of MDD, so that they can be offered more intensive support to
41
42
43
44
45 380 prevent CVD⁵⁹.

1
2
3 382 **ACKNOWLEDGEMENTS**
4
5

6 383 We are grateful to all participants of the UK Biobank cohort. UK Biobank was established by the
7
8 384 Wellcome Trust, the Medical Research Council, Department of Health, Scottish Government and the
9
10 385 Northwest Regional Development Agency. It has also had funding from the Welsh Assembly
11
12 386 Government and the British Heart Foundation. UK Biobank is hosted by the University of Manchester
13
14 387 and supported by the National Health Service (NHS). NG is supported by the Aitchison Family Clinical
15
16 388 Research Fellowship at the University of Glasgow and DJS is supported by a Lister Institute Prize
17
18 389 Fellowship. JC is supported by the Sackler Trust and the Wellcome Trust. Funding also acknowledged
19
20 390 from MRC Mental Health Data Pathfinder Award to DJS (MC_PC_17217).
21
22
23
24

25 391 **Footnotes**
26
27
28

29 392 **Authors Statement:** Contributors NG, JW, JP, JC, DS, SP and DM, contributed to study design and
30
31 393 writing of the manuscript. JP and DM contributed to data acquisition. NG conducted data processing
32
33 394 and statistical analyses.
34
35

36
37 395 **Funding:** Authors declare no support from any organisation for the submitted work;
38
39

40 396 **Competing interests:** All authors have completed the ICMJE uniform disclosure form at
41
42 397 http://www.icmje.org/coi_disclosure.pdf and no financial relationships with any organisations that
43
44 398 might have an interest in the submitted work in the previous three years; no other relationships or
45
46 399 activities that could appear to have influenced the submitted work.
47
48
49

50 400 **Ethics approval:** This study has been conducted using UK Biobank data. UK Biobank has received
51
52 401 ethics approval from the UK Biobank Research Ethics Committee (ref. 11/NW/0382).
53
54

55
56 402 **Data sharing statement:** The data used in this study are available via a direct application to UK
57
58 403 Biobank.
59
60

1
2
3 404 **Transparency statement:** The lead author affirms that this manuscript is an honest, accurate and
4
5 405 transparent account of the study being reported; that no important aspects of the study have been
6
7 406 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have
8
9
10 407 been explained.
11
12

13 408
14
15

16 409 **COMPETING INTERESTS STATEMENTS**
17

18
19 410 All authors have completed the ICMJE uniform disclosure form at
20
21 411 http://www.icmje.org/coi_disclosure.pdf and no financial relationships with any organisations that
22
23 412 might have an interest in the submitted work in the previous three years; no other relationships or
24
25 413 activities that could appear to have influenced the submitted work.
26
27
28

29 414
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

415 **References**

416

- 417 1. Organization. WH. The global burden of disease: 2004 update. Geneva, Switzerland.: WHO press.
418 2008.
- 419 2. Hare DL, Toukhsati SR, Johansson P, et al. Depression and cardiovascular disease: a clinical review.
420 *Eur Heart J* 2014;35(21):1365-72. doi: 10.1093/eurheartj/eh462
- 421 3. Kuo PL, Pu C. The contribution of depression to mortality among elderly with self-reported
422 hypertension: analysis using a national representative longitudinal survey. *J Hypertens*
423 2011;29(11):2084-90. doi: 10.1097/HJH.0b013e32834b59ad [published Online First:
424 2011/09/22]
- 425 4. Axon RN, Zhao Y, Egede LE. Association of depressive symptoms with all-cause and ischemic heart
426 disease mortality in adults with self-reported hypertension. *Am J Hypertens* 2010;23(1):30-7.
427 doi: 10.1038/ajh.2009.199
- 428 5. Hamer M, Batty GD, Stamatakis E, et al. The combined influence of hypertension and common
429 mental disorder on all-cause and cardiovascular disease mortality. *J Hypertens*
430 2010;28(12):2401-6. doi: 10.1097/HJH.0b013e32833e9d7c
- 431 6. Jani BD, Cavanagh J, Barry SJ, et al. Relationship Between Blood Pressure Values, Depressive
432 Symptoms, and Cardiovascular Outcomes in Patients With Cardiometabolic Disease. *Journal*
433 *of clinical hypertension (Greenwich, Conn)* 2016;18(10):1027-35. doi: 10.1111/jch.12813
434 [published Online First: 2016/04/05]
- 435 7. Taylor CB, Youngblood ME, Catellier D, et al. Effects of antidepressant medication on morbidity
436 and mortality in depressed patients after myocardial infarction. *Arch Gen Psychiatry*
437 2005;62(7):792-8. doi: 10.1001/archpsyc.62.7.792 [published Online First: 2005/07/06]
- 438 8. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide
439 data. *Lancet* 2005;365(9455):217-23. doi: 10.1016/S0140-6736(05)17741-1
- 440 9. Lawes CM, Vander Hoorn S, Rodgers A, et al. Global burden of blood-pressure-related disease,
441 2001. *Lancet* 2008;371(9623):1513-8. doi: 10.1016/S0140-6736(08)60655-8
- 442 10. Meng L, Chen D, Yang Y, et al. Depression increases the risk of hypertension incidence: a meta-
443 analysis of prospective cohort studies. *J Hypertens* 2012;30:842 - 51.
- 444 11. Wu EL, Chien IC, Lin CH, et al. Increased risk of hypertension in patients with major depressive
445 disorder: a population-based study. *J Psychosom Res* 2012;73(3):169-74. doi:
446 10.1016/j.jpsychores.2012.07.002
- 447 12. Li Z, Li Y, Chen L, et al. Prevalence of Depression in Patients With Hypertension: A Systematic
448 Review and Meta-Analysis. *Medicine (Baltimore)* 2015;94(31):e1317. doi:
449 10.1097/md.0000000000001317 [published Online First: 2015/08/08]
- 450 13. Johnson AD, Newton-Cheh C, Chasman DI, et al. Association of hypertension drug target genes
451 with blood pressure and hypertension in 86,588 individuals. *Hypertension* 2011;57(5):903-
452 10. doi: 10.1161/HYPERTENSIONAHA.110.158667
- 453 14. Casamassima F HJ, Fava M, Sachs GS, Smoller JW, Cassano GB, Lattanzi L, Fagerness J, Stange JP,
454 Perlis RH. Phenotypic effects of a bipolar liability gene among individuals with major
455 depressive disorder. . *Am J Med Genet B Neuropsychiatr Genet* 2010;153B:303-09.
- 456 15. Green EK, Grozeva D, Jones I, et al. The bipolar disorder risk allele at CACNA1C also confers risk
457 of recurrent major depression and of schizophrenia. *Molecular Psychiatry* 2010;15(10):1016-
458 22. doi: 10.1038/mp.2009.49
- 459 16. Ferreira MA, O'Donovan MC, Meng YA, et al. Collaborative genome-wide association analysis
460 supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat Genet* 2008;40(9):1056-8.
461 doi: 10.1038/ng.209
- 462 17. Consortium WTCC. Identification of risk loci with shared effects on five major psychiatric
463 disorders: a genome-wide analysis. *The Lancet* 2013;381(9875):1371-79.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 464 18. Scalco AZ, Scalco MZ, Azul JB, et al. Hypertension and depression. *Clinics (Sao Paulo)*
465 2005;60(3):241-50. doi: /S1807-59322005000300010
- 466 19. Boal AH, Smith DJ, McCallum L, et al. Monotherapy With Major Antihypertensive Drug Classes
467 and Risk of Hospital Admissions for Mood Disorders. *Hypertension* 2016;68(5):1132-38. doi:
468 10.1161/hypertensionaha.116.08188 [published Online First: 2016/10/14]
- 469 20. Licht CM, de Geus EJ, Seldenrijk A, et al. Depression is associated with decreased blood pressure,
470 but antidepressant use increases the risk for hypertension. *Hypertension* 2009;53(4):631-8.
471 doi: 10.1161/HYPERTENSIONAHA.108.126698
- 472 21. Crookes DM, Demmer RT, Keyes KM, et al. Depressive Symptoms, Antidepressant Use, and
473 Hypertension in Young Adulthood. *Epidemiology (Cambridge, Mass)* 2018;29(4):547-55. doi:
474 10.1097/ede.0000000000000840 [published Online First: 2018/04/10]
- 475 22. Diminic-Lisica I, Popovic B, Rebic J, et al. Outcome of treatment with antidepressants in patients
476 with hypertension and undetected depression. *Int J Psychiatry Med* 2014;47(2):115-29. doi:
477 10.2190/PM.47.2.c [published Online First: 2014/08/03]
- 478 23. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the
479 causes of a wide range of complex diseases of middle and old age. *PLoS Med*
480 2015;12(3):e1001779. doi: 10.1371/journal.pmed.1001779
- 481 24. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age,
482 and year: findings from the global burden of disease study 2010. *PLoS Med*
483 2013;10(11):e1001547. doi: 10.1371/journal.pmed.1001547
- 484 25. Ong KL, Cheung BM, Man YB, et al. Prevalence, awareness, treatment, and control of
485 hypertension among United States adults 1999-2004. *Hypertension* 2007;49(1):69-75. doi:
486 10.1161/01.hyp.0000252676.46043.18 [published Online First: 2006/12/13]
- 487 26. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of
488 hypertension, 1988-2008. *Jama* 2010;303(20):2043-50. doi: 10.1001/jama.2010.650
489 [published Online First: 2010/05/27]
- 490 27. Smith DJ, Nicholl BI, Cullen B, et al. Prevalence and characteristics of probable major depression
491 and bipolar disorder within UK biobank: cross-sectional study of 172,751 participants. *PLoS*
492 *One* 2013;8(11):e75362. doi: 10.1371/journal.pone.0075362
- 493 28. Martin DJ, Ul-Haq Z, Nicholl BI, et al. Cardiometabolic disease and features of depression and
494 bipolar disorder: population-based, cross-sectional study. *Br J Psychiatry* 2016;208(4):343-
495 51. doi: 10.1192/bjp.bp.114.157784
- 496 29. Ul-Haq Z, Smith DJ, Nicholl BI, et al. Gender differences in the association between adiposity and
497 probable major depression: a cross-sectional study of 140,564 UK Biobank participants. *BMC*
498 *psychiatry* 2014;14:153-53. doi: 10.1186/1471-244X-14-153
- 499 30. Sarkar C, Webster C, Gallacher J. Residential greenness and prevalence of major depressive
500 disorders: a cross-sectional, observational, associational study of 94 879 adult UK Biobank
501 participants. *The Lancet Planetary Health* 2018;2(4):e162-e73. doi:
502 [https://doi.org/10.1016/S2542-5196\(18\)30051-2](https://doi.org/10.1016/S2542-5196(18)30051-2)
- 503 31. Hall LS, Adams MJ, Arnau-Soler A, et al. Genome-wide meta-analyses of stratified depression in
504 Generation Scotland and UK Biobank. *Translational psychiatry* 2018;8(1):9-9. doi:
505 10.1038/s41398-017-0034-1
- 506 32. Howard DM, Adams MJ, Shiri M, et al. Genome-wide association study of depression
507 phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. *Nature*
508 *Communications* 2018;9(1):1470. doi: 10.1038/s41467-018-03819-3
- 509 33. Woodfield R, Grant I, Group UKBSO, et al. Accuracy of Electronic Health Record Data for
510 Identifying Stroke Cases in Large-Scale Epidemiological Studies: A Systematic Review from
511 the UK Biobank Stroke Outcomes Group. *PLOS ONE* 2015;10(10):e0140533. doi:
512 10.1371/journal.pone.0140533
- 513 34. Townsend P. Deprivation. *Journal of Social Policy* 2009;16(02):125. doi:
514 10.1017/s0047279400020341

- 1
2
3 515 35. Guo W, Bradbury KE, Reeves GK, et al. Physical activity in relation to body size and composition
4 516 in women in UK Biobank. *Annals of Epidemiology* 2015;25(6):406-13.e6. doi:
5 517 <http://dx.doi.org/10.1016/j.annepidem.2015.01.015>
6 518 36. Efron B. The Efficiency of Cox's Likelihood Function for Censored Data. *Journal of the American*
7 519 *Statistical Association*, 1977;72(359):557-65.
8 520 37. Schoenfeld D. Partial Residuals for the Proportional Hazards Regression-Model. *Biometrika*
9 521 1982;69(1):239-41. doi: Doi 10.2307/2335876
10 522 38. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk.
11 523 *Journal of the American Statistical Association* 1999;94(446):496-509. doi: 10.2307/2670170
12 524 39. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology*
13 525 (*Cambridge, Mass*) 1992;3(5):452-6. [published Online First: 1992/09/01]
14 526 40. Stata Statistical Software, version 12 [program]. College station, Texas.
15 527 41. Andersson T, Alfredsson L, Kallberg H, et al. Calculating measures of biological interaction.
16 528 *European journal of epidemiology* 2005;20(7):575-9. [published Online First: 2005/08/27]
17 529 42. Weich S, Pearce HL, Croft P, et al. Effect of anxiolytic and hypnotic drug prescriptions on
18 530 mortality hazards: retrospective cohort study. *BMJ* 2014;348:g1996. doi: 10.1136/bmj.g1996
19 531 43. Nichols M, Townsend N, Scarborough P, et al. Cardiovascular disease in Europe 2014:
20 532 epidemiological update. *European Heart Journal* 2014;35(42):2950-59. doi:
21 533 10.1093/eurheartj/ehu299
22 534 44. Kang HJ, Stewart R, Bae KY, et al. Predictive value of homocysteine for depression after acute
23 535 coronary syndrome. *Oncotarget* 2016;7(42):69032-40. doi: 10.18632/oncotarget.11966
24 536 45. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis
25 537 among patients with acute coronary syndrome: systematic review and recommendations: a
26 538 scientific statement from the American Heart Association. *Circulation* 2014;129(12):1350-69.
27 539 doi: 10.1161/CIR.0000000000000019
28 540 46. Aizenstein HJ, Baskys A, Boldrini M, et al. Vascular depression consensus report – a critical
29 541 update. *BMC Medicine* 2016;14(1):161. doi: 10.1186/s12916-016-0720-5
30 542 47. Goldstein CM, Gathright EC, Garcia S. Relationship between depression and medication
31 543 adherence in cardiovascular disease: the perfect challenge for the integrated care team.
32 544 *Patient preference and adherence* 2017;11:547-59. doi: 10.2147/PPA.S127277
33 545 48. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related
34 546 Characteristics of UK Biobank Participants With Those of the General Population. *American*
35 547 *journal of epidemiology* 2017;186(9):1026-34. doi: 10.1093/aje/kwx246 [published Online
36 548 First: 2017/06/24]
37 549 49. Hildrum B, Mykletun A, Holmen J, et al. Effect of anxiety and depression on blood pressure: 11-
38 550 year longitudinal population study. *British Journal of Psychiatry* 2018;193(2):108-13. doi:
39 551 10.1192/bjp.bp.107.045013 [published Online First: 01/02]
40 552 50. Paterniti S. Low blood pressure and risk of depression in the elderly: A prospective community-
41 553 based study. *The British Journal of Psychiatry* 2000;176(5):464-67. doi:
42 554 10.1192/bjp.176.5.464
43 555 51. Zhang P, Qi Y-X, Yao Q-P, et al. Neuropeptide Y Stimulates Proliferation and Migration of Vascular
44 556 Smooth Muscle Cells from Pregnancy Hypertensive Rats via Y1 and Y5 Receptors. *PLOS ONE*
45 557 2015;10(7):e0131124. doi: 10.1371/journal.pone.0131124
46 558 52. Morales-Medina JC, Dumont Y, Quirion R. A possible role of neuropeptide Y in depression and
47 559 stress. *Brain research* 2010;1314:194-205. doi:
48 560 <https://doi.org/10.1016/j.brainres.2009.09.077>
49 561 53. Pelletier G, Li S, Luu-The V, et al. Oestrogenic Regulation of Pro-Opiomelanocortin, Neuropeptide
50 562 Y and Corticotrophin-Releasing Hormone mRNAs in Mouse Hypothalamus. *Journal of*
51 563 *Neuroendocrinology* 2007;19(6):426-31. doi: 10.1111/j.1365-2826.2007.01548.x
52 564 54. Rosano GM, Panina G. Oestrogens and the heart. *Therapie* 1999;54(3):381-5. [published Online
53 565 First: 1999/09/29]

- 1
2
3 566 55. Gale CR, Čukić I, Batty GD, et al. When Is Higher Neuroticism Protective Against Death? Findings
4 567 From UK Biobank. *Psychological Science* 2017;28(9):1345-57. doi:
5 568 10.1177/0956797617709813
6 569 56. Cheng H, Montgomery S, Treglown L, et al. Emotional stability, conscientiousness, and self-
7 570 reported hypertension in adulthood. *Personality and Individual Differences* 2017;115:159-63.
8 571 doi: <https://doi.org/10.1016/j.paid.2016.02.034>
9 572 57. Barton DA, Dawood T, Lambert EA, et al. Sympathetic activity in major depressive disorder:
10 573 identifying those at increased cardiac risk? *J Hypertens* 2007;25(10):2117-24. doi:
11 574 10.1097/HJH.0b013e32829baae7 [published Online First: 2007/09/22]
12 575 58. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to
13 576 cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended
14 577 Cohort (SHHEC). *Heart* 2007;93(2):172-76. doi: 10.1136/hrt.2006.108167
15 578 59. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and
16 579 Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;336(7659):1475-82. doi:
17 580 10.1136/bmj.39609.449676.25
18
19
20
21 581
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

582 Table 1. Baseline characteristics for adverse cardiovascular outcomes

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 50798	N = 56035	N = 15098	N = 12929
Median age (range)*	54 (47 - 61)	61 (55 - 65)	53 (46 - 60)	60 (53 - 64)
Females, N (%)	29228 (57.54%)	25893 (46.21%)	10929 (72.39%)	7676 (59.37%)
Ethnicity, N (%)				
White	46147 (90.84%)	51249 (91.46%)	14247 (94.36%)	12272 (94.92%)
Asian/Asian British	1771 (3.49%)	1696 (3.03%)	261 (1.73%)	179 (1.38%)
Black/ Black British	1323 (2.6%)	1769 (3.16%)	219 (1.45%)	222 (1.72%)
Median Townsend score (range)*	-1.89 (-3.45 - 0.54)	-2.07 (-3.51 - 0.39)	-1.64 (-3.3 - 0.93)	-1.84 (-3.42 - 0.76)
Age at leaving full-time education, N (%)				
<16	5916 (11.65%)	12085 (21.57%)	1725 (11.43%)	2607 (20.16%)
16	10265 (20.21%)	11827 (21.11%)	3178 (21.05%)	2732 (21.13%)
>16	34090 (67.11%)	31480 (56.18%)	10090 (66.83%)	7503 (58.03%)
Total physical activity in metabolic	3.97 (1.68 - 8.03)	3.79 (1.51 - 8.03)	3.89 (1.66 - 8)	3.68 (1.49 - 7.95)
Sedentary time in hours, median (range)*	4 (3 - 6)	4.5 (3.5 - 6)	4.5 (3 - 6)	5 (3.5 - 6)

Diabetes, N (%)	1268 (2.5%)	3777 (6.74%)	380 (2.52%)	929 (7.19%)
Hypercholesterolaemia, N (%)	3011 (5.93%)	9210 (16.44%)	893 (5.91%)	2211 (17.1%)
Systolic BP in mmHg, median (range)*	125.5 (118 - 132)	149.5 (142 - 159.5)	124 (116 - 131)	147.5 (140.5 - 157.)
Body Mass Index, N (%)				
<18.5	389 (0.77%)	142 (0.25%)	103 (0.68%)	34 (0.26%)
18.5 – 25	22549 (44.39%)	13678 (24.41%)	6251 (41.4%)	2874 (22.23%)
25-30	20410 (40.18%)	25216 (45 %)	5936 (39.32%)	5389 (41.68%)
>30	7450 (14.67%)	16999 (30.34%)	2808 (18.6%)	4632 (35.83%)
Smoking status, N (%)				
Never smoked	30626 (60.29%)	31503 (56.22%)	7864 (52.09%)	6454 (49.92%)
Previously smoked	15056 (29.64%)	20140 (35.94%)	5118 (33.9%)	5065 (39.18%)
Current smoker	4970 (9.78%)	4199 (7.49%)	2093 (13.86%)	1381 (10.68%)
Alcohol frequency, N (%)				
Daily or almost daily	9450 (18.6%)	12970 (23.15%)	2736 (18.12%)	2881 (22.28%)
Three or four times a week	12175 (23.97%)	13033 (23.26%)	3253 (21.55%)	2837 (21.94%)
Once or twice a week	13644 (26.86%)	13889 (24.79%)	3880 (25.7%)	2916 (22.55%)

One to three times a month	6052 (11.91%)	5588 (9.97%)	2058 (13.63%)	1512 (11.69%)
Special occasions only	5534 (10.89%)	6330 (11.3%)	1904 (12.61%)	1729 (13.37%)
Never	3924 (7.72%)	4199 (7.49%)	1262 (8.36%)	1048 (8.11%)
Psychotropic medication, N (%)	1341 (2.64%)	1795 (3.2%)	2844 (18.84%)	2522 (19.51%)

583 All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value
 584 of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is
 585 an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households,
 586 households not owner-occupied and unemployment.

Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Peer review only

588 Table 2 Baseline characteristics for stroke outcomes

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 52502	N = 59724	N = 15581	N = 13947
Median age (range)*	54 (47 - 61)	61 (55 - 65)	54 (47 - 61)	60 (53 - 64)
Females, N (%)	29684 (56.54%)	26937 (45.1%)	11143 (71.52%)	8090 (58.01%)
Ethnicity, N (%)				
<i>White</i>	47697 (90.85%)	54578 (91.38%)	14697 (94.33%)	13212 (94.73%)
<i>Asian/Asian British</i>	1857 (3.54%)	1889 (3.16%)	280 (1.8%)	209 (1.5%)
<i>Black/ Black British</i>	1355 (2.58%)	1854 (3.1%)	223 (1.43%)	246 (1.76%)
Median Townsend score (range)*	-1.89 (-3.45 - 0.55)	-2.04 (-3.49 - 0.44)	-1.56 (-3.28 - 1.15)	-1.74 (-3.4 - 0.93)
Age at leaving full-time education, N (%)				
<16	6446 (12.28%)	13396 (22.43%)	1884 (12.09%)	2945 (21.12%)
16	10590 (20.17%)	12507 (20.94%)	3270 (20.99%)	2953 (21.17%)
>16	34914 (66.5%)	33114 (55.45%)	10317 (66.22%)	7947 (56.98%)
Total physical activity in metabolic	3.96 (1.67 - 8.02)	3.75 (1.5 - 8)	4.13 (1.67 - 8.36)	3.66 (1.45 - 7.83)
Sedentary time in hours, median (range)*	4 (3 - 6)	5 (3.5 - 6)	5 (3.5 - 6.5)	5 (4 - 7)

Diabetes, N (%)	1454 (2.77%)	4502 (7.54%)	449 (2.88%)	1163 (8.34%)
Hypercholesterolaemia, N (%)	3592 (6.84%)	10768 (18.03%)	1049 (6.73%)	2620 (18.79%)
Systolic BP in mmHg, median (range)*	125.5 (118 - 132)	149.5 (142 - 159.5)	127 (120.5 - 133)	147.5 (140.5 - 156.5)
Body Mass Index, N (%)				
<18.5	395 (0.75%)	151 (0.25%)	104 (0.67%)	38 (0.27%)
18.5 – 25	22967 (43.75%)	14242 (23.85%)	6374 (40.91%)	3017 (21.63%)
25-30	21185 (40.35%)	26817 (44.9%)	6149 (39.46%)	5769 (41.36%)
>30	7953 (15.15%)	18514 (31.%)	2954 (18.96%)	5123 (36.73%)
Smoking status, N (%)				
Never smoked	31318 (59.65%)	32982 (55.22%)	8052 (51.68%)	6834 (49%)
Previously smoked	15851 (30.19%)	22019 (36.87%)	5340 (34.27%)	5560 (39.87%)
Current smoker	5170 (9.85%)	4501 (7.54%)	2163 (13.88%)	1519 (10.89%)
Alcohol frequency, N (%)				
Daily or almost daily	9760 (18.59%)	13751 (23.02%)	2817 (18.08%)	3085 (22.12%)
Three or four times a week	12563 (23.93%)	13827 (23.15%)	3335 (21.4%)	3020 (21.65%)
Once or twice a week	14089 (26.84%)	14719 (24.65%)	3993 (25.63%)	3125 (22.41%)

One to three times a month	6220 (11.85%)	5971 (10%)	2122 (13.62%)	1627 (11.67%)
Special occasions only	5744 (10.94%)	6794 (11.38%)	1978 (12.69%)	1885 (13.52%)
Never	4102 (7.81%)	4630 (7.75%)	1330 (8.54%)	1199 (8.6%)
Psychotropic medication, N (%)	1408 (2.68%)	1996 (3.34%)	2976 (19.1%)	2778 (19.92%)

589 All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value
 590 of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is
 591 an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households,
 592 households not owner-occupied and unemployment.

594 Table 3: Risk of adverse cardiovascular event by clinical group: unadjusted, partially adjusted and fully adjusted models.

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.60	(2.39 - 2.82)	3.31x10 ⁻¹¹³	1.72	(1.57 - 1.88)	1.99x10 ⁻³³	1.36	(1.22 - 1.52)	2.92x10 ⁻⁸
MDD only	0.69	(0.51 - 0.94)	0.02	0.82	(0.6 - 1.13)	0.23	0.75	(0.54 - 1.04)	0.08
Hypertension and MDD	2.84	(2.55 - 3.17)	6.31x10 ⁻⁷⁷	2.27	(2.02 - 2.55)	2.75x10 ⁻⁴⁴	1.66	(1.45 - 1.9)	7.48x10 ⁻¹⁴
Time varying Variables									
MDD only	1.01	(1.004 - 1.02)	2.38x10 ⁻³	1.01	(1.004 - 1.02)	3.19x10 ⁻³	1.01	(1.004 - 1.02)	3.03x10 ⁻³

595

596 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of

597 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and

598 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

bmjopen-2018-024443 on 30 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 26, 2024 by guest. Protected by copyright.

Table 4: Risk of adverse cardiovascular event by clinical group: unadjusted, partially adjusted and fully adjusted models with hypertension as the comparator

Group	Unadjusted			Model 1 - Sociodemographic			Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
<i>Hypertension only</i>	1(ref)			1(ref)			1(ref)		
<i>No Hypertension - No MDD</i>	0.38	(0.35 - 0.42)	3.31x10 ⁻¹¹³	0.58	(0.53 - 0.63)	1.99x10 ⁻³³	0.73	(0.66 - 0.82)	2.92x10 ⁻⁸
<i>MDD only</i>	0.27	(0.2 - 0.36)	1.14x10 ⁻¹⁷	0.48	(0.35 - 0.66)	4.91x10 ⁻⁶	0.55	(0.4 - 0.76)	3.23x10 ⁻⁴
<i>Hypertension and MDD</i>	1.09	(0.996 - 1.2)	0.06	1.32	(1.2 - 1.46)	3.07x10 ⁻⁸	1.22	(1.1 - 1.35)	1.30x10 ⁻⁴
Time varying Variables									
<i>MDD only</i>	1.01	(1.004 - 1.02)	0.002	1.01	(1.004 - 1.02)	3.19x10 ⁻³	1.01	(1.004 - 1.02)	3.03x10 ⁻³

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

606 Table 5: Risk of stroke event by clinical group: unadjusted, partially adjusted and fully adjusted models.

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension- No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.55	(2.16 - 3.02)	3.84x10 ⁻²⁸	1.64	(1.38 - 1.96)	3.35x10 ⁻⁸	1.21	(0.97 - 1.51)	0.09
MDD only	1.14	(0.86 - 1.52)	0.37	1.37	(1.02 - 1.84)	0.037	1.20	(0.89 - 1.63)	0.24
Hypertension and MDD	2.67	(2.13 - 3.34)	9.79x10 ⁻¹⁸	2.05	(1.63 - 2.58)	1.08x10 ⁻⁹	1.37	(1.04 - 1.79)	0.02

607 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of
 608 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
 609 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

610

612 Table 6: Risk of stroke event by clinical group: unadjusted, partially adjusted and fully adjusted models with hypertension as the comparator

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
<i>Hypertension only</i>	1(ref)			1(ref)			1(ref)		
<i>No Hypertension - No MDD</i>	0.39	(0.33 - 0.46)	3.84x10 ⁻²⁸	0.61	(0.51 - 0.73)	3.35x10 ⁻⁸	0.82	(0.66 - 1.03)	0.09
<i>MDD only</i>	0.45	(0.34 - 0.58)	1.43x10 ⁻⁹	0.83	(0.63 - 1.1)	0.19	0.99	(0.73 - 1.35)	0.95
<i>Hypertension and MDD</i>	1.05	(0.86 - 1.27)	0.64	1.25	(1.03 - 1.52)	0.03	1.13	(0.92 - 1.39)	0.26

613 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of
614 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
615 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

616

617 Table 7: Fully adjusted HR compared with results from competing risks analysis for cardiovascular endpoints

Fully adjusted non-competing risks analysis Fully adjusted competing risks model

Group	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.36	(1.22- 1.52)	2.92x10 ⁻⁸	1.37	(1.22-1.53)	4 x10 ⁻⁸
MDD only	0.75	(0.54- 1.04)	0.08	0.76	(0.55-1.03)	0.08
Hypertension and MDD	1.66	(1.45- 1.9)	7.48x10 ⁻¹⁴	1.67	(1.45-1.91)	2.2 x10 ⁻¹³
tvc						
MDD only	1.01	(1.004- 1.02)	3.03x10 ⁻³	1.01	(1.004-1.02)	0.003

618 Adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking
 619 history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder,
 620 aHR = Adjusted hazard ratio, C.I. = Confidence interval.

bmjopen-2018-024433 on 30 September 2019. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

621 Table 8: Fully adjusted HR compared with results from competing risks analysis for stroke endpoints

Fully adjusted non-competing risks analysis **Fully adjusted competing risks model**

Group	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.21	(0.97- 1.51)	0.09	1.21	(0.96- 1.52)	0.1
MDD only	1.20	(0.89- 1.63)	0.24	1.20	(0.88- 1.64)	0.25
Hypertension and MDD	1.37	(1.04- 1.79)	0.02	1.36	(1.03- 1.8)	0.031

622 *Adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking*
 623 *history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder,*
 624 *aHR = Adjusted hazard ratio, C.I. = Confidence interval.*

625

626 Figure 1: Adjusted survival analysis graph for adverse cardiovascular outcome showing greatest hazard for the comorbid group. MDD appears protective compared to the
 627 comparator group initially, however, shows increased hazard after 41 months. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and
 628 ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
 629 psychotropic medication use (MDD = Major Depressive disorder)

630

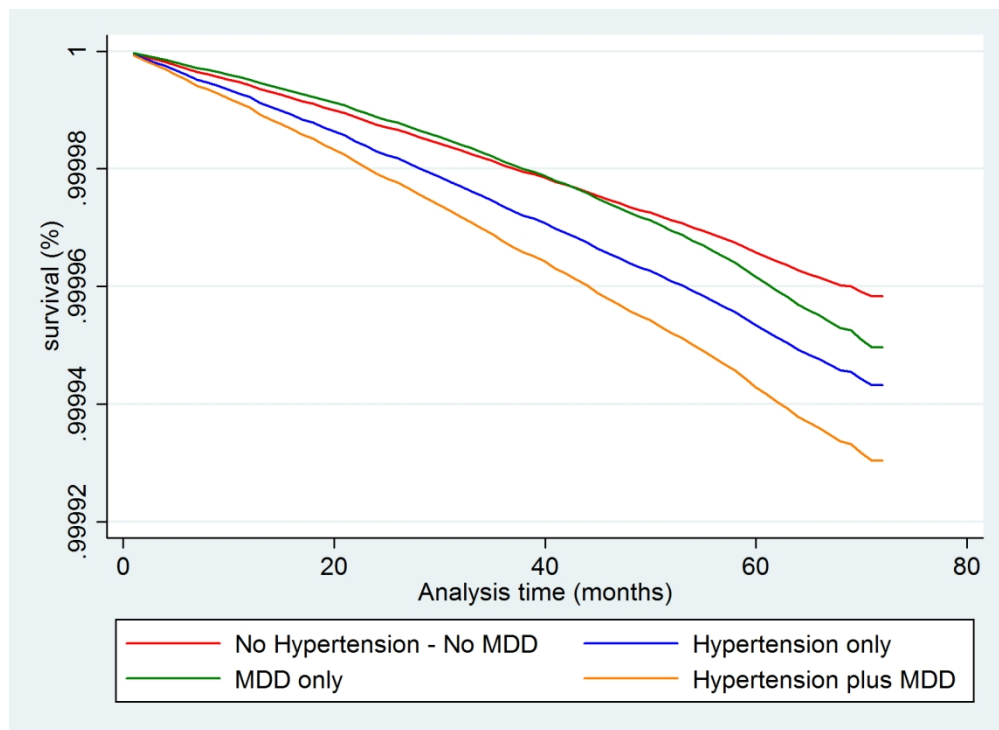
631 Figure 2: Adjusted survival analysis graph for stroke outcomes showing significantly increased hazard for comorbid Hypertension and MDD, with similar insignificant
 632 increased hazard trends for hypertension only and MDD only. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of
 633 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic
 634 medication use. (MDD = Major Depressive disorder)

1
2
3 635
4 636
5 637
6 638
7 639
8 640
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Figure 3: Log (-log) plot showing non-proportionality of MDD only survival over time. Paths between the comparator group and the MDD group cross at the 22.5 month mark. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. (MDD = Major Depressive disorder)

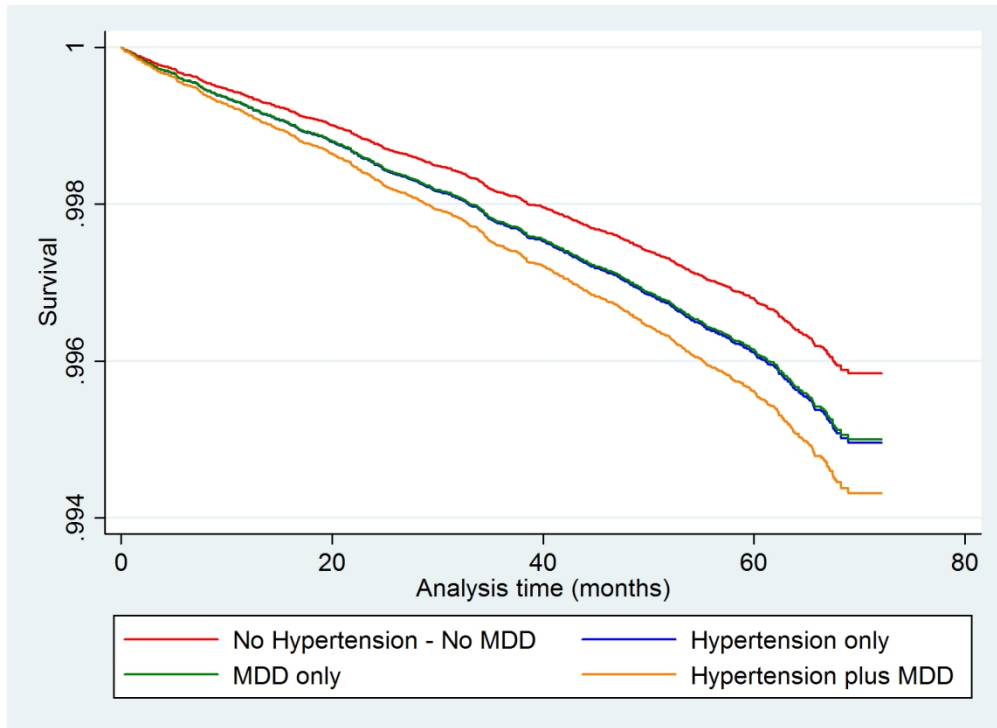
For peer review only

bmjopen-2018-024433 on 20 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.



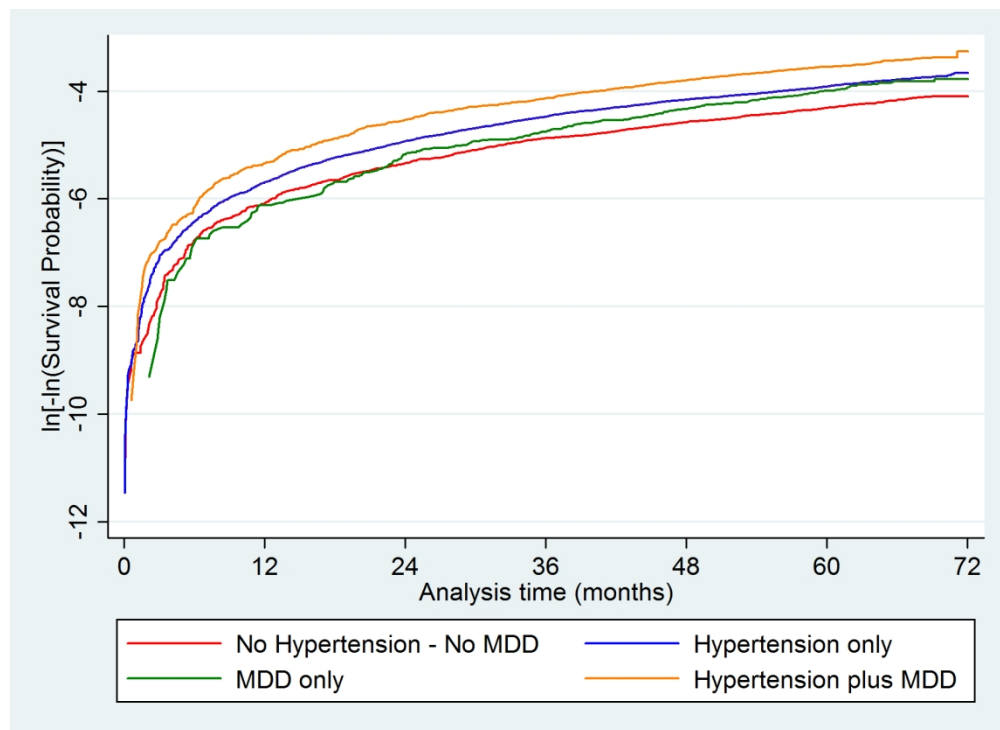
Adjusted survival analysis graph for adverse cardiovascular outcome showing greatest hazard for the comorbid group. MDD appears protective compared to the comparator group initially, however, shows increased hazard after 41 months. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use (MDD = Major Depressive disorder)

152x110mm (300 x 300 DPI)



Adjusted survival analysis graph for stroke outcomes showing significantly increased hazard for comorbid Hypertension and MDD, with similar insignificant increased hazard trends for hypertension only and MDD only. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. (MDD = Major Depressive disorder)

152x110mm (300 x 300 DPI)



Log (-log) plot showing non-proportionality of MDD only survival over time. Paths between the comparator group and the MDD group cross at the 22.5 month mark. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. (MDD = Major Depressive disorder)

152x110mm (300 x 300 DPI)

1
2
3 **Supplementary information for Impact of major depression on cardiovascular outcomes for**
4 **individuals with hypertension: prospective study in UK Biobank. Graham et al**
5
6
7

8 **METHODS**
9

10
11 **New-onset cardiovascular outcomes**
12

13
14
15 Date and cause of death were obtained from death certificates held by the National Health
16 Service (NHS) Information Centre for participants from England and Wales and the NHS
17 Central Register Scotland for participants from Scotland. Date and cause of hospital
18 admissions were identified via record linkage to Health Episode Statistics (HES) records for
19 England, the Patient Episode Database for Wales (PEDW) and to the Scottish Morbidity
20 Records (SMR) for Scotland. Detailed information about the record linkage procedure is
21 available online ¹². At the time of analysis, mortality data were available up to 31st January
22 2016 for England and Wales and 11th November 2015 for Scotland. Hospital admission data
23 were available for the Scottish, English and Welsh participants until the 31st August 2014,
24 31st March 2015, and 28th February 2015 respectively. Therefore, for new cardiovascular
25 events, end of follow up was classified as the hospital admission dates unless preceded by
26 the date of death or the date of first cardiovascular event. New onset cardiovascular events
27 were defined as an ICD 10 code of G45, G46, I20- I25, or I6 recorded on a death certificate
28 or hospital admission. Deaths that predated the assessment date were excluded from
29 analysis as presumed errors as were those in which data had only recorded a death date but
30 no cause of death or a cause of death but no death date. Participants that had hospital
31 admissions prior to the assessment date due to the aforementioned ICD10 codes were
32 excluded as were not first episode. In addition, ICD-9 codes 430-438, 410-414, 429 and
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 429.2 were also excluded. hospital records are not available for the entire lifetime of study
4
5 individuals, potentially missing some early cardiovascular events, as such those with self-
6
7 declared prior cardiovascular disease at baseline were also excluded.
8
9

10 11 **Blood Pressure**

12
13
14 Blood pressure was measured in a sitting position partway through the interview and at the
15
16 end of the interview using a digital blood pressure monitor (Omron HEM-7015IT.). Full
17
18 protocol is available online <https://biobank.ctsu.ox.ac.uk/crystal/docs/Bloodpressure.pdf>
19
20
21

22 23 24 25 **Depression definition**

26
27
28 The criteria for lifetime MDD were created via the the following questions via touchscreen
29
30 questionnaire were: *"Looking back over your life, have you ever had a time when you were feeling*
31
32 *depressed or down for at least a whole week?"* (depression); *"Have you ever had a period of time*
33
34 *lasting at least two days when you were so irritable that you found yourself shouting at people or*
35
36 *starting fights or arguments?"* (irritability); *"How many weeks was the longest period when you were*
37
38 *feeling depressed or down?"* (duration); *"Have you ever seen a general practitioner (GP) for nerves,*
39
40 *anxiety, tension or depression?"* (consulted GP); *"Have you ever seen a psychiatrist for nerves,*
41
42 *anxiety, tension or depression?"* (consulted psychiatrist). Participants were classified as having a
43
44 history of MDD if they reported at least one episode which comprised of depression and/or
45
46 irritability, with a duration of at least two weeks, plus had consulted with either a general
47
48 practitioner or psychiatrist for mental ill-health.
49
50
51

52 53 **Physical activity**

54
55
56 Physical activity was based on self-report, utilising the short form International Physical
57
58 Activity Questionnaire (IPAQ). Participants reported the frequency and duration of
59
60

1
2
3 moderate and vigorous activity along with walking undertaken in a typical week³. Data were
4
5 analysed in accordance with the IPAQ scoring protocol⁴ and total physical activity was
6
7 computed as the sum of walking, moderate and vigorous activity, measured as metabolic
8
9 equivalents (MET-hours/week). Physical activity was used in analyses as a continuous
10
11 variable. Participants who reported greater than 24 hours a day doing all activity were
12
13 classified as missing.
14
15
16

17 18 **Sedentary behaviour**

19
20
21 Sedentary behaviour duration was derived from the sum of self-reported time spent driving,
22
23 using computer and watching television. Those stating that they had performed “less than
24
25 an hour” of sedentary activities were coded as 0.5hrs to allow use of a continuous variable.
26
27 Participants who reported greater than 24 hours a day doing all activity were classified as
28
29 missing.
30
31
32

33 34 **Socio-demographic and other covariates**

35
36 Self-report on taking antihypertensive medication was taken from a question specific to
37
38 cardiovascular medications, where antihypertensive medication was an option to respond.
39
40 Area-based socioeconomic status was derived from postcode of residence, utilising the
41
42 census-derived Townsend deprivation index scored on housing, employment, social class
43
44 and car availability where a negative score represents greater affluence^{5 6}. Age was
45
46 calculated from dates of birth and baseline assessment date. Smoking status was
47
48 categorised into never, former and current smoking based on self-report, those who wished
49
50 not to answer were coded as missing. Drink frequency was categorised into daily, three or
51
52 four times a week, once or twice a week, one to three times a month, special occasions
53
54 only, and never based on self-report. Those who wished not to answer were coded as
55
56
57
58
59
60

1
2
3 missing. Medical history of diabetes and high cholesterol was collected from the self-
4 completed, baseline assessment questionnaire of medical conditions. Ethnicity was
5
6 categorised as Caucasian, black/mixed and Asian/mixed based on self-report. Other
7
8 ethnicities coded as missing due to small numbers. Age at completing full-time education
9
10 was categorised as (<16, 16, >16). Height and body weight were measured by trained nurses
11
12 during the initial assessment centre visit. Body mass index (BMI) was calculated as
13
14 (weight/height²) and the WHO criteria⁷ to classify BMI into: underweight <18.5, normal
15
16 weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.0 kg.m⁻². Psychotropic medication
17
18 use was defined by the presence of pharmaceuticals from British National Formulary (BNF)
19
20 chapters 4.1.1 to 4.3.4⁸ on self-report medication lists at baseline. Duration of hypertension
21
22 was calculated utilising age and age of hypertension diagnosis. Antihypertensive medication
23
24 count was calculated as the absolute number of ACE inhibitors, angiotensin II receptor
25
26 antagonists, calcium channel blockers, beta-blockers and thiazide diuretics prescribed to an
27
28 individual. Generic medication names were sought and cross-referenced with the BNF
29
30 chapters 2.2.1, 2.4, 2.5.5 and 2.6.2⁸.
31
32
33
34
35
36
37
38
39
40
41
42

43 **Statistical analysis:**

44
45
46 A best-fit multivariable regression spline model (stata command “mvr”) was used to find
47
48 the best model to adjust for non-linear covariates. For the adverse cardiovascular outcomes,
49
50 A single knot was fitted for age at age 50 and two knots were fitted for total physical activity
51
52 at 1.65 and 8.062 metabolic equivalent hours. In the male subgroup analysis two knots were
53
54 fitted for total physical activity at 1.7 and 8.507 metabolic equivalent hours, in the female
55
56 subgroup two knots were fitted for total physical activity at 1.57 and 3.75 and two knots
57
58
59
60

1
2
3 were fitted at systolic blood pressure 121.5 and 147.5. No bends were noted in any models
4
5
6 for the stroke outcomes.
7

8 9 **Model selection and covariate adjustment**

10
11 All variables were tested against outcome measures (cardiovascular outcomes and stroke outcomes)
12
13 using univariate analysis to assess appropriateness for inclusion in the final model. All covariates
14
15 were significantly associated with the outcomes. and were Two continuous variables, age and total
16
17 physical activity, expressed non-linearity within the main analysis and male subgroup analysis for
18
19 cardiovascular outcomes and as such regression splines were used with two and three knots
20
21 respectively. Two knots were included within the female subgroup analysis for physical activity. For
22
23 stroke outcome there were no bends in the main or sex-specific models.
24
25
26

27
28 Within the main analysis for cardiovascular outcomes, the groups of depression only, Asian/Asian
29
30 British ethnicity and BMI<18.5 covariates failed the proportionality assumption and as such, were
31
32 incorporated into the model as a time varying coefficients. Within the sex specific models depression
33
34 only failed the PH test within the female only analysis and ethnicity and BMI failed within the male
35
36 only analysis. For the stroke outcomes gender and BMI class failed the proportionality assumption
37
38 within the main analysis, with no failures within the sex-specific analysis. Analysis was repeated with
39
40 the hypertension only as the comparator group to assess for any significant difference between the
41
42 co-morbid group and the hypertension only group.
43
44
45

46 47 **Time varying covariates**

48
49
50 Due to the finding of MDD failing the proportionality assumption in the cardiovascular outcome in
51
52 the primary analysis a series of further analyses have been performed to find when the assumption
53
54 was not met. A log (-log) plot (fig 3) showed the proportionality assumption was broken at 22.5
55
56 months in the fully adjusted model in the primary analysis. As such, separate models were
57
58
59
60

1
2
3 performed prior to and after these points. Prior to 22.5months the HR for MDD shows a trend that is
4 reduced but insignificant (HR 0.82, 95%CI 0.6 - 1.13), becoming significantly increased after the 22.5
5 time point. (HR 1.27, 95%CI 1.06 - 1.52) (Table 9 supplementary digital content). Both stratified
6 models passed the proportionality assumption using Schoenfeld residuals. Similar to the major
7 analysis, the female model showed the MDD only group failing the proportionality assumption,
8 although this was at the 29 month time point. (tables 6 and 10 of the supplementary digital
9 content).

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

References

1. Palmer LJ. UK Biobank: bank on it. *Lancet* 2007;369(9578):1980-2. doi: 10.1016/S0140-6736(07)60924-6
2. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *Plos Medicine* 2015;12(3) doi: 10.1371/journal.pmed.1001779
3. Guo W, Bradbury KE, Reeves GK, et al. Physical activity in relation to body size and composition in women in UK Biobank. *Annals of Epidemiology* 2015;25(6):406-13.e6. doi: <http://dx.doi.org/10.1016/j.annepidem.2015.01.015>
4. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Medicine and science in sports and exercise* 2003;35(8):1381-95. doi: 10.1249/01.mss.0000078924.61453.fb [published Online First: 2003/08/06]
5. Townsend P. Deprivation. *Journal of Social Policy* 2009;16(02):125. doi: 10.1017/s0047279400020341
6. Townsend P, Phillimore M, Beattie A. Health and Deprivation: Inequality and the North. London: Croom Helm Ltd 1988.
7. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;894:i-xii, 1-253.
8. COMMITTEE. JF. British National Formulary. 67 ed. London: BMJ Group and Pharmaceutical Press 2014.

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Supplementary Tables and figures

Supplementary Table1: Descriptive analysis for adverse cardiovascular outcome – males only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N= 21570	N = 30142	N = 4169	N = 5253
Median age (range)*	54 (47 - 61)	61 (54 - 65)	53 (46 - 60)	59 (52 - 64)
Ethnicity, N (%)				
<i>White</i>	19562 (90.69%)	27808 (92.26%)	3923 (94.1%)	5001 (95.2%)
<i>Asian/Asian British</i>	863 (4.%)	969 (3.21%)	87 (2.09%)	86 (1.64%)
<i>Black/ Black British</i>	559 (2.59%)	780 (2.59%)	52 (1.25%)	54 (1.03%)
Median Townsend score (range)*	-1.87 (-3.47 - 0.59)	-2.08 (-3.53 - 0.41)	-1.58 (-3.3 - 1.07)	-1.81 (-3.44 - 0.78)
Age at leaving full-time education, N (%)				
<i><16</i>	2517 (11.67%)	6328 (20.99%)	464 (11.13%)	1005 (19.13%)
<i>16</i>	4473 (20.74%)	6235 (20.69%)	859 (20.6%)	1096 (20.86%)
<i>>16</i>	14344 (66.5%)	17257 (57.25%)	2807 (67.33%)	3118 (59.36%)
Total physical activity in metabolic	4.15 (1.75 - 8.51)	3.99 (1.65 - 8.51)	4.15 (1.7 - 8.36)	3.76 (1.54 - 7.97)

Sedentary time in hours, median (range)*	4.5 (3.5 - 6)	5 (3.5 - 6.5)	5 (3.5 - 6.5)	5 (4 - 7)
Diabetes, N (%)	721 (3.34%)	2401 (7.97%)	159 (3.81%)	477 (9.08%)
Hypercholesterolaemia, N (%)	1614 (7.48%)	5585 (18.53%)	363 (8.71%)	1056 (20.1%)
Systolic BP in mmHg, median (range)*	128 (121.5 - 133.5)	149.5 (142 - 159)	127.5 (120.5 - 133)	148 (141 - 157)
Body Mass Index, N (%)				
<18.5	74 (0.34%)	35 (0.12%)	22 (0.53%)	12 (0.23%)
18.5 – 25	7607 (35.27%)	5842 (19.38%)	1394 (33.44%)	890 (16.94%)
25-30	10594 (49.11%)	15114 (50.14%)	2019 (48.43%)	2532 (48.2%)
>30	3295 (15.28%)	9151 (30.36%)	734 (17.61%)	1819 (34.63%)
Smoking status, N (%)				
Never smoked	12038 (55.81%)	15145 (50.25%)	1999 (47.95%)	2268 (43.18%)
Previously smoked	6777 (31.42%)	12125 (40.23%)	1447 (34.71%)	2295 (43.69%)
Current smoker	2688 (12.46%)	2776 (9.21%)	716 (17.17%)	686 (13.06%)
Alcohol frequency, N (%)				
Daily or almost daily	4822 (22.36%)	8653 (28.71%)	969 (23.24%)	1503 (28.61%)
Three or four times a week	5718 (26.51%)	7913 (26.25%)	1022 (24.51%)	1323 (25.19%)

Once or twice a week	5932 (27.5%)	7546 (25.03%)	1063 (25.5%)	1178 (22.43%)
One to three times a month	2193 (10.17%)	2392 (7.94%)	440 (10.55%)	479 (9.12%)
Special occasions only	1554 (7.2%)	2154 (7.15%)	328 (7.87%)	423 (8.05%)
Never	1343 (6.23%)	1473 (4.89%)	345 (8.28%)	345 (6.57%)
Psychotropic medication, N (%)	398 (1.85%)	670 (2.22%)	678 (16.26%)	879 (16.73%)

All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.

bmjopen-2018-024443 on 30 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Supplementary Table 2: Descriptive analysis for adverse cardiovascular outcome – females only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N= 29228	N = 25893	N = 10929	N = 7676
Median age (range)*	54 (47 - 61)	61 (55 - 65)	53 (47 - 60)	60 (53 - 64)
Ethnicity, N (%)				
White	26585 (90.96%)	23441 (90.53%)	10324 (94.46%)	7271 (94.72%)
Asian/Asian British	908 (3.11%)	727 (2.81%)	174 (1.59%)	93 (1.21%)
Black/ Black British	764 (2.61%)	989 (3.82%)	167 (1.53%)	168 (2.19%)
Median Townsend score (range)*	-1.90 (-3.44 - 0.51)	-2.06 (-3.5 - 0.38)	-1.66 (-3.3 - 0.84)	-1.87 (-3.4 - 0.74)
Age at leaving full-time education, N (%)				
<16	3399 (11.63%)	5757 (22.23%)	1261 (11.54%)	1602 (20.87%)
16	5792 (19.82%)	5592 (21.6%)	2319 (21.22%)	1636 (21.31%)
>16	19746 (67.56%)	14223 (54.93%)	7283 (66.64%)	4385 (57.13%)
Total physical activity in metabolic	3.87 (1.65 - 7.71)	3.51 (1.37 - 7.59)	3.79 (1.65 - 7.91)	3.65 (1.45 - 7.93)
Sedentary time in hours, median (range)*	4 (3 - 5)	4 (3 - 5.5)	4 (3 - 5.5)	4.5 (3 - 6)

bmjopen-2018-024443 on 30 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Diabetes, N (%)	547 (1.87%)	1376 (5.31%)	221 (2.02%)	452 (5.89%)
Hypercholesterolaemia, N (%)	1397 (4.78%)	3625 (14.%)	530 (4.85%)	1155 (15.05%)
Systolic BP in mmHg, median (range)*	123.5 (115.5 - 130.5)	149.5 (142 - 160)	122.5 (114.5 - 130)	147.5 (140.5 - 157)
Body Mass Index, N (%)				
<18.5	315 (1.08%)	107 (0.41%)	81 (0.74%)	22 (0.29%)
18.5 – 25	14942 (51.12%)	7836 (30.26%)	4857 (44.44%)	1984 (25.85%)
25-30	9816 (33.58%)	10102 (39.01%)	3917 (35.84%)	2857 (37.22%)
>30	4155 (14.22%)	7848 (30.31%)	2074 (18.98%)	2813 (36.65%)
Smoking status, N (%)				
Never smoked	18588 (63.6%)	16358 (63.18%)	5865 (53.66%)	4186 (54.53%)
Previously smoked	8279 (28.33%)	8015 (30.95%)	3671 (33.59%)	2770 (36.09%)
Current smoker	2282 (7.81%)	1423 (5.5%)	1377 (12.6%)	695 (9.05%)
Alcohol frequency, N (%)				
Daily or almost daily	4628 (15.83%)	4317 (16.67%)	1767 (16.17%)	1378 (17.95%)
Three or four times a week	6457 (22.09%)	5120 (19.77%)	2231 (20.41%)	1514 (19.72%)
Once or twice a week	7712 (26.39%)	6343 (24.5%)	2817 (25.78%)	1738 (22.64%)

One to three times a month	3859 (13.2%)	3196 (12.34%)	1618 (14.8%)	1033 (13.46%)
Special occasions only	3980 (13.62%)	4176 (16.13%)	1576 (14.42%)	1306 (17.01%)
Never	2581 (8.83%)	2726 (10.53%)	917 (8.39%)	703 (9.16%)
Psychotropic medication, N (%)	943 (3.23%)	1125 (4.34%)	2166 (19.82%)	1643 (21.4%)

All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.

Supplementary Table 3: Descriptive analysis for stroke outcome – males only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 22816	N = 32787	N = 4438	N = 5857
Median age (range)*	55 (47 - 62.)	61 (54 - 65)	54 (47 - 61)	60 (53 - 64)
Ethnicity, N (%)				
White	20699 (90.72%)	30219 (92.17%)	4173 (94.03%)	5569 (95.08%)
Asian/Asian British	932 (4.08%)	1116 (3.4%)	102 (2.3%)	105 (1.79%)
Black/ Black British	576 (2.52%)	820 (2.5%)	53 (1.19%)	59 (1.01%)
Median Townsend score (range)*	-1.88 (-3.47 - 0.59)	-2.05 (-3.5 - 0.46)	-1.56 (-3.28 - 1.15)	1.74 (-3.4 - 0.93)
Age at leaving full-time education, N (%)				
<16	2900 (12.71%)	7256 (22.13%)	558 (12.57%)	1193 (20.37%)
16	4702 (20.61%)	6704 (20.45%)	909 (20.48%)	1222 (20.86%)
>16	14960 (65.57%)	18471 (56.34%)	2930 (66.02%)	3397 (58.%)
Total physical activity in metabolic	4.12 (1.74 - 8.48)	3.96 (1.65 - 8.44)	4.13 (1.67 - 8.36)	3.66 (1.45 - 7.83)
Sedentary time in hours, median (range)*	5 (3.5 - 6)	5 (4 - 7)	5 (3.5 - 6.5)	5 (4 - 7)

 bmjopen-2018-024433 on 30 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Diabetes, N (%)	873 (3.83%)	2951 (9.%)	208 (4.69%)	635 (10.84%)
Hypercholesterolaemia, N (%)	2045 (8.96%)	6736 (20.54%)	457 (10.3%)	2293 (22.08%)
Systolic BP in mmHg, median (range)*	128 (121.5 - 133.5)	149 (142 - 159)	127 (120.5 - 133)	147.5 (140.5 - 156.5)
Body Mass Index, N (%)				
<18.5	79 (0.35%)	39 (0.12%)	22 (0.5%)	12 (0.2%)
18.5 – 25	7867 (34.48%)	6215 (18.96%)	1452 (32.72%)	960 (16.39%)
25-30	11203 (49.1%)	16341 (49.84%)	2142 (48.26%)	2780 (47.46%)
>30	3667 (16.07%)	10192 (31.09%)	822 (18.52%)	2105 (35.94%)
Smoking status, N (%)				
Never smoked	12502 (54.79%)	16054 (48.96%)	2094 (47.18%)	2469 (42.15%)
Previously smoked	7399 (32.43%)	13603 (41.49%)	1582 (35.65%)	2610 (44.56%)
Current smoker	2836 (12.43%)	3013 (9.19%)	754 (16.99%)	770 (13.15%)
Alcohol frequency, N (%)				
Daily or almost daily	5085 (22.29%)	9309 (28.39%)	1021 (23.01%)	1645 (28.09%)
Three or four times a week	6039 (26.47%)	8556 (26.1%)	1077 (24.27%)	1450 (24.76%)
Once or twice a week	6264 (27.45%)	8161 (24.89%)	1121 (25.26%)	1305 (22.28%)

One to three times a month	2307 (10.11%)	2642 (8.06%)	478 (10.77%)	538 (9.19%)
Special occasions only	1666 (7.3%)	2394 (7.3%)	355 (8.%)	503 (8.59%)
Never	1444 (6.33%)	1711 (5.22%)	383 (8.63%)	414 (7.07%)
Psychotropic medication, N (%)	429 (1.88%)	793 (2.42%)	735 (16.56%)	1025 (17.5%)

All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.

Supplementary Table 4: Descriptive analysis for stroke outcome – females only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 29684	N = 26937	N = 11143	N = 8090
Median age (range)*	54 (47 - 61)	61 (56 - 65)	53 (47 - 60)	60 (54 - 64)
Ethnicity, N (%)				
White	26998 (90.95%)	24359 (90.43%)	10524 (94.44%)	7643 (94.47%)
Asian/Asian British	925 (3.12%)	773 (2.87%)	178 (1.6%)	104 (1.29%)
Black/ Black British	779 (2.62%)	1034 (3.84%)	170.00 (1.53%)	187 (2.31%)
Median Townsend score (range)*	-1.90 (-3.44 - 0.52)	-2.03 (-3.48 - 0.43)	-1.66 (-3.29 - 0.86)	-1.83 (-3.38 - 0.85)
Age at leaving full-time education, N (%)				
<16	3546 (11.95%)	6140 (22.79%)	1326 (11.9%)	1752 (21.66%)
16	5888 (19.84%)	5803 (21.54%)	2361 (21.19%)	1731 (21.4%)
>16	19954 (67.22%)	14643 (54.36%)	7387 (66.29%)	4550 (56.24%)
Total physical activity in metabolic	3.85 (1.65 - 7.7)	3.49 (1.35 - 7.57)	3.79 (1.65 - 7.89)	3.61 (1.41 - 7.87)

Sedentary time in hours, median (range)*	4.0 (3 - 5)	4.0 (3 - 5.5)	4.0 (3 - 5.5)	4.5 (3 - 6)
Diabetes, N (%)	581 (1.96%)	1551 (5.76%)	241 (2.16%)	528 (6.53%)
Hypercholesterolaemia, N (%)	1547 (5.21%)	4032 (14.97%)	592 (5.31%)	1327 (16.4%)
Systolic BP in mmHg, median (range)*	123.5 (115.5 - 131)	149.5 (142 - 160)	122.5 (114.5 - 130)	147.0 (140.5 - 157)
Body Mass Index, N (%)				
<18.5	316 (1.06%)	112 (0.42%)	82 (0.74%)	26 (0.32%)
18.5 – 25	15100 (50.87%)	8027 (29.8%)	4922 (44.17%)	2057 (25.43%)
25-30	9982 (33.63%)	10476 (38.89%)	4007 (35.96%)	2989 (36.95%)
>30	4286 (14.44%)	8322 (30.89%)	2132 (19.13%)	3018 (37.31%)
Smoking status, N (%)				
Never smoked	18816 (63.39%)	16928 (62.84%)	5958 (53.47%)	4365 (53.96%)
Previously smoked	8452 (28.47%)	8416 (31.24%)	3758 (33.73%)	2950 (36.46%)
Current smoker	2334 (7.86%)	1488 (5.52%)	1409 (12.64%)	749 (9.26%)
Alcohol frequency, N (%)				

Daily or almost daily	4675 (15.75%)	4442 (16.49%)	1796 (16.12%)	1440 (17.8%)
Three or four times a week	6524 (21.98%)	5271 (19.57%)	2258 (20.26%)	1570 (19.41%)
Once or twice a week	7825 (26.36%)	6558 (24.35%)	2872 (25.77%)	1820 (22.5%)
One to three times a month	3913 (13.18%)	3329 (12.36%)	1644 (14.75%)	1089 (13.46%)
Special occasions only	4078 (13.74%)	4400 (16.33%)	1623 (14.57%)	1382 (17.08%)
Never	2658 (8.95%)	2919 (10.84%)	947 (8.5%)	785 (9.7%)
Psychotropic medication, N (%)	979 (3.3%)	1203 (4.47%)	2241 (20.11%)	1753 (21.67%)

All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.

Supplementary Table 5: Risk of adverse cardiovascular event by clinical group, in males only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension- No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.21	(2.00-2.45)	2.28x10 ⁻⁵³	1.62	(1.46-1.83)	5.80x10 ⁻¹⁹	1.29	(1.13-1.47)	1.35x10 ⁻⁴
MDD only	1.17	(0.95-1.56)	0.12	1.18	(0.95-1.46)	0.12	1.12	(0.9-1.39)	0.3
Hypertension and MDD	2.46	(2.13-2.84)	3.12x10 ⁻³⁴	1.95	(1.68-2.27)	2.81x10 ⁻¹⁸	1.47	(1.24-1.74)	8.71x10 ⁻⁶

*Adjusted for sociodemographic factors (age, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I.= confidence interval

Supplementary Table 6: Risk of adverse cardiovascular event by clinical group, in females only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.75	(2.38 - 3.18)	6.16x10 ⁻⁴³	1.86	(1.6-2.17)	1.43x10 ⁻¹⁵	1.64	(1.33-2.02)	4.36x10 ⁻⁶
MDD only	0.67	(0.42-1.08)	0.10	0.72	(0.45-1.17)	0.19	0.68	(0.42-1.1)	0.12
Hypertension and MDD	3.68	(3.1-4.38)	5.62x10 ⁻⁴⁹	2.78	(1.58-3.29)	4.62x10 ⁻²⁹	2.18	(1.82-2.52)	4.76x10 ⁻¹¹
Time varying Variables									
MDD only	1.02	(1.006-1.03)	2.45x10 ⁻³	1.02	(1.005-1.03)	4.00x10 ⁻³	1.02	(1.004-1.03)	6.19x10 ⁻³

*Adjusted for sociodemographic factors (age, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval

Supplementary Table 7: Risk of stroke event by clinical group, in males only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.43	(1.95 - 3.03)	1.92x10 ⁻¹⁵	1.74	(1.38 - 2.19)	2.58x10 ⁻⁶	1.19	(0.9 - 1.5)	0.22
MDD only	1.45	(0.96 - 2.2)	0.07	1.65	(1.09 - 2.5)	0.02	1.49	(0.97 - 2.29)	0.07
Hypertension and MDD	2.39	(1.74 - 3.27)	7.34x10 ⁻⁸	1.87	(1.35 - 2.6)	1.55x10 ⁻⁴	1.20	(0.83 - 1.74)	0.33

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = confidence interval

bmjopen-2018-024433 on 30 September 2019. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Supplementary Table 8: Risk of stroke event by clinical group, in females only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.38	(1.84 - 3.09)	6.50x10 ⁻¹¹	1.51	(1.14 - 1.99)	3.63x10 ⁻³	1.25	(0.88 - 1.79)	0.21
MDD only	1.09	(0.73 - 1.62)	0.67	1.15	(0.76 - 1.75)	0.51	0.99	(0.64 - 1.53)	0.98
Hypertension and MDD	3.05	(2.22 - 4.21)	8.71x10 ⁻¹²	2.22	(1.59 - 3.08)	2.27x10 ⁻⁶	1.62	(1.08 - 2.42)	0.02

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = confidence interval

Supplementary Table 9: Time stratified analysis by moment of proportional hazards failure for adverse cardiovascular outcomes (stratified at 22.5 months)

Fully adjusted* model pre-22.5 months Fully adjusted* model post-22.5 months

Group	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.36	(1.12 - 1.66)	0.002	1.36	(1.19 - 1.55)	5.06x10 ⁻⁶
MDD only	0.82	(0.60 - 1.13)	0.22	1.27	(1.06 - 1.52)	0.01
Hypertension and MDD	1.75	(1.39 - 2.21)	2.62x10 ⁻⁶	1.62	(1.38 - 1.90)	5.72x10 ⁻⁹

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.

MDD = Major depressive disorder, aHR =adjusted hazard ratio, C.I.= Confidence interval

bmjopen-2018-024444 on 30 September 2019. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Supplementary Table 10: Time stratified analysis by moment of proportional hazards failure for adverse cardiovascular outcomes (females only - stratified at 29 months)

Fully adjusted* model pre-29 months Fully adjusted* model post-29 months

Group	HR	95% C.I.	p-value	HR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.49	(1.06 - 2.08)	0.02	1.75	(1.33 - 2.30)	5.56x10 ⁻⁵
MDD only	0.73	(0.48 - 1.10)	0.13	1.58	(1.19 - 2.09)	0.002
Hypertension and MDD	1.80	(1.24 - 2.62)	0.002	2.47	(1.83 - 3.33)	2.89x10 ⁻⁹

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.

MDD = Major depressive disorder, aHR =adjusted hazard ratio, C.I.= Confidence interval

Supplementary Table 11: Relative excess risk due to interaction results on fully adjusted* models

Analysis	RERI	95% C.I.
Adverse cardiovascular outcome before 22.5 months	0.563	(0.189 - 0.938)
Adverse cardiovascular outcome after 22.5 months	-0.009	(-0.293 - 0.275)
Adverse cardiovascular outcome (males only)	0.058	(-0.240 - 0.357)
Adverse cardiovascular outcome (females only)before 29 months	0.588	(0.074 - 1.103)
Adverse cardiovascular outcome (females only)after 29 months	0.142	(-0.447 - 0.732)
Stroke outcome	-0.047	(-0.485 - 0.391)
Stroke outcome (males only)	-0.480	(-1.195 - 0.234)
Stroke outcome (females only)	0.372	(-0.216 - 0.959)

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.

RERI = Relative excess risk due to interaction, C.I.= Confidence interval

Supplementary Table 12: Comparison of additional hypertension factors (medication and diagnosis duration) across groups

	No Hypertension – No MDD	Hypertension only	MDD only	Hypertension and MDD
Antihypertensive medication prescription, N (%)	1,265 (2.49)	19,045 (33.99)	476 (3.04)	5,037 (37.34)
Number of antihypertensive medications, N (range)*	1 (1-1)	1 (1-2)	1 (1-1)	1 (1- 2)
Reported a duration of hypertension, N (%)	1,376 (2.71)	16,709 (29.82)	678 (4.22)	4,525 (33.55)
Duration of hypertension in years, median (range)*	6 (2-14)	8 (4-13)	6 (3-14)	8 (4 - 14)

*Median quantity of antihypertensive medications and median duration of hypertensive diagnosis presented for those on antihypertensive medications and supplied an age of hypertension diagnosis, respectively. MDD = Major Depressive disorder

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7

1		#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
2				
3				
4	Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
5				
6				
7				
8				
9				
10	Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-8
11				
12				
13				
14				
15				
16				
17				
18	Bias	#9	Describe any efforts to address potential sources of bias	6
19				
20	Study size	#10	Explain how the study size was arrived at	6
21				
22				
23	Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	See note 1
24				
25				
26				
27				
28	Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8-9
29				
30				
31				
32		#12b	Describe any methods used to examine subgroups and interactions	See note 2
33				
34				
35				
36		#12c	Explain how missing data were addressed	6-7
37				
38		#12d	If applicable, explain how loss to follow-up was addressed	1
39				
40				
41		#12e	Describe any sensitivity analyses	9
42				
43	Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	10
44				
45				
46				
47				
48				
49				
50				
51		#13b	Give reasons for non-participation at each stage	6,7
52				
53		#13c	Consider use of a flow diagram	n/a
54				
55				
56	Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	10
57				
58				
59				
60				

		confounders. Give information separately for exposed and unexposed groups if applicable.	
	#14b	Indicate number of participants with missing data for each variable of interest	See note 3
	#14c	Summarise follow-up time (eg, average and total amount)	10
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	6
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
	#16b	Report category boundaries when continuous variables were categorized	n/a
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	See note 4
Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

Author notes

1. 6,7,8,9, supplementary

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

- 1 2. 8-9, supplementary
- 2
- 3 3. n/a (supplementary)
- 4
- 5 4. 11-12, supplemental
- 6

7 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License
8 CC-BY. This checklist was completed on 25. May 2018 using <http://www.goodreports.org/>, a tool
9 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ Open

Impact of major depression on cardiovascular outcomes for individuals with hypertension: prospective survival analysis in UK Biobank.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024433.R2
Article Type:	Original research
Date Submitted by the Author:	20-Mar-2019
Complete List of Authors:	Graham, Nicholas; University of Glasgow Institute of Health and Wellbeing, Gartnavel Royal Hospital 1055 Great Western Road Glasgow, UK G12 0XH Ward, Joey; University of Glasgow Institute of Health and Wellbeing Mackay, Daniel; University of Glasgow Institute of Health and Wellbeing Pell, J. P.; University of Glasgow Institute of Health and Wellbeing Cavanagh, Jonathan; University of Glasgow Institute of Health and Wellbeing Padmanabhan, Sandosh; University of Glasgow, Institute of Cardiovascular and Medical Sciences, British Heart Foundation Glasgow Cardiovascular Research Centre Smith, Daniel; University of Glasgow, Institute of Health and Wellbeing
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Cardiovascular medicine
Keywords:	EPIDEMIOLOGY, mortality, cardiovascular disease, morbidity, depression, Hypertension < CARDIOLOGY

SCHOLARONE™
Manuscripts

1
2
3 1 **Impact of major depression on cardiovascular outcomes for individuals with hypertension:**
4
5 2 **prospective survival analysis in UK Biobank.**
6
7

8 3 **Short title: Outcomes of Hypertension plus Depression**
9

10
11 4 Nicholas A GRAHAM^{*a}, Clinical Research Fellow
12

13
14 5 Joey WARD^a, Research Fellow
15

16
17 6 Daniel MACKAY^b, Reader in Public Health
18

19
20 7 Jill PELL^b, Professor of Public Health
21

22
23 8 Jonathan CAVANAGH^c, Professor of Psychiatry
24

25
26 9 Sandosh PADMANABHAN^d, Professor of Cardiovascular Genomics and Therapeutics
27

28
29 10 Daniel J. SMITH^a, Professor of Psychiatry.
30

31
32 11 Number of Supplementary files: 1
33

34
35 12 Word count of Manuscript: 3,969 (exc. Tables, references, abstract, summary and Author contribution
36
37 13 statements)
38

39
40 14 Word count of Supplementary file: 1,455 (exc. tables)
41

42
43 15 Number of tables and figures: 18 tables (including 12 in supplementary digital content) and 3 figures
44

45
46 16 ^aInstitute of Health and Wellbeing, University of Glasgow, Gartnavel Royal Hospital, 1055 Great
47

48
49 17 Western Road, Glasgow G12 OXH. ^bInstitute of Health and Wellbeing, University of Glasgow, Public
50

51
52 18 Health, 1 Lilybank Gardens, Glasgow G12 8RZ. ^cInstitute of Health and Wellbeing, Centre for
53

54
55 19 Immunobiology, Sir Graeme Davies Building College of Medical, Veterinary and Life Sciences
56

57
58 20 University of Glasgow. ^dInstitute of Cardiovascular and Medical Sciences, British Heart Foundation
59

60
21 Glasgow Cardiovascular Research centre, University of Glasgow, Glasgow G12 8TA.

1
2
3 22 *corresponding author: nicholas.graham@glasgow.ac.uk, phone: +44 0141 211 3918,
4
5

6 23 **CONFLICTS OF INTEREST:** None.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

25 **ABSTRACT**

26 **Objectives:** To assess whether a history of major depressive disorder (MDD) in middle-aged
27 individuals with hypertension influences first-onset cardiovascular disease outcomes.

28 **Design:** Prospective cohort survival analysis using Cox proportional hazards regression with a median
29 follow-up of 63 months (702,902 person-years). Four mutually exclusive groups were compared:
30 hypertension only (n=56,035), MDD only (n=15,098), comorbid hypertension plus MDD (n=12,929),
31 and an unaffected (no hypertension, no MDD) comparison group (n=50,798).

32 **Setting:** UK Biobank

33 **Participants:** UK Biobank participants without cardiovascular disease aged 39–70 who completed
34 psychiatric questions relating ICD-10 diagnostic criteria on a touchscreen questionnaire at baseline
35 interview in 2006–2010 (n=134,860).

36 **Primary and Secondary outcome measures:** First-onset adverse cardiovascular outcomes leading to
37 hospital admission or death (ICD-10 codes I20-I259, I60-69 and G45- G46), adjusted in a stepwise
38 manner for sociodemographic, health and lifestyle features. Secondary analyses were performed
39 looking specifically at stroke outcomes (ICD-10 codes I60-69 and G45- G46) and in gender-separated
40 models.

41 **Results:** Relative to controls, adjusted hazard ratios (HRs) for adverse cardiovascular outcomes were
42 increased for the hypertension only group (HR=1.36, 95%CI 1.22-1.52) and were higher still for the
43 comorbid hypertension plus MDD group (HR=1.66, 95%CI 1.45-1.9). HRs for the comorbid
44 hypertension plus MDD group were significantly raised compared to hypertension alone (HR=1.22,
45 95%CI 1.1-1.35). Interaction measured using relative excess risk due to interaction (RERI) and
46 likelihood ratios (LR) were identified at baseline (RERI=0.563, 95%CI 0.189 - 0.938; LR chi 6.38, p=
47 0.0116) but not maintained during follow-up.

48 **Limitations:** Possible selection bias in UK Biobank and inability to assess for levels of medication
49 adherence.

1
2
3 50 **Conclusions:** Comorbid hypertension and MDD conferred greater hazard than hypertension alone
4
5 51 for adverse cardiovascular outcomes, although evidence of interaction between hypertension and
6
7 52 MDD was inconsistent over time. Future cardiovascular risk prediction tools may benefit from the
8
9 53 inclusion of questions about prior history of depressive disorders.
10
11

12 54 Word count of Abstract: 299
13
14

15 55 **Key words:** epidemiology, mortality, morbidity, depression; hypertension, cardiovascular disease
16
17

18 56

19
20 57 Article Summary
21

22 58 **STRENGTHS AND LIMITATIONS**

- 23
24 59 • Methodological advantages over previous studies, including a very large sample size,
25
26 60 adjustment for a more comprehensive range of confounders, and the inclusion of non-fatal
27
28 61 adverse cardiovascular events from hospital admission data and death registry data.
29
30 62 • Definition of prior MDD history was based on ICD-10 diagnostic criteria (rather than a score
31
32 63 on a symptoms questionnaire) and our composite definition of hypertension incorporated
33
34 64 past history, current medication and objective blood pressure measurements.
35
36 65 • Although analyses were adjusted for a broad range of baseline factors (such as smoking
37
38 66 status, BMI, psychotropic medication use and diabetes), we were unable to account for how
39
40 67 these factors may have changed over the course of follow-up, or assess adherence to
41
42 68 cardiovascular medications.
43
44 69 • Trained nurses interviewed UK Biobank participants, but the self-report nature of some of
45
46 70 these data may represent a limitation.
47
48 71 • UK Biobank may have issues with respect to selection biases. For example, individuals with
49
50 72 more severe MDD may have been less likely to volunteer.
51
52
53
54
55
56
57
58
59
60

74 INTRODUCTION

75 By 2030 major depressive disorder (MDD) and cardiovascular disease (CVD) will be the two leading
76 causes of disability worldwide¹. MDD is associated with CVD and worse long-term outcomes². To
77 date, survival analysis in comorbid hypertension and MDD have focussed on all-cause death³⁻⁵
78 cardiovascular death⁵ or incorporated individuals with previous CVD³⁻⁶, and have suggested a
79 possible additive interaction between hypertension and MDD on survival^{5 6}. MDD is well known to
80 worsen post-cardiovascular event survival^{6 7}. The contribution on survival to first-onset CVD is less
81 clear when MDD is stratified by hypertension and no prior study has assessed comorbid MDD and
82 hypertension on first episode CVD. Within this study we look specifically at first-onset events,
83 irrespective of whether they lead to death or not.

84 Hypertension is extremely common (affecting 1 billion people worldwide)⁸ and is responsible for
85 50% of all CVD⁹. It is commonly comorbid with MDD^{10 11}, with recent meta-analysis showing 27% of
86 individuals with hypertension having MDD¹² and population-based studies showing a hypertension
87 prevalence of 21% in those with MDD¹¹. A biological link has been found by genome-wide
88 association studies, showing calcium-channel genes, important in blood pressure (BP) control and
89 hypertension¹³, also act to increase risk for MDD^{14 15} and bipolar disorder (BD)^{16 17}. The sympathetic
90 nervous system (SNS), Renin-angiotensin system, the immune system and the cortisol stress
91 response system are all also implicated in both conditions¹⁸. Medication management of both
92 conditions are also thought to impact one another with side effects of psychotropic medications
93 including raised BP and vice versa¹⁹⁻²¹, although there is contrary evidence suggesting either
94 medication or MDD may in actual fact be protective of hypertension^{20 22}.

95 Here we make use of prospective data from the UK Biobank cohort²³ to test the hypothesis that a
96 lifetime history of MDD in individuals with hypertension impacts adversely on first-episode
97 cardiovascular events. We also assess whether MDD exacerbates the effects of hypertension as a
98 risk factor for CVD.

1
2
3 99 **METHODS**
4
5

6 100 **Study design**
7
8

9 101 This was a population cohort study using data from UK Biobank. Four mutually exclusive groups
10
11 102 (hypertension only, MDD only, hypertension plus MDD, and a comparison group) were compared for
12
13
14 103 adverse CVD and stroke outcomes.
15

16
17 104 **Sample description**
18

19
20 105 UK Biobank is a large cohort of 502,655 participants recruited between April 2007 and July 2010
21
22 106 from 21 assessment centres located across Great Britain²³. Participants aged 39-70 were invited to
23
24 107 take participate if registered with the NHS and lived within a reasonable distance of an assessment
25
26 108 centre. At baseline assessment participants completed a series of detailed assessments relating to
27
28 109 lifestyle and medical history on touchscreen questionnaire and have a range of physical health
29
30 110 measurements, including body mass index (BMI) and BP taken by a nurse. UK Biobank was approved
31
32 111 by the North West NHS Multi-Centre Research Ethics Committee and all participants provided
33
34 112 written informed consent to participate. This analysis is part of UK Biobank approved application
35
36 113 number 7155.
37
38
39
40

41 114 During the last two years of recruitment, questions relating to mood disorder features were added
42
43 115 to the baseline assessment schedule questionnaire. From the 172,729 participants asked these
44
45 116 questions, 134,860 provided sufficient responses to be included in our analysis. Participants were
46
47 117 excluded based on the following *a priori* criteria: a history of BD (n=1,831) or schizophrenia (n=262);
48
49 118 where there were insufficient data provided by participants to clearly rule out MDD (n= 25,520) or
50
51 119 hypertension (n=1,080); and where there were coding errors for date and/or time of death (n=4).
52
53 120 These exclusions were based on self-report (individuals who listed schizophrenia or BD from a list of
54
55 121 pre-existing medical conditions), or criteria for BD as per Smith et al,²⁴ or where they responded
56
57 122 "don't know" or "prefer not to answer" to questions or data was missing that would limit our ability
58
59
60

1
2
3 123 to exclude the presence of hypertension or MDD. Participants were further excluded from the
4
5 124 adverse CVD outcome if they had a record of CVD prior to recruitment (self-reported angina,
6
7 125 myocardial infarction (MI) or stroke based on specific questions, or previous hospital admission for
8
9 126 angina, MI or stroke) (n= 9,172). For the stroke outcome this exclusion was limited to a record of
10
11 127 stroke prior to baseline assessment (self-report or previous hospital admission for stroke) (n=2,280).
12
13
14

15 128 **Classification of hypertension and MDD**

16
17
18 129 Participants were defined as having hypertension if either: *a*) mean BP at baseline was greater than
19
20 130 clinically-defined criteria over two measurements (systolic BP greater than or equal to 140 mmHg or
21
22 131 diastolic BP greater than or equal to 90 mmHg. Where only one reading was available this was used
23
24 132 (n=1,571)); or *b*) self-reported 'hypertension diagnosed by a doctor' plus self-report of currently
25
26 133 taking antihypertensive medication. This composite classification was used to ensure that
27
28 134 undiagnosed hypertensive participants were not misclassified and is in line with similar
29
30 135 epidemiological studies^{5 25 26}. The requirement for antihypertensive use in the context of a history of
31
32 136 hypertension was incorporated to limit those on beta-blockers for anxiety. According to these
33
34 137 criteria, n=68,964 participants (51.1% of the sample) had hypertension for the adverse
35
36 138 cardiovascular outcomes analysis and n=73,671 participants (52% of the sample) had hypertension
37
38 139 in the stroke outcome analysis.
39
40
41
42
43

44 140 A history of lifetime MDD was defined according to the criteria for mood disorders developed by Smith
45
46 141 et al^{24 27} and has been used in further papers²⁷⁻³¹. (n=28,027 adverse cardiovascular outcomes;
47
48 142 n=29,528 stroke outcomes). Participants were classified as having a history of MDD if they reported
49
50 143 at least one episode, which comprised of depression and/or irritability, with a duration of at least two
51
52 144 weeks, plus had consulted with either a general practitioner or psychiatrist for mental ill-health. This
53
54 145 classification followed the structured diagnostic approach within the International Classification of
55
56 146 Diseases²⁴ and is described in more detail within the supplementary content.
57
58
59
60

1
2
3 147 For the adverse cardiovascular outcomes, the remainder of the sample, with no history of
4
5 148 hypertension or MDD (n=50,798) were classified as a comparator group. The three mutually
6
7 149 exclusive diagnostic groups for this study were therefore: hypertension only (n=56,035); MDD only
8
9
10 150 (n=15,098) and hypertension plus MDD (n= 12,929). For the stroke outcomes, the mutually exclusive
11
12 151 groups were hypertension only (n=59,724); MDD only (n=15,581) and hypertension plus MDD (n=
13
14 152 13,947) and no hypertension – no MDD (n=52,502).

17 153 **Outcomes**

18
19
20 154 The primary outcome was defined as a first-episode cardiovascular event leading to hospital
21
22 155 admission or death, specifically angina, MI, or chronic ischaemic heart disease (ICD-10 codes I20-
23
24 156 I259), and transient ischaemic attack (TIA) or stroke (ICD-10 codes I60-69 and G45- G46). A
25
26
27 157 secondary outcome was defined as stroke leading to hospital admission or death (ICD-10 codes I60-
28
29 158 69 and G45- G46)³² due to the strength of relationship hypertension has with this outcome in
30
31 159 particular⁹. Admission data were obtained from Hospital Episode Statistics in England, Patient
32
33
34 160 Episode Database for Wales and Scottish Morbidity Records in Scotland. Mortality outcomes were
35
36 161 obtained from the National Health Service (NHS) Information Centre for England and Wales and
37
38 162 from the NHS Central Register for Scotland. Individuals who died from a non-cardiovascular
39
40 163 cause/stroke were censored at the time of death but not recorded as having an event. Admission
41
42 164 data were available for Scottish, English and Welsh participants until 31 August 2014, 31 March 2015
43
44 165 and 28 February 2015 respectively. End of follow-up was classified as these dates unless preceded by
45
46 166 date of death or the date of first cardiovascular admission.

50 167 **Confounding variables**

51
52
53 168 Information on potential confounding factors was available for age, sex, socioeconomic status
54
55 169 (Townsend score)³³, self-reported ethnicity, age of leaving full-time education, diabetes, body mass
56
57
58 170 index (BMI), systolic BP, hypercholesterolemia, alcohol use, smoking history, sedentary behaviour
59
60

1
2
3 171 (number of hours each day spent sitting at a computer, television or driving), physical activity levels³⁴
4
5 172 and psychotropic medication use. Specific details on these variables are provided in supplementary
6
7 173 content.

10 174 **Analyses**

14 175 Baseline characteristics were compared between groups using Chi-squared tests for categorical
15
16 176 variables and Kruskal Wallis for continuous variables. Confounding variables were assessed for
17
18 177 differences in adverse cardiovascular outcomes using log rank sums. For the four groups of interest
19
20 178 we assessed associations with adverse cardiovascular outcomes using Cox proportional hazard
21
22 179 regression and the Efron method for ties³⁵. Models were applied in a staged process in line with
23
24 180 previous studies³⁻⁵ and reported as unadjusted (model one), partially adjusted (model two) and fully
25
26 181 adjusted (model three). Model two adjusted for sociodemographic factors (age, sex, Townsend
27
28 182 score, age of leaving full time education and ethnicity) and model three additionally adjusted for
29
30 183 health and lifestyle factors (diabetes, hypercholesterolemia, BMI, smoking history, alcohol use,
31
32 184 systolic BP, sedentary hours per day, physical activity and psychotropic medication use). The
33
34 185 proportionality of hazard assumption was assessed using Schoenfeld residuals³⁶. We compared our
35
36 186 fully adjusted models with results from competing risk analyses using the Fine and Grey approach³⁷,
37
38 187 incorporating non-cardiovascular deaths as a competing event for cardiovascular events, and non-
39
40 188 stroke deaths for stroke events. The relative excess risk due to interaction (RERI)³⁸ was calculated to
41
42 189 assess for additivity in the risk. This was done at each month where the proportionality assumption
43
44 190 for the variables of interest was not met. All analyses were performed with Stata statistical software,
45
46 191 version 12³⁹ with the exception of RERI which was calculated using the Microsoft Excel method of
47
48 192 Andersson and colleagues, which allows for comparison of adjusted outcomes⁴⁰. Presence of
49
50 193 multiplicative interaction was calculated using the likelihood ratio test.⁴¹

54
55
56
57 194 Psychotropic medication use was included as a confounding variable because of reports that they
58
59 195 may increase risk of mortality⁴² but we also conducted a sensitivity analysis which excluded

1
2
3 196 participants who were taking psychotropic medication. Sub-group analyses looking separately at
4
5 197 hazard ratios (HR) in male and female groups only was also carried out to assess for any gender
6
7 198 specific differences in light of differing rates of depression and adverse cardiovascular events in each
8
9
10 199 gender^{43 24}.

200 ***Time-varying coefficients.***

201 In the context of Schoenfeld residuals showing non-proportionality, models with time varying
202 coefficients were used. In addition, log(-log) plots were carried out to find the time point at which
203 the proportionality assumption failed. Following this, the data will be stratified by time at this time
204 point, effectively creating two separate survival analyses pre and post the failure time point.

205 **Patient involvement**

206 Although patients were not directly involved with the design of the specific research questions in
207 this study, the hypotheses tested were developed in the context of clinical experience that
208 depression and hypertension may interact to impact on CVD. UK Biobank has an active and ongoing
209 programme of participant involvement: www.ukbiobank.ac.uk/participants/. The outcome
210 measures used were those provided by the UK Biobank data collection protocol, the design of which
211 had input from participants. UK Biobank also has a website and social media streams to disseminate
212 research findings and hosts an annual scientific meeting, which includes cohort participants.

213 **RESULTS**

214 The final sample for adverse cardiovascular outcome included 134,860 participants followed for a
215 median duration of 63 months (702,901.6 person-years follow-up, mean 62.5 months). In total
216 3,685 (2.73%) participants had a first-episode cardiovascular event during the follow-up period (total
217 number of all deaths plus non-fatal cardiovascular events = 5,788) and 910 (0.64%) participants had
218 a first-episode stroke event (total number of all deaths plus non-fatal stroke events = 7,317).

1
2
3 219 Table 1 describes the baseline characteristics of the four groups. In general, the hypertension only
4
5 220 and comorbid hypertension plus MDD groups were older, had higher BMI and were more likely to
6
7 221 have diabetes and hypercholesterolemia. The MDD only and comorbid hypertension plus MDD
8
9 222 groups had a higher proportion of women and were more likely to be current smokers (table 1).
10
11
12 223 Gender-separated descriptive tables are shown in the supplementary content (Supplementary tables
13
14 224 1 and 2).

15
16
17 225 The sample for stroke-specific outcomes included 141,754 participants followed for a median
18
19 226 duration of 63 months (735247.7 person-years follow-up, mean 62.2 months). Table 2 describes the
20
21 227 baseline characteristics of the four groups which display similar characteristics to the adverse CVD
22
23 228 outcome groups. Gender-separated descriptive tables are shown in the supplementary content
24
25 229 (Supplementary tables 3 and 4).

29 230 **Adverse cardiovascular outcomes**

31
32 231 Within the main analysis and the female only subgroup analysis, MDD failed the proportional
33
34 232 hazards assumption. Table 3 presents unadjusted and multivariate-adjusted Hazard ratios (aHR) for
35
36 233 adverse cardiovascular outcomes. In the fully adjusted model, relative to the comparator group, the
37
38 234 aHR for adverse cardiovascular outcomes was significantly raised for hypertension only (aHR=1.36,
39
40 235 95%CI 1.22-1.52) and higher still for comorbid hypertension plus MDD (aHR=1.66, 95%CI 1.46-1.9)
41
42 236 but reduced for MDD only (aHR=0.55, 95%CI 0.46-0.76). Although the MDD only HR was noted to
43
44 237 increase over time as a time-varying coefficient. With the exception of MDD, these findings were
45
46 238 robust to sensitivity-analysis excluding those on psychotropic medication (sensitivity analysis
47
48 239 aHR=1.43, 95%CI 1.27-1.62; aHR=1.72, 95%CI 1.49-1.999, aHR=0.74, 95%CI 0.52-1.06 respectively).
49
50 240 Table 4 presents HRs and aHRs for adverse cardiovascular outcomes using the hypertension only
51
52 241 group as comparator. In the fully adjusted model, relative to hypertension, the aHR for adverse
53
54 242 cardiovascular outcomes was significantly raised for comorbid hypertension plus MDD (aHR=1.22,
55
56
57
58
59
60

243 95%CI 1.1-1.35, sensitivity-analysis aHR= 1.20, 95%CI 1.08-1.34). An adjusted survival plot is shown
244 in figure 1.

245 Within the sub-analysis, the male-only model showed a significant increase in HR for hypertension
246 (male aHR 1.29, 95% CI 1.13-1.47) (supplementary table 5) and comorbid MDD and hypertension
247 (male aHR 1.47, 95%CI 1.24-1.74). However, the difference between comorbid disease and
248 hypertension only was not statistically significant (aHR 1.14, 95%CI 0.995-1.3). The female only sub-
249 analysis showed an increase in HR for hypertension (aHR 1.64, 95%CI 1.33-2.02) and a greater
250 increase in comorbid MDD and hypertension (aHR 2.18, 95%CI 1.82-2.92) (table 6 of the
251 supplementary content). The difference between comorbid disease and hypertension only was also
252 statistically significant (aHR 1.33, 95%CI 1.14- 1.56). Sensitivity analysis supported these findings.

253 **Stroke Outcomes**

254 None of the independent variables for stroke outcome failed the proportionality assumption. Table 5
255 presents HRs and aHRs for stroke outcomes. In the fully adjusted model, the aHR for stroke was
256 insignificantly raised for hypertension only (aHR=1.21, 95%CI 0.97-1.51) and depression only
257 (aHR=1.20, 95%CI 0.89-1.63) but significantly raised for comorbid hypertension plus MDD (aHR=1.37,
258 95%CI 1.04-1.79). In the hypertension comparator group, no group was significantly different from
259 hypertension only (table 6). Similar trends were shown in the gender subset analysis but not
260 reaching significance (supplementary Tables 7-8). An adjusted survival plot is shown in figure 2.
261 Again, all results were supported by sensitivity analysis excluding those on psychotropic medication.

262 **Interaction, time stratified analysis and competing risk analysis**

263 Survival analysis stratified by time is described and included within the supplementary content
264 (supplementary tables 9, 10 and figure 3). There was evidence of interaction between hypertension
265 and MDD at baseline for the overall cardiovascular outcome analysis before the 22.5 month time
266 point (RERI=0.563, 95%CI 0.189 - 0.938. Likelihood ratio p-value 0.0116) and the female only

1
2
3 267 cardiovascular endpoint analysis before the 29 month time point (RERI=0.588, 95%CI 0.074 - 1.103.
4
5 268 Likelihood ratio p-value 0.031). However, after these time points there was no evidence of
6
7 269 interaction. Supplementary table 11 shows the full results for this analysis. Competing risk analysis
8
9
10 270 showed no significant difference from the main analyses for cardiovascular outcomes or stroke
11
12 271 outcomes (tables 7-8)

13
14
15 272

17 273 **DISCUSSION**

18
19
20
21 274 In this large population cohort of middle-aged adults without CVD (adjusted for a broad range of
22
23 275 confounders), individuals with co-morbid hypertension and MDD were at increased risk of CVD when
24
25 276 compared to those with hypertension alone, MDD alone and neither condition. There was some
26
27 277 evidence of interaction between hypertension and MDD at baseline, but not throughout follow-up
28
29 278 and only within both subgroups. Differences between co-morbid disease and either disease alone or
30
31 279 no disease were more marked in females. For stroke outcomes, comorbid depression and
32
33 280 hypertension was the only group that showed significantly increased HRs.

34 35 36 37 281 **Previous research**

38
39
40
41 282 Our findings expand upon previous research from UK Biobank looking at CVD in those with BD and
42
43 283 MDD²⁷. It was found that there were significantly increased odds of having 'any CVD' (fully adjusted
44
45 284 OR 1.15 CI 1.12–1.19) or hypertension (fully adjusted OR 1.15 CI 1.13–1.18) if depressed, with even
46
47 285 higher odds for stroke (fully adjusted OR 1.26 CI 1.13–1.40). There are distinct differences between
48
49 286 our current paper and the previous publication. Follow-up data within UK-Biobank has been released
50
51 287 to allow meaningful prospective studies be conducted. Thus, the current paper has the benefits of
52
53 288 using hospital records and death certification for outcomes, rather than self-reported data. We are
54
55 289 also able to make inferences about the direction of effect regarding MDD and CVD and assess the
56
57
58
59
60

1
2
3 290 influence of hypertension and MDD over time, both in isolation and when comorbid, and assess for
4
5 291 statistical interaction to inform on whether there may be a biological interaction.
6
7
8 292 Other survival analyses in hypertension/MDD comorbidity have focussed primarily on mortality
9
10 293 outcomes. In the National Health and Nutrition Epidemiologic Follow-up Study in the United States³¹
11
12 294 and the Taiwanese Survey of Health and Living Status³², individuals with self-reported hypertension
13
14 295 plus depressive symptoms (compared to a reference group with neither) had increased all-cause
15
16 296 mortality (aHR=1.39, 95%CI 1.14-1.69, aHR=1.54, 95%CI 1.29-1.83, respectively)³⁴ with the former
17
18 297 also showing increased CVD specific mortality (aHR=1.59, 95%CI 1.08-2.34)⁴. Similarly, Hamer and
19
20 298 colleagues⁵ reported a prospective analysis of common mental disorder on mortality outcomes in
21
22 299 individuals with hypertension versus those without hypertension in participants from the Health
23
24 300 Survey for England and the Scottish Health Survey (1994–2004), finding that risk of CVD death was
25
26 301 highest in the group with comorbid disease.
27
28
29
30

31 **Strengths**

32
33
34 303 These observations are broadly consistent with our results but our study has a number of
35
36 304 methodological advantages, including a very large sample size, adjustment of analyses for a more
37
38 305 comprehensive range of confounders, and a focus on first-episode non-fatal and fatal adverse
39
40 306 cardiovascular events. We also used a definition of prior MDD history which was based on
41
42 307 diagnostic criteria within ICD-10 (rather than a threshold score on a depressive symptoms or general
43
44 308 wellbeing scale) and our composite definition of hypertension incorporated past history, baseline
45
46 309 medication and BP measurements. Lifetime MDD is thought to be under-reported in the literature.
47
48 310 However, using current symptom scores may reduce power and precision because a smaller number
49
50 311 of respondents would be identified as having an episode of MDD.⁴⁴ Given that we are assessing
51
52 312 outcomes for which risk accumulates over a lifetime, we felt that a primary focus on lifetime
53
54 313 episodes was appropriate. We believe our lifetime definition to be better suited as it offers a view
55
56 314 depression and depressive symptoms over the course of a lifespan as opposed the past week. Also,
57
58
59
60

1
2
3 315 within our current study we were able to exclude those with previous self-declared or hospital
4
5 316 admission CVD, as previous studies show depression may result from CVD^{45 46} and worsen
6
7 317 prognosis⁴⁶
8
9

10 318 **Limitations**

11
12
13
14 319 However, some limitations are acknowledged. Recruitment criteria for UK Biobank may lead to
15
16 320 selection bias. Specifically, age-restrictions may lead to underrepresentation of early-onset
17
18 321 hypertension and those with more severe MDD may be less inclined to attend for assessment. We
19
20 322 also acknowledge limitations with our classifications of MDD and hypertension, which were primarily
21
22 323 self-report rather than formal diagnostic assessments. Although we have excluded prior
23
24 324 cardiovascular events where possible, the MDD plus hypertension sub-type may capture older
25
26 325 individuals with a degree of vascular depression, which has an established association with raised
27
28 326 BP⁴⁷. In addition, although we adjust for a host of risk factors at baseline such as smoking status, BMI
29
30 327 and psychotropic medication, we are limited by the lack of follow-up data, which could show change
31
32 328 and modification of said risk factors over time. Similarly, we were unable to assess for medication
33
34 329 adherence and transitions from one investigatory group to another. Participants who are aware of or
35
36 330 had sought treatment for MDD may also have complicated our findings, however, our sensitivity
37
38 331 analysis excluded those using pharmaceutical treatments and was in keeping with our main findings.
39
40 332 Such modifications could explain the non-proportional nature of the depression group, which may in
41
42 333 itself be a predictor of poor medication adherence⁴⁸. Although adherence to medication was not
43
44 334 formally assessed, the number and duration of antihypertensive medications used in the
45
46 335 hypertension plus MDD group was the same as for the hypertension only group (supplementary
47
48 336 content, table 12). As such, worse outcomes in the MDD plus hypertension group are not explained
49
50 337 by less intensive antihypertensive treatment at baseline. The end-points used for stroke and
51
52 338 cardiovascular events also require to be further validated, however are in line with previous
53
54 339 epidemiological studies⁵ and have been suggested in previous papers in UK Biobank³².
55
56
57
58
59
60

1
2
3 340 Cardiovascular endpoints have not, to our knowledge, been validated within UKbiobank, however
4
5 341 we do not feel that this will bias the results towards any particular group. The amelioration of the
6
7 342 aHR suggests other covariates contribute considerably to the risk. This is important in the context of
8
9
10 343 increased rates of diabetes, hypercholesterolemia and obesity along with lower socio-economic
11
12 344 status in the hypertension only and comorbid groups and as such we may be seeing the summation
13
14 345 of CV risk factors. Finally, the overall recruitment rate to UK Biobank was low (at around 6%);
15
16 346 however, the large final cohort size, the depth and diversity of phenotype data collected at baseline,
17
18 347 and the wide sociodemographic representation of participants all make our findings highly relevant
19
20 348 to UK primary care settings. While UK Biobank participants cannot be used to provide
21
22 349 representative disease prevalence and incidence rates, valid assessment of exposure-disease
23
24 350 relationships are nonetheless widely generalizable and do not require participants to be
25
26 351 representative of the UK population at large⁴⁹, although findings will not be generalizable to other
27
28 352 countries.
29
30
31
32

33 **Possible mechanisms**

34
35
36 354 Our finding that a history of MDD, in the context of a current diagnosis of hypertension increased
37
38 355 the risk of first-episode CVD is complicated by the time varying risk that MDD conveys to CVD. Sub-
39
40 356 sample analysis show this time-varying aspect is gender-specific to females. Within our sample, the
41
42 357 MDD group has a slightly reduced BP compared to comparators. Previously, reduced BP has been
43
44 358 put forth as being causative of MDD and therefore reducing CVD risk²⁰, but findings from
45
46 359 longitudinal studies are inconsistent with regards to direction of effect^{50 51}. Potential menopausal
47
48 360 effects are tempting explanations. Common factors for BP and mood such as neuropeptide Y^{52 53} may
49
50 361 also influence cardiovascular outcomes. Neuropeptide Y has a complex relationship with oestrogen⁵⁴
51
52 362 and both have dampening effect on the SNS⁵⁵.
53
54
55
56

57 363 Personality factors may also play a role. MDD correlates highly with neuroticism which, although
58
59 364 inconsistent, may be protective of CVD⁵⁶. Conscientiousness traits may lead to better outcomes⁵⁷
60

1
2
3 365 and it is possible that this trait has been selected for within UK Biobank. Despite this early reduced
4
5 366 risk, due to the time varying nature of MDD, MDD has increased risk in the latter aspects of the time-
6
7 367 stratified analyses for the full and female only analyses (supplementary table 9 and 10). The findings
8
9 368 from our study in this context suggest MDDs role as a risk factor for CVD and its relationship with BP
10
11 369 may be much more complex than initially thought, in particular within female populations however
12
13 370 further investigation is clearly needed.

14
15
16
17 371 We can see in the hypertension only baseline models that comorbid hypertension and depression
18
19 372 convey a significantly greater risk than hypertension alone. Individuals with either hypertension or
20
21 373 depression may have increased sympathetic stimulation that is increased further in comorbid states
22
23 374 leading to worse outcomes⁵⁸.

24
25
26
27 375

28 29 376 **CONCLUSIONS**

30
31
32 377 Overall, our findings may have important implications for routine clinical practice, particularly within
33
34 378 primary care settings and further demonstrate the complex relationship between depression and
35
36 379 hypertension. Although evidence of an interaction is inconsistent, we found that comorbid
37
38 380 hypertension and depression conferred greater hazard than hypertension alone for adverse
39
40 381 cardiovascular outcomes. This significant finding remained after adjustment for factors such as BMI,
41
42 382 smoking status and diabetes and was robust to sensitivity analysis excluding those on psychotropic
43
44 383 medication. One implication is that clinicians should be more aware of the negative long-term
45
46 384 impact on CVD outcomes caused by a history of MDD in the context of hypertension. Although this
47
48 385 work awaits replication and testing in other cohorts and settings, further work in this field may
49
50 386 suggest that future iterations of CVD risk prediction tools, such as ASSIGN⁵⁹, would benefit from the
51
52 387 addition of a question on whether individuals have a past history of MDD, to facilitate more
53
54 388 intensive support to prevent CVD⁶⁰.

1
2
3 390 **ACKNOWLEDGEMENTS**
4
5

6 391 We are grateful to all participants of the UK Biobank cohort. UK Biobank was established by the
7
8 392 Wellcome Trust, the Medical Research Council, Department of Health, Scottish Government and the
9
10 393 Northwest Regional Development Agency. It has also had funding from the Welsh Assembly
11
12 394 Government and the British Heart Foundation. UK Biobank is hosted by the University of Manchester
13
14 395 and supported by the National Health Service (NHS). NG is supported by the Aitchison Family Clinical
15
16 396 Research Fellowship at the University of Glasgow and DJS is supported by a Lister Institute Prize
17
18 397 Fellowship. JC is supported by the Sackler Trust and the Wellcome Trust. Funding also acknowledged
19
20 398 from MRC Mental Health Data Pathfinder Award to DJS (MC_PC_17217).
21
22
23
24

25 399 **Footnotes**
26
27
28

29 400 **Authors Statement:** Contributors NG, JW, JP, JC, DS, SP and DM, contributed to study design and
30
31 401 writing of the manuscript. JP and DM contributed to data acquisition. NG conducted data processing
32
33 402 and statistical analyses.
34
35

36
37 403 **Funding:** Authors declare no support from any organisation for the submitted work;
38
39

40 404 **Competing interests:** All authors have completed the ICMJE uniform disclosure form at
41
42 405 http://www.icmje.org/coi_disclosure.pdf and no financial relationships with any organisations that
43
44 406 might have an interest in the submitted work in the previous three years; no other relationships or
45
46 407 activities that could appear to have influenced the submitted work.
47
48
49

50 408 **Ethics approval:** This study has been conducted using UK Biobank data. UK Biobank has received
51
52 409 ethics approval from the UK Biobank Research Ethics Committee (ref. 11/NW/0382).
53
54

55
56 410 **Data sharing statement:** The data used in this study are available via a direct application to UK
57
58 411 Biobank.
59
60

1
2
3 412 **Transparency statement:** The lead author affirms that this manuscript is an honest, accurate and
4
5 413 transparent account of the study being reported; that no important aspects of the study have been
6
7 414 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have
8
9
10 415 been explained.
11
12

13 416
14
15

16 417 **COMPETING INTERESTS STATEMENTS**
17

18
19 418 All authors have completed the ICMJE uniform disclosure form at
20
21 419 http://www.icmje.org/coi_disclosure.pdf and no financial relationships with any organisations that
22
23 420 might have an interest in the submitted work in the previous three years; no other relationships or
24
25 421 activities that could appear to have influenced the submitted work.
26
27
28

29 422
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

423 **References**

424

- 425 1. Organization. WH. The global burden of disease: 2004 update. Geneva, Switzerland.: WHO press.
426 2008.
- 427 2. Hare DL, Toukhsati SR, Johansson P, et al. Depression and cardiovascular disease: a clinical review.
428 *Eur Heart J* 2014;35(21):1365-72. doi: 10.1093/eurheartj/eh462
- 429 3. Kuo PL, Pu C. The contribution of depression to mortality among elderly with self-reported
430 hypertension: analysis using a national representative longitudinal survey. *J Hypertens*
431 2011;29(11):2084-90. doi: 10.1097/HJH.0b013e32834b59ad [published Online First:
432 2011/09/22]
- 433 4. Axon RN, Zhao Y, Egede LE. Association of depressive symptoms with all-cause and ischemic heart
434 disease mortality in adults with self-reported hypertension. *Am J Hypertens* 2010;23(1):30-7.
435 doi: 10.1038/ajh.2009.199
- 436 5. Hamer M, Batty GD, Stamatakis E, et al. The combined influence of hypertension and common
437 mental disorder on all-cause and cardiovascular disease mortality. *J Hypertens*
438 2010;28(12):2401-6. doi: 10.1097/HJH.0b013e32833e9d7c
- 439 6. Jani BD, Cavanagh J, Barry SJ, et al. Relationship Between Blood Pressure Values, Depressive
440 Symptoms, and Cardiovascular Outcomes in Patients With Cardiometabolic Disease. *Journal*
441 *of clinical hypertension (Greenwich, Conn)* 2016;18(10):1027-35. doi: 10.1111/jch.12813
442 [published Online First: 2016/04/05]
- 443 7. Taylor CB, Youngblood ME, Catellier D, et al. Effects of antidepressant medication on morbidity
444 and mortality in depressed patients after myocardial infarction. *Arch Gen Psychiatry*
445 2005;62(7):792-8. doi: 10.1001/archpsyc.62.7.792 [published Online First: 2005/07/06]
- 446 8. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide
447 data. *Lancet* 2005;365(9455):217-23. doi: 10.1016/S0140-6736(05)17741-1
- 448 9. Lawes CM, Vander Hoorn S, Rodgers A, et al. Global burden of blood-pressure-related disease,
449 2001. *Lancet* 2008;371(9623):1513-8. doi: 10.1016/S0140-6736(08)60655-8
- 450 10. Meng L, Chen D, Yang Y, et al. Depression increases the risk of hypertension incidence: a meta-
451 analysis of prospective cohort studies. *J Hypertens* 2012;30:842 - 51.
- 452 11. Wu EL, Chien IC, Lin CH, et al. Increased risk of hypertension in patients with major depressive
453 disorder: a population-based study. *J Psychosom Res* 2012;73(3):169-74. doi:
454 10.1016/j.jpsychores.2012.07.002
- 455 12. Li Z, Li Y, Chen L, et al. Prevalence of Depression in Patients With Hypertension: A Systematic
456 Review and Meta-Analysis. *Medicine (Baltimore)* 2015;94(31):e1317. doi:
457 10.1097/md.0000000000001317 [published Online First: 2015/08/08]
- 458 13. Johnson AD, Newton-Cheh C, Chasman DI, et al. Association of hypertension drug target genes
459 with blood pressure and hypertension in 86,588 individuals. *Hypertension* 2011;57(5):903-
460 10. doi: 10.1161/HYPERTENSIONAHA.110.158667
- 461 14. Casamassima F HJ, Fava M, Sachs GS, Smoller JW, Cassano GB, Lattanzi L, Fagerness J, Stange JP,
462 Perlis RH. Phenotypic effects of a bipolar liability gene among individuals with major
463 depressive disorder. . *Am J Med Genet B Neuropsychiatr Genet* 2010;153B:303-09.
- 464 15. Green EK, Grozeva D, Jones I, et al. The bipolar disorder risk allele at CACNA1C also confers risk
465 of recurrent major depression and of schizophrenia. *Molecular Psychiatry* 2010;15(10):1016-
466 22. doi: 10.1038/mp.2009.49
- 467 16. Ferreira MA, O'Donovan MC, Meng YA, et al. Collaborative genome-wide association analysis
468 supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat Genet* 2008;40(9):1056-8.
469 doi: 10.1038/ng.209
- 470 17. Consortium WTCC. Identification of risk loci with shared effects on five major psychiatric
471 disorders: a genome-wide analysis. *The Lancet* 2013;381(9875):1371-79.

- 1
2
3 472 18. Scalco AZ, Scalco MZ, Azul JB, et al. Hypertension and depression. *Clinics (Sao Paulo)*
4 473 2005;60(3):241-50. doi: /S1807-59322005000300010
5 474 19. Boal AH, Smith DJ, McCallum L, et al. Monotherapy With Major Antihypertensive Drug Classes
6 475 and Risk of Hospital Admissions for Mood Disorders. *Hypertension* 2016;68(5):1132-38. doi:
7 476 10.1161/hypertensionaha.116.08188 [published Online First: 2016/10/14]
8 477 20. Licht CM, de Geus EJ, Seldenrijk A, et al. Depression is associated with decreased blood pressure,
9 478 but antidepressant use increases the risk for hypertension. *Hypertension* 2009;53(4):631-8.
10 479 doi: 10.1161/HYPERTENSIONAHA.108.126698
11 480 21. Crookes DM, Demmer RT, Keyes KM, et al. Depressive Symptoms, Antidepressant Use, and
12 481 Hypertension in Young Adulthood. *Epidemiology (Cambridge, Mass)* 2018;29(4):547-55. doi:
13 482 10.1097/ede.0000000000000840 [published Online First: 2018/04/10]
14 483 22. Diminic-Lisica I, Popovic B, Rebic J, et al. Outcome of treatment with antidepressants in patients
15 484 with hypertension and undetected depression. *Int J Psychiatry Med* 2014;47(2):115-29. doi:
16 485 10.2190/PM.47.2.c [published Online First: 2014/08/03]
17 486 23. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the
18 487 causes of a wide range of complex diseases of middle and old age. *PLoS Med*
19 488 2015;12(3):e1001779. doi: 10.1371/journal.pmed.1001779
20 489 24. Smith DJ, Nicholl BI, Cullen B, et al. Prevalence and characteristics of probable major depression
21 490 and bipolar disorder within UK biobank: cross-sectional study of 172,751 participants. *PLoS*
22 491 *One* 2013;8(11):e75362. doi: 10.1371/journal.pone.0075362
23 492 25. Ong KL, Cheung BM, Man YB, et al. Prevalence, awareness, treatment, and control of
24 493 hypertension among United States adults 1999-2004. *Hypertension* 2007;49(1):69-75. doi:
25 494 10.1161/01.hyp.0000252676.46043.18 [published Online First: 2006/12/13]
26 495 26. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of
27 496 hypertension, 1988-2008. *Jama* 2010;303(20):2043-50. doi: 10.1001/jama.2010.650
28 497 [published Online First: 2010/05/27]
29 498 27. Martin DJ, Ul-Haq Z, Nicholl BI, et al. Cardiometabolic disease and features of depression and
30 499 bipolar disorder: population-based, cross-sectional study. *Br J Psychiatry* 2016;208(4):343-
31 500 51. doi: 10.1192/bjp.bp.114.157784
32 501 28. Ul-Haq Z, Smith DJ, Nicholl BI, et al. Gender differences in the association between adiposity and
33 502 probable major depression: a cross-sectional study of 140,564 UK Biobank participants. *BMC*
34 503 *psychiatry* 2014;14:153-53. doi: 10.1186/1471-244X-14-153
35 504 29. Sarkar C, Webster C, Gallacher J. Residential greenness and prevalence of major depressive
36 505 disorders: a cross-sectional, observational, associational study of 94 879 adult UK Biobank
37 506 participants. *The Lancet Planetary Health* 2018;2(4):e162-e73. doi:
38 507 [https://doi.org/10.1016/S2542-5196\(18\)30051-2](https://doi.org/10.1016/S2542-5196(18)30051-2)
39 508 30. Hall LS, Adams MJ, Arnau-Soler A, et al. Genome-wide meta-analyses of stratified depression in
40 509 Generation Scotland and UK Biobank. *Translational psychiatry* 2018;8(1):9-9. doi:
41 510 10.1038/s41398-017-0034-1
42 511 31. Howard DM, Adams MJ, Shiralil M, et al. Genome-wide association study of depression
43 512 phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. *Nature*
44 513 *Communications* 2018;9(1):1470. doi: 10.1038/s41467-018-03819-3
45 514 32. Woodfield R, Grant I, Group UKBSO, et al. Accuracy of Electronic Health Record Data for
46 515 Identifying Stroke Cases in Large-Scale Epidemiological Studies: A Systematic Review from
47 516 the UK Biobank Stroke Outcomes Group. *PLOS ONE* 2015;10(10):e0140533. doi:
48 517 10.1371/journal.pone.0140533
49 518 33. Townsend P. Deprivation. *Journal of Social Policy* 2009;16(02):125. doi:
50 519 10.1017/s0047279400020341
51 520 34. Guo W, Bradbury KE, Reeves GK, et al. Physical activity in relation to body size and composition
52 521 in women in UK Biobank. *Annals of Epidemiology* 2015;25(6):406-13.e6. doi:
53 522 <http://dx.doi.org/10.1016/j.annepidem.2015.01.015>

- 1
2
3 523 35. Efron B. The Efficiency of Cox's Likelihood Function for Censored Data. *Journal of the American*
4 524 *Statistical Association*, 1977;72(359):557-65.
- 5 525 36. Schoenfeld D. Partial Residuals for the Proportional Hazards Regression-Model. *Biometrika*
6 526 1982;69(1):239-41. doi: Doi 10.2307/2335876
- 7 527 37. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk.
8 528 *Journal of the American Statistical Association* 1999;94(446):496-509. doi: 10.2307/2670170
- 9 529 38. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology*
10 530 *(Cambridge, Mass)* 1992;3(5):452-6. [published Online First: 1992/09/01]
- 11 531 39. Stata Statistical Software, version 12 [program]. College station, Texas.
- 12 532 40. Andersson T, Alfredsson L, Kallberg H, et al. Calculating measures of biological interaction.
13 533 *European journal of epidemiology* 2005;20(7):575-9. [published Online First: 2005/08/27]
- 14 534 41. Marshall SW. Power for tests of interaction: effect of raising the Type I error rate. *Epidemiologic*
15 535 *Perspectives & Innovations* 2007;4(1):4. doi: 10.1186/1742-5573-4-4
- 16 536 42. Weich S, Pearce HL, Croft P, et al. Effect of anxiolytic and hypnotic drug prescriptions on
17 537 mortality hazards: retrospective cohort study. *BMJ* 2014;348:g1996. doi: 10.1136/bmj.g1996
- 18 538 43. Nichols M, Townsend N, Scarborough P, et al. Cardiovascular disease in Europe 2014:
19 539 epidemiological update. *European Heart Journal* 2014;35(42):2950-59. doi:
20 540 10.1093/eurheartj/ehu299
- 21 541 44. Patten SB. Accumulation of major depressive episodes over time in a prospective study indicates
22 542 that retrospectively assessed lifetime prevalence estimates are too low. *BMC psychiatry*
23 543 2009;9:19-19. doi: 10.1186/1471-244X-9-19
- 24 544 45. Kang HJ, Stewart R, Bae KY, et al. Predictive value of homocysteine for depression after acute
25 545 coronary syndrome. *Oncotarget* 2016;7(42):69032-40. doi: 10.18632/oncotarget.11966
- 26 546 46. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis
27 547 among patients with acute coronary syndrome: systematic review and recommendations: a
28 548 scientific statement from the American Heart Association. *Circulation* 2014;129(12):1350-69.
29 549 doi: 10.1161/CIR.0000000000000019
- 30 550 47. Aizenstein HJ, Baskys A, Boldrini M, et al. Vascular depression consensus report – a critical
31 551 update. *BMC Medicine* 2016;14(1):161. doi: 10.1186/s12916-016-0720-5
- 32 552 48. Goldstein CM, Gathright EC, Garcia S. Relationship between depression and medication
33 553 adherence in cardiovascular disease: the perfect challenge for the integrated care team.
34 554 *Patient preference and adherence* 2017;11:547-59. doi: 10.2147/PPA.S127277
- 35 555 49. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related
36 556 Characteristics of UK Biobank Participants With Those of the General Population. *American*
37 557 *journal of epidemiology* 2017;186(9):1026-34. doi: 10.1093/aje/kwx246 [published Online
38 558 First: 2017/06/24]
- 39 559 50. Hildrum B, Mykletun A, Holmen J, et al. Effect of anxiety and depression on blood pressure: 11-
40 560 year longitudinal population study. *British Journal of Psychiatry* 2018;193(2):108-13. doi:
41 561 10.1192/bjp.bp.107.045013 [published Online First: 01/02]
- 42 562 51. Paterniti S. Low blood pressure and risk of depression in the elderly: A prospective community-
43 563 based study. *The British Journal of Psychiatry* 2000;176(5):464-67. doi:
44 564 10.1192/bjp.176.5.464
- 45 565 52. Zhang P, Qi Y-X, Yao Q-P, et al. Neuropeptide Y Stimulates Proliferation and Migration of Vascular
46 566 Smooth Muscle Cells from Pregnancy Hypertensive Rats via Y1 and Y5 Receptors. *PLOS ONE*
47 567 2015;10(7):e0131124. doi: 10.1371/journal.pone.0131124
- 48 568 53. Morales-Medina JC, Dumont Y, Quirion R. A possible role of neuropeptide Y in depression and
49 569 stress. *Brain research* 2010;1314:194-205. doi:
50 570 <https://doi.org/10.1016/j.brainres.2009.09.077>
- 51 571 54. Pelletier G, Li S, Luu-The V, et al. Oestrogenic Regulation of Pro-Opiomelanocortin, Neuropeptide
52 572 Y and Corticotrophin-Releasing Hormone mRNAs in Mouse Hypothalamus. *Journal of*
53 573 *Neuroendocrinology* 2007;19(6):426-31. doi: 10.1111/j.1365-2826.2007.01548.x

- 1
2
3 574 55. Rosano GM, Panina G. Oestrogens and the heart. *Therapie* 1999;54(3):381-5. [published Online
4 575 First: 1999/09/29]
5 576 56. Gale CR, Čukić I, Batty GD, et al. When Is Higher Neuroticism Protective Against Death? Findings
6 577 From UK Biobank. *Psychological Science* 2017;28(9):1345-57. doi:
7 578 10.1177/0956797617709813
8 579 57. Cheng H, Montgomery S, Treglown L, et al. Emotional stability, conscientiousness, and self-
9 580 reported hypertension in adulthood. *Personality and Individual Differences* 2017;115:159-63.
10 581 doi: <https://doi.org/10.1016/j.paid.2016.02.034>
11 582 58. Barton DA, Dawood T, Lambert EA, et al. Sympathetic activity in major depressive disorder:
12 583 identifying those at increased cardiac risk? *J Hypertens* 2007;25(10):2117-24. doi:
13 584 10.1097/HJH.0b013e32829baae7 [published Online First: 2007/09/22]
14 585 59. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to
15 586 cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended
16 587 Cohort (SHHEC). *Heart* 2007;93(2):172-76. doi: 10.1136/hrt.2006.108167
17 588 60. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and
18 589 Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;336(7659):1475-82. doi:
19 590 10.1136/bmj.39609.449676.25
20
21
22
23 591

peer review only

592 **Table 1. Baseline characteristics for adverse cardiovascular outcomes**

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 50798	N = 56035	N = 15098	N = 12929
Median age (range)*	54 (47 - 61)	61 (55 - 65)	53 (46 - 60)	60 (53 - 64)
Females, N (%)	29228 (57.54%)	25893 (46.21%)	10929 (72.39%)	7676 (59.37%)
Ethnicity, N (%)				
White	46147 (90.84%)	51249 (91.46%)	14247 (94.36%)	12272 (94.92%)
Asian/Asian British	1771 (3.49%)	1696 (3.03%)	261 (1.73%)	179 (1.38%)
Black/ Black British	1323 (2.6%)	1769 (3.16%)	219 (1.45%)	222 (1.72%)
Median Townsend score (range)*	-1.89 (-3.45 - 0.54)	-2.07 (-3.51 - 0.39)	-1.64 (-3.3 - 0.93)	-1.84 (-3.42 - 0.76)
Age at leaving full-time education, N (%)				
<16	5916 (11.65%)	12085 (21.57%)	1725 (11.43%)	2607 (20.16%)
16	10265 (20.21%)	11827 (21.11%)	3178 (21.05%)	2732 (21.13%)
>16	34090 (67.11%)	31480 (56.18%)	10090 (66.83%)	7503 (58.03%)
Total physical activity in metabolic	3.97 (1.68 - 8.03)	3.79 (1.51 - 8.03)	3.89 (1.66 - 8)	3.68 (1.49 - 7.95)
Sedentary time in hours, median (range)*	4 (3 - 6)	4.5 (3.5 - 6)	4.5 (3 - 6)	5 (3.5 - 6)

bmjopen-2018-024433 on 30 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Diabetes, N (%)	1268 (2.5%)	3777 (6.74%)	380 (2.52%)	929 (7.19%)
Hypercholesterolaemia, N (%)	3011 (5.93%)	9210 (16.44%)	893 (5.91%)	2211 (17.1%)
Systolic BP in mmHg, median (range)*	125.5 (118 - 132)	149.5 (142 - 159.5)	124 (116 - 131)	147.5 (140.5 - 157.)
Body Mass Index, N (%)				
<18.5	389 (0.77%)	142 (0.25%)	103 (0.68%)	34 (0.26%)
18.5 – 25	22549 (44.39%)	13678 (24.41%)	6251 (41.4%)	2874 (22.23%)
25-30	20410 (40.18%)	25216 (45 %)	5936 (39.32%)	5389 (41.68%)
>30	7450 (14.67%)	16999 (30.34%)	2808 (18.6%)	4632 (35.83%)
Smoking status, N (%)				
Never smoked	30626 (60.29%)	31503 (56.22%)	7864 (52.09%)	6454 (49.92%)
Previously smoked	15056 (29.64%)	20140 (35.94%)	5118 (33.9%)	5065 (39.18%)
Current smoker	4970 (9.78%)	4199 (7.49%)	2093 (13.86%)	1381 (10.68%)
Alcohol frequency, N (%)				
Daily or almost daily	9450 (18.6%)	12970 (23.15%)	2736 (18.12%)	2881 (22.28%)
Three or four times a week	12175 (23.97%)	13033 (23.26%)	3253 (21.55%)	2837 (21.94%)
Once or twice a week	13644 (26.86%)	13889 (24.79%)	3880 (25.7%)	2916 (22.55%)

One to three times a month	6052 (11.91%)	5588 (9.97%)	2058 (13.63%)	1512 (11.69%)
Special occasions only	5534 (10.89%)	6330 (11.3%)	1904 (12.61%)	1729 (13.37%)
Never	3924 (7.72%)	4199 (7.49%)	1262 (8.36%)	1048 (8.11%)
Psychotropic medication, N (%)	1341 (2.64%)	1795 (3.2%)	2844 (18.84%)	2522 (19.51%)

593 All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value
 594 of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is
 595 an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households,
 596 households not owner-occupied and unemployment.

Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Peer review only

598 Table 2 Baseline characteristics for stroke outcomes

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 52502	N = 59724	N = 15581	N = 13947
Median age (range)*	54 (47 - 61)	61 (55 - 65)	54 (47 - 61)	60 (53 - 64)
Females, N (%)	29684 (56.54%)	26937 (45.1%)	11143 (71.52%)	8090 (58.01%)
Ethnicity, N (%)				
<i>White</i>	47697 (90.85%)	54578 (91.38%)	14697 (94.33%)	13212 (94.73%)
<i>Asian/Asian British</i>	1857 (3.54%)	1889 (3.16%)	280 (1.8%)	209 (1.5%)
<i>Black/ Black British</i>	1355 (2.58%)	1854 (3.1%)	223 (1.43%)	246 (1.76%)
Median Townsend score (range)*	-1.89 (-3.45 - 0.55)	-2.04 (-3.49 - 0.44)	-1.56 (-3.28 - 1.15)	-1.74 (-3.4 - 0.93)
Age at leaving full-time education, N (%)				
<16	6446 (12.28%)	13396 (22.43%)	1884 (12.09%)	2945 (21.12%)
16	10590 (20.17%)	12507 (20.94%)	3270 (20.99%)	2953 (21.17%)
>16	34914 (66.5%)	33114 (55.45%)	10317 (66.22%)	7947 (56.98%)
Total physical activity in metabolic	3.96 (1.67 - 8.02)	3.75 (1.5 - 8)	4.13 (1.67 - 8.36)	3.66 (1.45 - 7.83)
Sedentary time in hours, median (range)*	4 (3 - 6)	5 (3.5 - 6)	5 (3.5 - 6.5)	5 (4 - 7)

Diabetes, N (%)	1454 (2.77%)	4502 (7.54%)	449 (2.88%)	1163 (8.34%)
Hypercholesterolaemia, N (%)	3592 (6.84%)	10768 (18.03%)	1049 (6.73%)	2620 (18.79%)
Systolic BP in mmHg, median (range)*	125.5 (118 - 132)	149.5 (142 - 159.5)	127 (120.5 - 133)	147.5 (140.5 - 156.5)
Body Mass Index, N (%)				
<18.5	395 (0.75%)	151 (0.25%)	104 (0.67%)	38 (0.27%)
18.5 – 25	22967 (43.75%)	14242 (23.85%)	6374 (40.91%)	3017 (21.63%)
25-30	21185 (40.35%)	26817 (44.9%)	6149 (39.46%)	5769 (41.36%)
>30	7953 (15.15%)	18514 (31.%)	2954 (18.96%)	5123 (36.73%)
Smoking status, N (%)				
Never smoked	31318 (59.65%)	32982 (55.22%)	8052 (51.68%)	6834 (49%)
Previously smoked	15851 (30.19%)	22019 (36.87%)	5340 (34.27%)	5560 (39.87%)
Current smoker	5170 (9.85%)	4501 (7.54%)	2163 (13.88%)	1519 (10.89%)
Alcohol frequency, N (%)				
Daily or almost daily	9760 (18.59%)	13751 (23.02%)	2817 (18.08%)	3085 (22.12%)
Three or four times a week	12563 (23.93%)	13827 (23.15%)	3335 (21.4%)	3020 (21.65%)
Once or twice a week	14089 (26.84%)	14719 (24.65%)	3993 (25.63%)	3125 (22.41%)

One to three times a month	6220 (11.85%)	5971 (10%)	2122 (13.62%)	1627 (11.67%)
Special occasions only	5744 (10.94%)	6794 (11.38%)	1978 (12.69%)	1885 (13.52%)
Never	4102 (7.81%)	4630 (7.75%)	1330 (8.54%)	1199 (8.6%)
Psychotropic medication, N (%)	1408 (2.68%)	1996 (3.34%)	2976 (19.1%)	2778 (19.92%)

599 All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value
 600 of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is
 601 an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households,
 602 households not owner-occupied and unemployment.

604 Table 3: Risk of adverse cardiovascular event by clinical group: unadjusted, partially adjusted and fully adjusted models.

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.60	(2.39 - 2.82)	3.31x10 ⁻¹¹³	1.72	(1.57 - 1.88)	1.99x10 ⁻³³	1.36	(1.22 - 1.52)	2.92x10 ⁻⁸
MDD only	0.69	(0.51 - 0.94)	0.02	0.82	(0.6 - 1.13)	0.23	0.75	(0.54 - 1.04)	0.08
Hypertension and MDD	2.84	(2.55 - 3.17)	6.31x10 ⁻⁷⁷	2.27	(2.02 - 2.55)	2.75x10 ⁻⁴⁴	1.66	(1.45 - 1.9)	7.48x10 ⁻¹⁴
Time varying Variables									
MDD only	1.01	(1.004 - 1.02)	2.38x10 ⁻³	1.01	(1.004 - 1.02)	3.19x10 ⁻³	1.01	(1.004 - 1.02)	3.03x10 ⁻³

605

606 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of

607 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and

608 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

bmjopen-2018-024443 on 30 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 26, 2024 by guest. Protected by copyright.

610 Table 4: Risk of adverse cardiovascular event by clinical group: unadjusted, partially adjusted and fully adjusted models with hypertension as the
611 comparator

Group	Unadjusted			Model 1 - Sociodemographic			Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
<i>Hypertension only</i>	1(ref)			1(ref)			1(ref)		
<i>No Hypertension - No MDD</i>	0.38	(0.35 - 0.42)	3.31x10 ⁻¹¹³	0.58	(0.53 - 0.63)	1.99x10 ⁻³³	0.73	(0.66 - 0.82)	2.92x10 ⁻⁸
<i>MDD only</i>	0.27	(0.2 - 0.36)	1.14x10 ⁻¹⁷	0.48	(0.35 - 0.66)	4.91x10 ⁻⁶	0.55	(0.4 - 0.76)	3.23x10 ⁻⁴
<i>Hypertension and MDD</i>	1.09	(0.996 - 1.2)	0.06	1.32	(1.2 - 1.46)	3.07x10 ⁻⁸	1.22	(1.1 - 1.35)	1.30x10 ⁻⁴
Time varying Variables									
<i>MDD only</i>	1.01	(1.004 - 1.02)	0.002	1.01	(1.004 - 1.02)	3.19x10 ⁻³	1.01	(1.004 - 1.02)	3.03x10 ⁻³

612 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of
613 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
614 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

616 Table 5: Risk of stroke event by clinical group: unadjusted, partially adjusted and fully adjusted models.

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension- No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.55	(2.16 - 3.02)	3.84x10 ⁻²⁸	1.64	(1.38 - 1.96)	3.35x10 ⁻⁸	1.21	(0.97 - 1.51)	0.09
MDD only	1.14	(0.86 - 1.52)	0.37	1.37	(1.02 - 1.84)	0.037	1.20	(0.89 - 1.63)	0.24
Hypertension and MDD	2.67	(2.13 - 3.34)	9.79x10 ⁻¹⁸	2.05	(1.63 - 2.58)	1.08x10 ⁻⁹	1.37	(1.04 - 1.79)	0.02

617 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of
 618 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
 619 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

620

622 Table 6: Risk of stroke event by clinical group: unadjusted, partially adjusted and fully adjusted models with hypertension as the comparator

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
<i>Hypertension only</i>	1(ref)			1(ref)			1(ref)		
<i>No Hypertension - No MDD</i>	0.39	(0.33 - 0.46)	3.84x10 ⁻²⁸	0.61	(0.51 - 0.73)	3.35x10 ⁻⁸	0.82	(0.66 - 1.03)	0.09
<i>MDD only</i>	0.45	(0.34 - 0.58)	1.43x10 ⁻⁹	0.83	(0.63 - 1.1)	0.19	0.99	(0.73 - 1.35)	0.95
<i>Hypertension and MDD</i>	1.05	(0.86 - 1.27)	0.64	1.25	(1.03 - 1.52)	0.03	1.13	(0.92 - 1.39)	0.26

623 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of
 624 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
 625 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

626

627 Table 7: Fully adjusted HR compared with results from competing risks analysis for cardiovascular endpoints

Fully adjusted non-competing risks analysis Fully adjusted competing risks model

Group	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.36	(1.22- 1.52)	2.92x10 ⁻⁸	1.37	(1.22-1.53)	4 x10 ⁻⁸
MDD only	0.75	(0.54- 1.04)	0.08	0.76	(0.55-1.03)	0.08
Hypertension and MDD	1.66	(1.45- 1.9)	7.48x10 ⁻¹⁴	1.67	(1.45-1.91)	2.2 x10 ⁻¹³
tvc						
MDD only	1.01	(1.004- 1.02)	3.03x10 ⁻³	1.01	(1.004-1.02)	0.003

628 Adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking
 629 history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder,
 630 aHR = Adjusted hazard ratio, C.I. = Confidence interval.

bmjopen-2018-024433 on 30 September 2019. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

631 Table 8: Fully adjusted HR compared with results from competing risks analysis for stroke endpoints

Fully adjusted non-competing risks analysis Fully adjusted competing risks model

Group	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.21	(0.97- 1.51)	0.09	1.21	(0.96- 1.52)	0.1
MDD only	1.20	(0.89- 1.63)	0.24	1.20	(0.88- 1.64)	0.25
Hypertension and MDD	1.37	(1.04- 1.79)	0.02	1.36	(1.03- 1.8)	0.031

632 Adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking
 633 history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder,
 634 aHR = Adjusted hazard ratio, C.I. = Confidence interval.

635

636 Figure 1: Adjusted survival analysis graph for adverse cardiovascular outcome showing greatest hazard for the comorbid group. MDD appears protective compared to the
 637 comparator group initially, however, shows increased hazard after 41 months. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and
 638 ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
 639 psychotropic medication use (MDD = Major Depressive disorder)

640

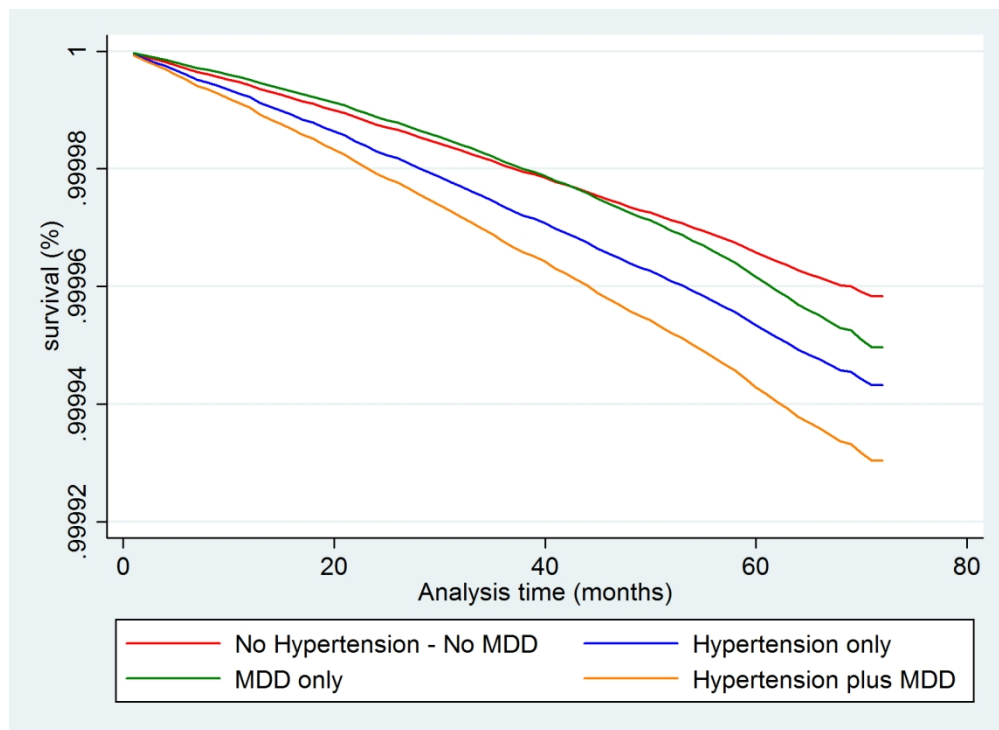
641 Figure 2: Adjusted survival analysis graph for stroke outcomes showing significantly increased hazard for comorbid Hypertension and MDD, with similar insignificant
 642 increased hazard trends for hypertension only and MDD only. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of
 643 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic
 644 medication use. (MDD = Major Depressive disorder)

1
2
3 645
4 646
5 647
6 648
7 649
8 650
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Figure 3: Log (-log) plot showing non-proportionality of MDD only survival over time. Paths between the comparator group and the MDD group cross at the 22.5 month mark. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. (MDD = Major Depressive disorder)

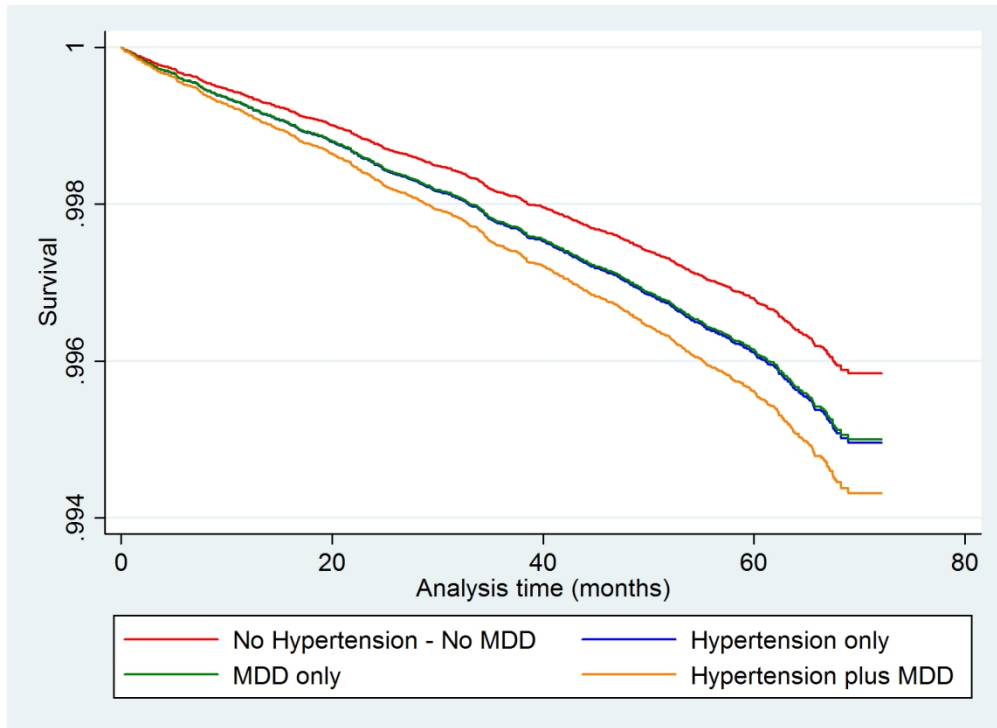
For peer review only

bmjopen-2018-024433 on 20 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.



Adjusted survival analysis graph for adverse cardiovascular outcome showing greatest hazard for the comorbid group. MDD appears protective compared to the comparator group initially, however, shows increased hazard after 41 months. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use (MDD = Major Depressive disorder)

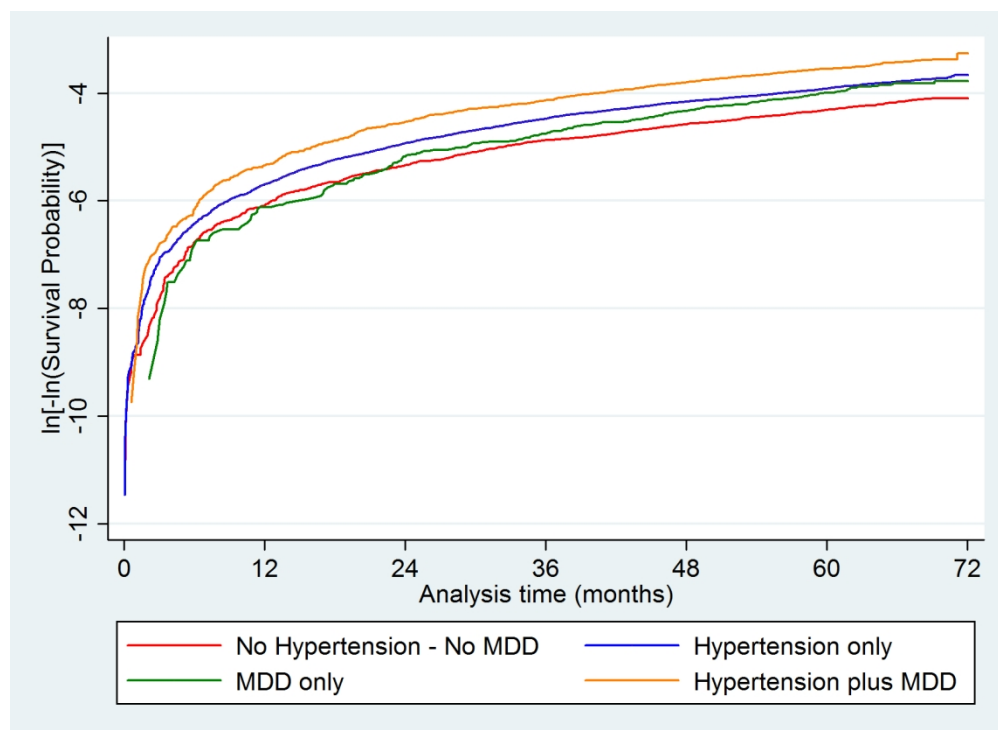
152x110mm (300 x 300 DPI)



Adjusted survival analysis graph for stroke outcomes showing significantly increased hazard for comorbid Hypertension and MDD, with similar insignificant increased hazard trends for hypertension only and MDD only. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. (MDD = Major Depressive disorder)

152x110mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Log (-log) plot showing non-proportionality of MDD only survival over time. Paths between the comparator group and the MDD group cross at the 22.5 month mark. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. (MDD = Major Depressive disorder)

152x110mm (300 x 300 DPI)

1
2
3 **Supplementary information for Impact of major depression on cardiovascular outcomes for**
4 **individuals with hypertension: prospective study in UK Biobank. Graham et al**
5
6
7

8 **METHODS**
9

10
11 **New-onset cardiovascular outcomes**
12

13
14
15 Date and cause of death were obtained from death certificates held by the National Health
16 Service (NHS) Information Centre for participants from England and Wales and the NHS
17 Central Register Scotland for participants from Scotland. Date and cause of hospital
18 admissions were identified via record linkage to Health Episode Statistics (HES) records for
19 England, the Patient Episode Database for Wales (PEDW) and to the Scottish Morbidity
20 Records (SMR) for Scotland. Detailed information about the record linkage procedure is
21 available online ¹². At the time of analysis, mortality data were available up to 31st January
22 2016 for England and Wales and 11th November 2015 for Scotland. Hospital admission data
23 were available for the Scottish, English and Welsh participants until the 31st August 2014,
24 31st March 2015, and 28th February 2015 respectively. Therefore, for new cardiovascular
25 events, end of follow up was classified as the hospital admission dates unless preceded by
26 the date of death or the date of first cardiovascular event. New onset cardiovascular events
27 were defined as an ICD 10 code of G45, G46, I20- I25, or I6 recorded on a death certificate
28 or hospital admission. Deaths that predated the assessment date were excluded from
29 analysis as presumed errors as were those in which data had only recorded a death date but
30 no cause of death or a cause of death but no death date. Participants that had hospital
31 admissions prior to the assessment date due to the aforementioned ICD10 codes were
32 excluded as were not first episode. In addition, ICD-9 codes 430-438, 410-414, 429 and
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 429.2 were also excluded. hospital records are not available for the entire lifetime of study
4
5 individuals, potentially missing some early cardiovascular events, as such those with self-
6
7 declared prior cardiovascular disease at baseline were also excluded.
8
9

10 11 **Blood Pressure**

12
13
14 Blood pressure was measured in a sitting position partway through the interview and at the
15
16 end of the interview using a digital blood pressure monitor (Omron HEM-7015IT.). Full
17
18 protocol is available online <https://biobank.ctsu.ox.ac.uk/crystal/docs/Bloodpressure.pdf>
19
20
21

22 23 24 25 **Depression definition**

26
27
28 The criteria for lifetime MDD were created via the the following questions via touchscreen
29
30 questionnaire were: "*Looking back over your life, have you ever had a time when you were feeling*
31
32 *depressed or down for at least a whole week?*" (depression); "*Have you ever had a period of time*
33
34 *lasting at least two days when you were so irritable that you found yourself shouting at people or*
35
36 *starting fights or arguments?*" (irritability); "*How many weeks was the longest period when you were*
37
38 *feeling depressed or down?*" (duration); "*Have you ever seen a general practitioner (GP) for nerves,*
39
40 *anxiety, tension or depression?*" (consulted GP); "*Have you ever seen a psychiatrist for nerves,*
41
42 *anxiety, tension or depression?*" (consulted psychiatrist). Participants were classified as having a
43
44 history of MDD if they reported at least one episode which comprised of depression and/or
45
46 irritability, with a duration of at least two weeks, plus had consulted with either a general
47
48 practitioner or psychiatrist for mental ill-health.
49
50
51

52 53 **Physical activity**

54
55
56 Physical activity was based on self-report, utilising the short form International Physical
57
58 Activity Questionnaire (IPAQ). Participants reported the frequency and duration of
59
60

1
2
3 moderate and vigorous activity along with walking undertaken in a typical week³. Data were
4
5 analysed in accordance with the IPAQ scoring protocol⁴ and total physical activity was
6
7 computed as the sum of walking, moderate and vigorous activity, measured as metabolic
8
9 equivalents (MET-hours/week). Physical activity was used in analyses as a continuous
10
11 variable. Participants who reported greater than 24 hours a day doing all activity were
12
13 classified as missing.
14
15
16

17 18 **Sedentary behaviour**

19
20
21 Sedentary behaviour duration was derived from the sum of self-reported time spent driving,
22
23 using computer and watching television. Those stating that they had performed “less than
24
25 an hour” of sedentary activities were coded as 0.5hrs to allow use of a continuous variable.
26
27 Participants who reported greater than 24 hours a day doing all activity were classified as
28
29 missing.
30
31
32

33 34 **Socio-demographic and other covariates**

35
36 Self-report on taking antihypertensive medication was taken from a question specific to
37
38 cardiovascular medications, where antihypertensive medication was an option to respond.
39
40 Area-based socioeconomic status was derived from postcode of residence, utilising the
41
42 census-derived Townsend deprivation index scored on housing, employment, social class
43
44 and car availability where a negative score represents greater affluence^{5 6}. Age was
45
46 calculated from dates of birth and baseline assessment date. Smoking status was
47
48 categorised into never, former and current smoking based on self-report, those who wished
49
50 not to answer were coded as missing. Drink frequency was categorised into daily, three or
51
52 four times a week, once or twice a week, one to three times a month, special occasions
53
54 only, and never based on self-report. Those who wished not to answer were coded as
55
56
57
58
59
60

1
2
3 missing. Medical history of diabetes and high cholesterol was collected from the self-
4 completed, baseline assessment questionnaire of medical conditions. Ethnicity was
5
6 categorised as Caucasian, black/mixed and Asian/mixed based on self-report. Other
7
8 ethnicities coded as missing due to small numbers. Age at completing full-time education
9
10 was categorised as (<16, 16, >16). Height and body weight were measured by trained nurses
11
12 during the initial assessment centre visit. Body mass index (BMI) was calculated as
13
14 (weight/height²) and the WHO criteria⁷ to classify BMI into: underweight <18.5, normal
15
16 weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.0 kg.m⁻². Psychotropic medication
17
18 use was defined by the presence of pharmaceuticals from British National Formulary (BNF)
19
20 chapters 4.1.1 to 4.3.4⁸ on self-report medication lists at baseline. Duration of hypertension
21
22 was calculated utilising age and age of hypertension diagnosis. Antihypertensive medication
23
24 count was calculated as the absolute number of ACE inhibitors, angiotensin II receptor
25
26 antagonists, calcium channel blockers, beta-blockers and thiazide diuretics prescribed to an
27
28 individual. Generic medication names were sought and cross-referenced with the BNF
29
30 chapters 2.2.1, 2.4, 2.5.5 and 2.6.2⁸.

31 32 33 34 35 36 37 38 39 40 41 42 43 **Statistical analysis:**

44
45
46 A best-fit multivariable regression spline model (stata command “mrvs”) was used to find
47
48 the best model to adjust for non-linear covariates. For the adverse cardiovascular outcomes,
49
50 A single knot was fitted for age at age 50 and two knots were fitted for total physical activity
51
52 at 1.65 and 8.062 metabolic equivalent hours. In the male subgroup analysis two knots were
53
54 fitted for total physical activity at 1.7 and 8.507 metabolic equivalent hours, in the female
55
56 subgroup two knots were fitted for total physical activity at 1.57 and 3.75 and two knots
57
58
59
60

1
2
3 were fitted at systolic blood pressure 121.5 and 147.5. No bends were noted in any models
4
5 for the stroke outcomes.
6
7

8 9 **Model selection and covariate adjustment**

10
11 All variables were tested against outcome measures (cardiovascular outcomes and stroke outcomes)
12
13 using univariate analysis to assess appropriateness for inclusion in the final model. All covariates
14
15 were significantly associated with the outcomes. and were Two continuous variables, age and total
16
17 physical activity, expressed non-linearity within the main analysis and male subgroup analysis for
18
19 cardiovascular outcomes and as such regression splines were used with two and three knots
20
21 respectively. Two knots were included within the female subgroup analysis for physical activity. For
22
23 stroke outcome there were no bends in the main or sex-specific models.
24
25
26

27
28 Within the main analysis for cardiovascular outcomes, the groups of depression only, Asian/Asian
29
30 British ethnicity and BMI<18.5 covariates failed the proportionality assumption and as such, were
31
32 incorporated into the model as a time varying coefficients. Within the sex specific models depression
33
34 only failed the PH test within the female only analysis and ethnicity and BMI failed within the male
35
36 only analysis. For the stroke outcomes gender and BMI class failed the proportionality assumption
37
38 within the main analysis, with no failures within the sex-specific analysis. Analysis was repeated with
39
40 the hypertension only as the comparator group to assess for any significant difference between the
41
42 co-morbid group and the hypertension only group.
43
44
45

46 47 **Time varying covariates**

48
49 Due to the finding of MDD failing the proportionality assumption in the cardiovascular outcome in
50
51 the primary analysis a series of further analyses have been performed to find when the assumption
52
53 was not met. A log (-log) plot (fig 3) showed the proportionality assumption was broken at 22.5
54
55 months in the fully adjusted model in the primary analysis. As such, separate models were
56
57
58
59
60

1
2
3 performed prior to and after these points. Prior to 22.5months the HR for MDD shows a trend that is
4 reduced but insignificant (HR 0.82, 95%CI 0.6 - 1.13), becoming significantly increased after the 22.5
5 time point. (HR 1.27, 95%CI 1.06 - 1.52) (Table 9 supplementary digital content). Both stratified
6 models passed the proportionality assumption using Schoenfeld residuals. Similar to the major
7 analysis, the female model showed the MDD only group failing the proportionality assumption,
8 although this was at the 29 month time point. (tables 6 and 10 of the supplementary digital
9 content).

For peer review only

References

1. Palmer LJ. UK Biobank: bank on it. *Lancet* 2007;369(9578):1980-2. doi: 10.1016/S0140-6736(07)60924-6
2. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *Plos Medicine* 2015;12(3) doi: 10.1371/journal.pmed.1001779
3. Guo W, Bradbury KE, Reeves GK, et al. Physical activity in relation to body size and composition in women in UK Biobank. *Annals of Epidemiology* 2015;25(6):406-13.e6. doi: <http://dx.doi.org/10.1016/j.annepidem.2015.01.015>
4. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Medicine and science in sports and exercise* 2003;35(8):1381-95. doi: 10.1249/01.mss.0000078924.61453.fb [published Online First: 2003/08/06]
5. Townsend P. Deprivation. *Journal of Social Policy* 2009;16(02):125. doi: 10.1017/s0047279400020341
6. Townsend P, Phillimore M, Beattie A. Health and Deprivation: Inequality and the North. London: Croom Helm Ltd 1988.
7. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;894:i-xii, 1-253.
8. COMMITTEE. JF. British National Formulary. 67 ed. London: BMJ Group and Pharmaceutical Press 2014.

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Supplementary Tables and figures

Supplementary Table1: Descriptive analysis for adverse cardiovascular outcome – males only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N= 21570	N = 30142	N = 4169	N = 5253
Median age (range)*	54 (47 - 61)	61 (54 - 65)	53 (46 - 60)	59 (52 - 64)
Ethnicity, N (%)				
<i>White</i>	19562 (90.69%)	27808 (92.26%)	3923 (94.1%)	5001 (95.2%)
<i>Asian/Asian British</i>	863 (4.%)	969 (3.21%)	87 (2.09%)	86 (1.64%)
<i>Black/ Black British</i>	559 (2.59%)	780 (2.59%)	52 (1.25%)	54 (1.03%)
Median Townsend score (range)*	-1.87 (-3.47 - 0.59)	-2.08 (-3.53 - 0.41)	-1.58 (-3.3 - 1.07)	-1.81 (-3.44 - 0.78)
Age at leaving full-time education, N (%)				
<i><16</i>	2517 (11.67%)	6328 (20.99%)	464 (11.13%)	1005 (19.13%)
<i>16</i>	4473 (20.74%)	6235 (20.69%)	859 (20.6%)	1096 (20.86%)
<i>>16</i>	14344 (66.5%)	17257 (57.25%)	2807 (67.33%)	3118 (59.36%)
Total physical activity in metabolic	4.15 (1.75 - 8.51)	3.99 (1.65 - 8.51)	4.15 (1.7 - 8.36)	3.76 (1.54 - 7.97)

Sedentary time in hours, median (range)*	4.5 (3.5 - 6)	5 (3.5 - 6.5)	5 (3.5 - 6.5)	5 (4 - 7)
Diabetes, N (%)	721 (3.34%)	2401 (7.97%)	159 (3.81%)	477 (9.08%)
Hypercholesterolaemia, N (%)	1614 (7.48%)	5585 (18.53%)	363 (8.71%)	1056 (20.1%)
Systolic BP in mmHg, median (range)*	128 (121.5 - 133.5)	149.5 (142 - 159)	127.5 (120.5 - 133)	148 (141 - 157)
Body Mass Index, N (%)				
<18.5	74 (0.34%)	35 (0.12%)	22 (0.53%)	12 (0.23%)
18.5 – 25	7607 (35.27%)	5842 (19.38%)	1394 (33.44%)	890 (16.94%)
25-30	10594 (49.11%)	15114 (50.14%)	2019 (48.43%)	2532 (48.2%)
>30	3295 (15.28%)	9151 (30.36%)	734 (17.61%)	1819 (34.63%)
Smoking status, N (%)				
Never smoked	12038 (55.81%)	15145 (50.25%)	1999 (47.95%)	2268 (43.18%)
Previously smoked	6777 (31.42%)	12125 (40.23%)	1447 (34.71%)	2295 (43.69%)
Current smoker	2688 (12.46%)	2776 (9.21%)	716 (17.17%)	686 (13.06%)
Alcohol frequency, N (%)				
Daily or almost daily	4822 (22.36%)	8653 (28.71%)	969 (23.24%)	1503 (28.61%)
Three or four times a week	5718 (26.51%)	7913 (26.25%)	1022 (24.51%)	1323 (25.19%)

Once or twice a week	5932 (27.5%)	7546 (25.03%)	1063 (25.5%)	1178 (22.43%)
One to three times a month	2193 (10.17%)	2392 (7.94%)	440 (10.55%)	479 (9.12%)
Special occasions only	1554 (7.2%)	2154 (7.15%)	328 (7.87%)	423 (8.05%)
Never	1343 (6.23%)	1473 (4.89%)	345 (8.28%)	345 (6.57%)
Psychotropic medication, N (%)	398 (1.85%)	670 (2.22%)	678 (16.26%)	879 (16.73%)

All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.

bmjopen-2018-024443 on 30 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Supplementary Table 2: Descriptive analysis for adverse cardiovascular outcome – females only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N= 29228	N = 25893	N = 10929	N = 7676
Median age (range)*	54 (47 - 61)	61 (55 - 65)	53 (47 - 60)	60 (53 - 64)
Ethnicity, N (%)				
White	26585 (90.96%)	23441 (90.53%)	10324 (94.46%)	7271 (94.72%)
Asian/Asian British	908 (3.11%)	727 (2.81%)	174 (1.59%)	93 (1.21%)
Black/ Black British	764 (2.61%)	989 (3.82%)	167 (1.53%)	168 (2.19%)
Median Townsend score (range)*	-1.90 (-3.44 - 0.51)	-2.06 (-3.5 - 0.38)	-1.66 (-3.3 - 0.84)	-1.87 (-3.4 - 0.74)
Age at leaving full-time education, N (%)				
<16	3399 (11.63%)	5757 (22.23%)	1261 (11.54%)	1602 (20.87%)
16	5792 (19.82%)	5592 (21.6%)	2319 (21.22%)	1636 (21.31%)
>16	19746 (67.56%)	14223 (54.93%)	7283 (66.64%)	4385 (57.13%)
Total physical activity in metabolic	3.87 (1.65 - 7.71)	3.51 (1.37 - 7.59)	3.79 (1.65 - 7.91)	3.65 (1.45 - 7.93)
Sedentary time in hours, median (range)*	4 (3 - 5)	4 (3 - 5.5)	4 (3 - 5.5)	4.5 (3 - 6)

bmjopen-2018-024443 on 30 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Diabetes, N (%)	547 (1.87%)	1376 (5.31%)	221 (2.02%)	452 (5.89%)
Hypercholesterolaemia, N (%)	1397 (4.78%)	3625 (14.%)	530 (4.85%)	1155 (15.05%)
Systolic BP in mmHg, median (range)*	123.5 (115.5 - 130.5)	149.5 (142 - 160)	122.5 (114.5 - 130)	147.5 (140.5 - 157)
Body Mass Index, N (%)				
<18.5	315 (1.08%)	107 (0.41%)	81 (0.74%)	22 (0.29%)
18.5 – 25	14942 (51.12%)	7836 (30.26%)	4857 (44.44%)	1984 (25.85%)
25-30	9816 (33.58%)	10102 (39.01%)	3917 (35.84%)	2857 (37.22%)
>30	4155 (14.22%)	7848 (30.31%)	2074 (18.98%)	2813 (36.65%)
Smoking status, N (%)				
Never smoked	18588 (63.6%)	16358 (63.18%)	5865 (53.66%)	4186 (54.53%)
Previously smoked	8279 (28.33%)	8015 (30.95%)	3671 (33.59%)	2770 (36.09%)
Current smoker	2282 (7.81%)	1423 (5.5%)	1377 (12.6%)	695 (9.05%)
Alcohol frequency, N (%)				
Daily or almost daily	4628 (15.83%)	4317 (16.67%)	1767 (16.17%)	1378 (17.95%)
Three or four times a week	6457 (22.09%)	5120 (19.77%)	2231 (20.41%)	1514 (19.72%)
Once or twice a week	7712 (26.39%)	6343 (24.5%)	2817 (25.78%)	1738 (22.64%)

One to three times a month	3859 (13.2%)	3196 (12.34%)	1618 (14.8%)	1033 (13.46%)
Special occasions only	3980 (13.62%)	4176 (16.13%)	1576 (14.42%)	1306 (17.01%)
Never	2581 (8.83%)	2726 (10.53%)	917 (8.39%)	703 (9.16%)
Psychotropic medication, N (%)	943 (3.23%)	1125 (4.34%)	2166 (19.82%)	1643 (21.4%)

All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.

Supplementary Table 3: Descriptive analysis for stroke outcome – males only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 22816	N = 32787	N = 4438	N = 5857
Median age (range)*	55 (47 - 62.)	61 (54 - 65)	54 (47 - 61)	60 (53 - 64)
Ethnicity, N (%)				
White	20699 (90.72%)	30219 (92.17%)	4173 (94.03%)	5569 (95.08%)
Asian/Asian British	932 (4.08%)	1116 (3.4%)	102 (2.3%)	105 (1.79%)
Black/ Black British	576 (2.52%)	820 (2.5%)	53 (1.19%)	59 (1.01%)
Median Townsend score (range)*	-1.88 (-3.47 - 0.59)	-2.05 (-3.5 - 0.46)	-1.56 (-3.28 - 1.15)	1.74 (-3.4 - 0.93)
Age at leaving full-time education, N (%)				
<16	2900 (12.71%)	7256 (22.13%)	558 (12.57%)	1193 (20.37%)
16	4702 (20.61%)	6704 (20.45%)	909 (20.48%)	1222 (20.86%)
>16	14960 (65.57%)	18471 (56.34%)	2930 (66.02%)	3397 (58.%)
Total physical activity in metabolic	4.12 (1.74 - 8.48)	3.96 (1.65 - 8.44)	4.13 (1.67 - 8.36)	3.66 (1.45 - 7.83)
Sedentary time in hours, median (range)*	5 (3.5 - 6)	5 (4 - 7)	5 (3.5 - 6.5)	5 (4 - 7)

 bmjopen-2018-024433 on 30 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Diabetes, N (%)	873 (3.83%)	2951 (9.%)	208 (4.69%)	635 (10.84%)
Hypercholesterolaemia, N (%)	2045 (8.96%)	6736 (20.54%)	457 (10.3%)	2293 (22.08%)
Systolic BP in mmHg, median (range)*	128 (121.5 - 133.5)	149 (142 - 159)	127 (120.5 - 133)	147.5 (140.5 - 156.5)
Body Mass Index, N (%)				
<18.5	79 (0.35%)	39 (0.12%)	22 (0.5%)	12 (0.2%)
18.5 – 25	7867 (34.48%)	6215 (18.96%)	1452 (32.72%)	960 (16.39%)
25-30	11203 (49.1%)	16341 (49.84%)	2142 (48.26%)	2780 (47.46%)
>30	3667 (16.07%)	10192 (31.09%)	822 (18.52%)	2105 (35.94%)
Smoking status, N (%)				
Never smoked	12502 (54.79%)	16054 (48.96%)	2094 (47.18%)	2469 (42.15%)
Previously smoked	7399 (32.43%)	13603 (41.49%)	1582 (35.65%)	2610 (44.56%)
Current smoker	2836 (12.43%)	3013 (9.19%)	754 (16.99%)	770 (13.15%)
Alcohol frequency, N (%)				
Daily or almost daily	5085 (22.29%)	9309 (28.39%)	1021 (23.01%)	1645 (28.09%)
Three or four times a week	6039 (26.47%)	8556 (26.1%)	1077 (24.27%)	1450 (24.76%)
Once or twice a week	6264 (27.45%)	8161 (24.89%)	1121 (25.26%)	1305 (22.28%)

One to three times a month	2307 (10.11%)	2642 (8.06%)	478 (10.77%)	538 (9.19%)
Special occasions only	1666 (7.3%)	2394 (7.3%)	355 (8.%)	503 (8.59%)
Never	1444 (6.33%)	1711 (5.22%)	383 (8.63%)	414 (7.07%)
Psychotropic medication, N (%)	429 (1.88%)	793 (2.42%)	735 (16.56%)	1025 (17.5%)

All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.

Supplementary Table 4: Descriptive analysis for stroke outcome – females only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 29684	N = 26937	N = 11143	N = 8090
Median age (range)*	54 (47 - 61)	61 (56 - 65)	53 (47 - 60)	60 (54 - 64)
Ethnicity, N (%)				
White	26998 (90.95%)	24359 (90.43%)	10524 (94.44%)	7643 (94.47%)
Asian/Asian British	925 (3.12%)	773 (2.87%)	178 (1.6%)	104 (1.29%)
Black/ Black British	779 (2.62%)	1034 (3.84%)	170.00 (1.53%)	187 (2.31%)
Median Townsend score (range)*	-1.90 (-3.44 - 0.52)	-2.03 (-3.48 - 0.43)	-1.66 (-3.29 - 0.86)	-1.83 (-3.38 - 0.85)
Age at leaving full-time education, N (%)				
<16	3546 (11.95%)	6140 (22.79%)	1326 (11.9%)	1752 (21.66%)
16	5888 (19.84%)	5803 (21.54%)	2361 (21.19%)	1731 (21.4%)
>16	19954 (67.22%)	14643 (54.36%)	7387 (66.29%)	4550 (56.24%)
Total physical activity in metabolic	3.85 (1.65 - 7.7)	3.49 (1.35 - 7.57)	3.79 (1.65 - 7.89)	3.61 (1.41 - 7.87)

Sedentary time in hours, median (range)*	4.0 (3 - 5)	4.0 (3 - 5.5)	4.0 (3 - 5.5)	4.5 (3 - 6)
Diabetes, N (%)	581 (1.96%)	1551 (5.76%)	241 (2.16%)	528 (6.53%)
Hypercholesterolaemia, N (%)	1547 (5.21%)	4032 (14.97%)	592 (5.31%)	1327 (16.4%)
Systolic BP in mmHg, median (range)*	123.5 (115.5 - 131)	149.5 (142 - 160)	122.5 (114.5 - 130)	147.0 (140.5 - 157)
Body Mass Index, N (%)				
<18.5	316 (1.06%)	112 (0.42%)	82 (0.74%)	26 (0.32%)
18.5 – 25	15100 (50.87%)	8027 (29.8%)	4922 (44.17%)	2057 (25.43%)
25-30	9982 (33.63%)	10476 (38.89%)	4007 (35.96%)	2989 (36.95%)
>30	4286 (14.44%)	8322 (30.89%)	2132 (19.13%)	3018 (37.31%)
Smoking status, N (%)				
Never smoked	18816 (63.39%)	16928 (62.84%)	5958 (53.47%)	4365 (53.96%)
Previously smoked	8452 (28.47%)	8416 (31.24%)	3758 (33.73%)	2950 (36.46%)
Current smoker	2334 (7.86%)	1488 (5.52%)	1409 (12.64%)	749 (9.26%)
Alcohol frequency, N (%)				

Daily or almost daily	4675 (15.75%)	4442 (16.49%)	1796 (16.12%)	1440 (17.8%)
Three or four times a week	6524 (21.98%)	5271 (19.57%)	2258 (20.26%)	1570 (19.41%)
Once or twice a week	7825 (26.36%)	6558 (24.35%)	2872 (25.77%)	1820 (22.5%)
One to three times a month	3913 (13.18%)	3329 (12.36%)	1644 (14.75%)	1089 (13.46%)
Special occasions only	4078 (13.74%)	4400 (16.33%)	1623 (14.57%)	1382 (17.08%)
Never	2658 (8.95%)	2919 (10.84%)	947 (8.5%)	785 (9.7%)
Psychotropic medication, N (%)	979 (3.3%)	1203 (4.47%)	2241 (20.11%)	1753 (21.67%)

All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.

Supplementary Table 5: Risk of adverse cardiovascular event by clinical group, in males only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension- No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.21	(2.00-2.45)	2.28x10 ⁻⁵³	1.62	(1.46-1.83)	5.80x10 ⁻¹⁹	1.29	(1.13-1.47)	1.35x10 ⁻⁴
MDD only	1.17	(0.95-1.56)	0.12	1.18	(0.95-1.46)	0.12	1.12	(0.9-1.39)	0.3
Hypertension and MDD	2.46	(2.13-2.84)	3.12x10 ⁻³⁴	1.95	(1.68-2.27)	2.81x10 ⁻¹⁸	1.47	(1.24-1.74)	8.71x10 ⁻⁶

*Adjusted for sociodemographic factors (age, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I.= confidence interval

Supplementary Table 6: Risk of adverse cardiovascular event by clinical group, in females only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.75	(2.38 - 3.18)	6.16x10 ⁻⁴³	1.86	(1.6-2.17)	1.43x10 ⁻¹⁵	1.64	(1.33-2.02)	4.36x10 ⁻⁶
MDD only	0.67	(0.42-1.08)	0.10	0.72	(0.45-1.17)	0.19	0.68	(0.42-1.1)	0.12
Hypertension and MDD	3.68	(3.1-4.38)	5.62x10 ⁻⁴⁹	2.78	(1.58-3.29)	4.62x10 ⁻²⁹	2.18	(1.82-2.52)	4.76x10 ⁻¹¹
Time varying Variables									
MDD only	1.02	(1.006-1.03)	2.45x10 ⁻³	1.02	(1.005-1.03)	4.00x10 ⁻³	1.02	(1.004-1.03)	6.19x10 ⁻³

*Adjusted for sociodemographic factors (age, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval

Supplementary Table 7: Risk of stroke event by clinical group, in males only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.43	(1.95 - 3.03)	1.92x10 ⁻¹⁵	1.74	(1.38 - 2.19)	2.58x10 ⁻⁶	1.19	(0.9 - 1.5)	0.22
MDD only	1.45	(0.96 - 2.2)	0.07	1.65	(1.09 - 2.5)	0.02	1.49	(0.97 - 2.29)	0.07
Hypertension and MDD	2.39	(1.74 - 3.27)	7.34x10 ⁻⁸	1.87	(1.35 - 2.6)	1.55x10 ⁻⁴	1.20	(0.83 - 1.74)	0.33

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = confidence interval

bmjopen-2018-024433 on 30 September 2019. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Supplementary Table 8: Risk of stroke event by clinical group, in females only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.38	(1.84 - 3.09)	6.50x10 ⁻¹¹	1.51	(1.14 - 1.99)	3.63x10 ⁻³	1.25	(0.88 - 1.79)	0.21
MDD only	1.09	(0.73 - 1.62)	0.67	1.15	(0.76 - 1.75)	0.51	0.99	(0.64 - 1.53)	0.98
Hypertension and MDD	3.05	(2.22 - 4.21)	8.71x10 ⁻¹²	2.22	(1.59 - 3.08)	2.27x10 ⁻⁶	1.62	(1.08 - 2.42)	0.02

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = confidence interval

Supplementary Table 9: Time stratified analysis by moment of proportional hazards failure for adverse cardiovascular outcomes (stratified at 22.5 months)

Fully adjusted* model pre-22.5 months Fully adjusted* model post-22.5 months

Group	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.36	(1.12 - 1.66)	0.002	1.36	(1.19 - 1.55)	5.06x10 ⁻⁶
MDD only	0.82	(0.60 - 1.13)	0.22	1.27	(1.06 - 1.52)	0.01
Hypertension and MDD	1.75	(1.39 - 2.21)	2.62x10 ⁻⁶	1.62	(1.38 - 1.90)	5.72x10 ⁻⁹

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.

MDD = Major depressive disorder, aHR =adjusted hazard ratio, C.I.= Confidence interval

Supplementary Table 10: Time stratified analysis by moment of proportional hazards failure for adverse cardiovascular outcomes (females only - stratified at 29 months)

Fully adjusted* model pre-29 months Fully adjusted* model post-29 months

Group	HR	95% C.I.	p-value	HR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.49	(1.06 - 2.08)	0.02	1.75	(1.33 - 2.30)	5.56x10 ⁻⁵
MDD only	0.73	(0.48 - 1.10)	0.13	1.58	(1.19 - 2.09)	0.002
Hypertension and MDD	1.80	(1.24 - 2.62)	0.002	2.47	(1.83 - 3.33)	2.89x10 ⁻⁹

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.

MDD = Major depressive disorder, aHR =adjusted hazard ratio, C.I.= Confidence interval

Supplementary Table 11: Relative excess risk due to interaction results on fully adjusted* models

Analysis	RERI	95% C.I.	LR test chi	p-value
Adverse cardiovascular outcome before 22.5 months	0.563	(0.189 - 0.938)	6.38	0.0116
Adverse cardiovascular outcome after 22.5 months	-0.009	(-0.293 - 0.275)	0.33	0.563
Adverse cardiovascular outcome (males only)	0.058	(-0.240 - 0.357)	0.02	0.899
Adverse cardiovascular outcome (females only)before 29 months	0.588	(0.074 - 1.103)	4.65	0.031
Adverse cardiovascular outcome (females only)after 29 months	0.142	(-0.447 - 0.732)	0.42	0.5173
Stroke outcome	-0.047	(-0.485 - 0.391)	0.12	0.7271
Stroke outcome (males only)	-0.480	(-1.195 - 0.234)	2.2	0.1376
Stroke outcome (females only)	0.372	(-0.216 - 0.959)	1.01	0.314

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.

RERI = Relative excess risk due to interaction, C.I.= Confidence interval

Supplementary Table 12: Comparison of additional hypertension factors (medication and diagnosis duration) across groups

	No Hypertension – No MDD	Hypertension only	MDD only	Hypertension and MDD
Antihypertensive medication prescription, N (%)	1,265 (2.49)	19,045 (33.99)	476 (3.04)	5,037 (37.34)
Number of antihypertensive medications, N (range)*	1 (1-1)	1 (1-2)	1 (1-1)	1 (1- 2)
Reported a duration of hypertension, N (%)	1,376 (2.71)	16,709 (29.82)	678 (4.42)	4,525 (33.55)
Duration of hypertension in years, median (range)*	6 (2-14)	8 (4-13)	6 (3-14)	8 (4 - 14)

*Median quantity of antihypertensive medications and median duration of hypertensive diagnosis presented for those on antihypertensive medications and supplied an age of hypertension diagnosis, respectively. MDD = Major Depressive disorder

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7

1		#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
2				
3				
4	Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
5				
6				
7				
8				
9				
10	Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-8
11				
12				
13				
14				
15				
16				
17				
18	Bias	#9	Describe any efforts to address potential sources of bias	6
19				
20	Study size	#10	Explain how the study size was arrived at	6
21				
22				
23	Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	See note 1
24				
25				
26				
27				
28	Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8-9
29				
30				
31				
32		#12b	Describe any methods used to examine subgroups and interactions	See note 2
33				
34				
35				
36		#12c	Explain how missing data were addressed	6-7
37				
38		#12d	If applicable, explain how loss to follow-up was addressed	1
39				
40				
41		#12e	Describe any sensitivity analyses	9
42				
43	Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	10
44				
45				
46				
47				
48				
49				
50				
51		#13b	Give reasons for non-participation at each stage	6,7
52				
53		#13c	Consider use of a flow diagram	n/a
54				
55				
56	Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	10
57				
58				
59				
60				

		confounders. Give information separately for exposed and unexposed groups if applicable.	
	#14b	Indicate number of participants with missing data for each variable of interest	See note 3
	#14c	Summarise follow-up time (eg, average and total amount)	10
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	6
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
	#16b	Report category boundaries when continuous variables were categorized	n/a
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	See note 4
Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

Author notes

1. 6,7,8,9, supplementary

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

- 1 2. 8-9, supplementary
- 2
- 3 3. n/a (supplementary)
- 4
- 5 4. 11-12, supplemental
- 6

7 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License
8 CC-BY. This checklist was completed on 25. May 2018 using <http://www.goodreports.org/>, a tool
9 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ Open

Impact of major depression on cardiovascular outcomes for individuals with hypertension: prospective survival analysis in UK Biobank.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024433.R3
Article Type:	Original research
Date Submitted by the Author:	22-Aug-2019
Complete List of Authors:	Graham, Nicholas; University of Glasgow Institute of Health and Wellbeing, Gartnavel Royal Hospital 1055 Great Western Road Glasgow, UK G12 0XH Ward, Joey; University of Glasgow Institute of Health and Wellbeing Mackay, Daniel; University of Glasgow Institute of Health and Wellbeing Pell, J. P.; University of Glasgow Institute of Health and Wellbeing Cavanagh, Jonathan; University of Glasgow Institute of Health and Wellbeing Padmanabhan, Sandosh; University of Glasgow, Institute of Cardiovascular and Medical Sciences, British Heart Foundation Glasgow Cardiovascular Research Centre Smith, Daniel; University of Glasgow, Institute of Health and Wellbeing
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Cardiovascular medicine
Keywords:	EPIDEMIOLOGY, mortality, cardiovascular disease, morbidity, depression, Hypertension < CARDIOLOGY

SCHOLARONE™
Manuscripts

1
2
3 **1 Impact of major depression on cardiovascular outcomes for individuals with hypertension:**
4
5 **2 prospective survival analysis in UK Biobank.**
6
7

8 **3 Short title: Outcomes of Hypertension plus Depression**
9

10
11 4 Nicholas A GRAHAM*^a, Clinical Research Fellow
12

13
14 5 Joey WARD^a, Research Fellow
15

16
17 6 Daniel MACKAY^b, Reader in Public Health
18

19
20 7 Jill PELL^b, Professor of Public Health
21

22
23 8 Jonathan CAVANAGH^c, Professor of Psychiatry
24

25
26 9 Sandosh PADMANABHAN^d, Professor of Cardiovascular Genomics and Therapeutics
27

28
29 10 Daniel J. SMITH^a, Professor of Psychiatry.
30

31
32 11 Number of Supplementary files: 1
33

34
35 12 Word count of Manuscript: 3,969 (exc. Tables, references, abstract, summary and Author contribution
36
37 13 statements)
38

39
40 14 Word count of Supplementary file: 1,455 (exc. tables)
41

42
43 15 Number of tables and figures: 18 tables (including 12 in supplementary digital content) and 3 figures
44

45
46 16 ^aInstitute of Health and Wellbeing, University of Glasgow, Gartnavel Royal Hospital, 1055 Great
47

48
49 17 Western Road, Glasgow G12 OXH. ^bInstitute of Health and Wellbeing, University of Glasgow, Public
50

51
52 18 Health, 1 Lilybank Gardens, Glasgow G12 8RZ. ^cInstitute of Health and Wellbeing, Centre for
53

54
55 19 Immunobiology, Sir Graeme Davies Building College of Medical, Veterinary and Life Sciences
56

57
58 20 University of Glasgow. ^dInstitute of Cardiovascular and Medical Sciences, British Heart Foundation
59

60
21 Glasgow Cardiovascular Research centre, University of Glasgow, Glasgow G12 8TA.

1
2
3 22 *corresponding author: nicholas.graham@glasgow.ac.uk, phone: +44 0141 211 3918,
4
5

6 23 **CONFLICTS OF INTEREST:** None.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3 25 **ABSTRACT**
4
5

6 26 **Objectives:** To assess whether a history of major depressive disorder (MDD) in middle-aged
7
8 27 individuals with hypertension influences first-onset cardiovascular disease outcomes.

9
10 28 **Design:** Prospective cohort survival analysis using Cox proportional hazards regression with a median
11
12 29 follow-up of 63 months (702,902 person-years). Four mutually exclusive groups were compared:
13
14 30 hypertension only (n=56,035), MDD only (n=15,098), comorbid hypertension plus MDD (n=12,929),
15
16 31 and an unaffected (no hypertension, no MDD) comparison group (n=50,798).
17
18

19 32 **Setting:** UK Biobank

20
21
22 33 **Participants:** UK Biobank participants without cardiovascular disease aged 39–70 who completed
23
24 34 psychiatric questions relating ICD-10 diagnostic criteria on a touchscreen questionnaire at baseline
25
26 35 interview in 2006–2010 (n=134,860).
27
28

29 36 **Primary and Secondary outcome measures:** First-onset adverse cardiovascular outcomes leading to
30
31 37 hospital admission or death (ICD-10 codes I20-I259, I60-69 and G45- G46), adjusted in a stepwise
32
33 38 manner for sociodemographic, health and lifestyle features. Secondary analyses were performed
34
35 39 looking specifically at stroke outcomes (ICD-10 codes I60-69 and G45- G46) and in gender-separated
36
37 40 models.
38
39

40 41 **Results:** Relative to controls, adjusted hazard ratios (HRs) for adverse cardiovascular outcomes were
41
42 42 increased for the hypertension only group (HR=1.36, 95%CI 1.22-1.52) and were higher still for the
43
44 43 comorbid hypertension plus MDD group (HR=1.66, 95%CI 1.45-1.9). HRs for the comorbid
45
46 44 hypertension plus MDD group were significantly raised compared to hypertension alone (HR=1.22,
47
48 45 95%CI 1.1-1.35). Interaction measured using relative excess risk due to interaction (RERI) and
49
50 46 likelihood ratios (LR) were identified at baseline (RERI=0.563, 95%CI 0.189 - 0.938; LR chi 6.38, p=
51
52 47 0.0116) but not maintained during follow-up.
53
54

55 48 **Limitations:** Possible selection bias in UK Biobank and inability to assess for levels of medication
56
57 49 adherence.
58
59
60

1
2
3 50 **Conclusions:** Comorbid hypertension and MDD conferred greater hazard than hypertension alone
4
5 51 for adverse cardiovascular outcomes, although evidence of interaction between hypertension and
6
7 52 MDD was inconsistent over time. Future cardiovascular risk prediction tools may benefit from the
8
9 53 inclusion of questions about prior history of depressive disorders.
10
11

12 54 Word count of Abstract: 299
13
14

15 55 **Key words:** epidemiology, mortality, morbidity, depression; hypertension, cardiovascular disease
16
17

18 56
19

20 57 Article Summary
21

22 58 **STRENGTHS AND LIMITATIONS**

- 23
24 59 • Methodological advantages over previous studies, including a very large sample size,
25
26 60 adjustment for a more comprehensive range of confounders, and the inclusion of non-fatal
27
28 61 adverse cardiovascular events from hospital admission data and death registry data.
29
30 62 • Definition of prior MDD history was based on ICD-10 diagnostic criteria (rather than a score
31
32 63 on a symptoms questionnaire) and our composite definition of hypertension incorporated
33
34 64 past history, current medication and objective blood pressure measurements.
35
36 65 • Although analyses were adjusted for a broad range of baseline factors (such as smoking
37
38 66 status, BMI, psychotropic medication use and diabetes), we were unable to account for how
39
40 67 these factors may have changed over the course of follow-up, or assess adherence to
41
42 68 cardiovascular medications.
43
44 69 • Trained nurses interviewed UK Biobank participants, but the self-report nature of some of
45
46 70 these data may represent a limitation.
47
48 71 • UK Biobank may have issues with respect to selection biases. For example, individuals with
49
50 72 more severe MDD may have been less likely to volunteer.
51
52
53
54
55
56
57
58
59
60

74 INTRODUCTION

75 By 2030 major depressive disorder (MDD) and cardiovascular disease (CVD) will be the two leading
76 causes of disability worldwide¹. MDD is associated with CVD and worse long-term outcomes². To
77 date, survival analysis in comorbid hypertension and MDD have focussed on all-cause death³⁻⁵
78 cardiovascular death⁵ or incorporated individuals with previous CVD³⁻⁶, and have suggested a
79 possible additive interaction between hypertension and MDD on survival^{5 6}. MDD is well known to
80 worsen post-cardiovascular event survival^{6 7}. The contribution on survival to first-onset CVD is less
81 clear when MDD is stratified by hypertension and no prior study has assessed comorbid MDD and
82 hypertension on first episode CVD. Within this study we look specifically at first-onset events,
83 irrespective of whether they lead to death or not.

84 Hypertension is extremely common (affecting 1 billion people worldwide)⁸ and is responsible for
85 50% of all CVD⁹. It is commonly comorbid with MDD^{10 11}, with recent meta-analysis showing 27% of
86 individuals with hypertension having MDD¹² and population-based studies showing a hypertension
87 prevalence of 21% in those with MDD¹¹. A biological link has been found by genome-wide
88 association studies, showing calcium-channel genes, important in blood pressure (BP) control and
89 hypertension¹³, also act to increase risk for MDD^{14 15} and bipolar disorder (BD)^{16 17}. The sympathetic
90 nervous system (SNS), Renin-angiotensin system, the immune system and the cortisol stress
91 response system are all also implicated in both conditions¹⁸. Medication management of both
92 conditions are also thought to impact one another with side effects of psychotropic medications
93 including raised BP and vice versa¹⁹⁻²¹, although there is contrary evidence suggesting either
94 medication or MDD may in actual fact be protective of hypertension^{20 22}.

95 Here we make use of prospective data from the UK Biobank cohort²³ to test the hypothesis that a
96 lifetime history of MDD in individuals with hypertension impacts adversely on first-episode
97 cardiovascular events. We also assess whether MDD exacerbates the effects of hypertension as a
98 risk factor for CVD.

99 **METHODS**

100 **Study design**

101 This was a population cohort study using data from UK Biobank. Four mutually exclusive groups
102 (hypertension only, MDD only, hypertension plus MDD, and a comparison group) were compared for
103 adverse CVD and stroke outcomes.

104 **Sample description**

105 UK Biobank is a large cohort of 502,655 participants recruited between April 2007 and July 2010
106 from 21 assessment centres located across Great Britain²³. Participants aged 39-70 were invited to
107 take participate if registered with the NHS and lived within a reasonable distance of an assessment
108 centre. At baseline assessment participants completed a series of detailed assessments relating to
109 lifestyle and medical history on touchscreen questionnaire and have a range of physical health
110 measurements, including body mass index (BMI) and BP taken by a nurse. UK Biobank was approved
111 by the North West NHS Multi-Centre Research Ethics Committee and all participants provided
112 written informed consent to participate. This analysis is part of UK Biobank approved application
113 number 7155.

114 During the last two years of recruitment, questions relating to mood disorder features were added
115 to the baseline assessment schedule questionnaire. From the 172,729 participants asked these
116 questions, 134,860 provided sufficient responses to be included in our analysis. Participants were
117 excluded based on the following *a priori* criteria: a history of BD (n=1,831) or schizophrenia (n=262);
118 where there were insufficient data provided by participants to clearly rule out MDD (n= 25,520) or
119 hypertension (n=1,080); and where there were coding errors for date and/or time of death (n=4).
120 These exclusions were based on self-report (individuals who listed schizophrenia or BD from a list of
121 pre-existing medical conditions), or criteria for BD as per Smith et al,²⁴ or where they responded
122 "don't know" or "prefer not to answer" to questions or data was missing that would limit our ability

1
2
3 123 to exclude the presence of hypertension or MDD. Participants were further excluded from the
4
5 124 adverse CVD outcome if they had a record of CVD prior to recruitment (self-reported angina,
6
7 125 myocardial infarction (MI) or stroke based on specific questions, or previous hospital admission for
8
9 126 angina, MI or stroke) (n= 9,172). For the stroke outcome this exclusion was limited to a record of
10
11 127 stroke prior to baseline assessment (self-report or previous hospital admission for stroke) (n=2,280).
12
13
14

15 128 **Classification of hypertension and MDD**

16
17
18 129 Participants were defined as having hypertension if either: *a*) mean BP at baseline was greater than
19
20 130 clinically-defined criteria over two measurements (systolic BP greater than or equal to 140 mmHg or
21
22 131 diastolic BP greater than or equal to 90 mmHg. Where only one reading was available this was used
23
24 132 (n=1,571)); or *b*) self-reported 'hypertension diagnosed by a doctor' plus self-report of currently
25
26 133 taking antihypertensive medication. This composite classification was used to ensure that
27
28 134 undiagnosed hypertensive participants were not misclassified and is in line with similar
29
30 135 epidemiological studies^{5 25 26}. The requirement for antihypertensive use in the context of a history of
31
32 136 hypertension was incorporated to limit those on beta-blockers for anxiety. According to these
33
34 137 criteria, n=68,964 participants (51.1% of the sample) had hypertension for the adverse
35
36 138 cardiovascular outcomes analysis and n=73,671 participants (52% of the sample) had hypertension
37
38 139 in the stroke outcome analysis.
39
40
41
42
43

44 140 A history of lifetime MDD was defined according to the criteria for mood disorders developed by Smith
45
46 141 et al^{24 27} and has been used in further papers²⁷⁻³¹ (n=28,027 adverse cardiovascular outcomes;
47
48 142 n=29,528 stroke outcomes). Participants were classified as having a history of MDD if they reported
49
50 143 at least one episode, which comprised of depression and/or irritability, with a duration of at least two
51
52 144 weeks, plus had consulted with either a general practitioner or psychiatrist for mental ill-health. This
53
54 145 classification followed the structured diagnostic approach within the International Classification of
55
56 146 Diseases²⁴ and is described in more detail within the supplementary content.
57
58
59
60

1
2
3 147 For the adverse cardiovascular outcomes, the remainder of the sample, with no history of
4
5 148 hypertension or MDD (n=50,798) were classified as a comparator group. The three mutually
6
7 149 exclusive diagnostic groups for this study were therefore: hypertension only (n=56,035); MDD only
8
9
10 150 (n=15,098) and hypertension plus MDD (n= 12,929). For the stroke outcomes, the mutually exclusive
11
12 151 groups were hypertension only (n=59,724); MDD only (n=15,581) and hypertension plus MDD (n=
13
14 152 13,947) and no hypertension – no MDD (n=52,502).

17 153 **Outcomes**

18
19
20 154 The primary outcome was defined as a first-episode cardiovascular event leading to hospital
21
22 155 admission or death, specifically angina, MI, or chronic ischaemic heart disease (ICD-10 codes I20-
23
24 156 I259), and transient ischaemic attack (TIA) or stroke (ICD-10 codes I60-69 and G45- G46). A
25
26
27 157 secondary outcome was defined as stroke leading to hospital admission or death (ICD-10 codes I60-
28
29 158 69 and G45- G46)³² due to the strength of relationship hypertension has with this outcome in
30
31 159 particular⁹. Admission data were obtained from Hospital Episode Statistics in England, Patient
32
33
34 160 Episode Database for Wales and Scottish Morbidity Records in Scotland. Mortality outcomes were
35
36 161 obtained from the National Health Service (NHS) Information Centre for England and Wales and
37
38 162 from the NHS Central Register for Scotland. Individuals who died from a non-cardiovascular
39
40 163 cause/stroke were censored at the time of death but not recorded as having an event. Admission
41
42 164 data were available for Scottish, English and Welsh participants until 31 August 2014, 31 March 2015
43
44 165 and 28 February 2015 respectively. End of follow-up was classified as these dates unless preceded by
45
46 166 date of death or the date of first cardiovascular admission.

50 167 **Confounding variables**

51
52
53 168 Information on potential confounding factors was available for age, sex, socioeconomic status
54
55 169 (Townsend score)³³, self-reported ethnicity, age of leaving full-time education, diabetes, body mass
56
57 170 index (BMI), systolic BP, hypercholesterolemia, alcohol use, smoking history, sedentary behaviour
58
59
60

1
2
3 171 (number of hours each day spent sitting at a computer, television or driving), physical activity levels³⁴
4
5 172 and psychotropic medication use. Specific details on these variables are provided in supplementary
6
7 173 content.

10 174 **Analyses**

14 175 Baseline characteristics were compared between groups using Chi-squared tests for categorical
15
16 176 variables and Kruskal Wallis for continuous variables. Confounding variables were assessed for
17
18 177 differences in adverse cardiovascular outcomes using log rank sums. For the four groups of interest
19
20 178 we assessed associations with adverse cardiovascular outcomes using Cox proportional hazard
21
22 179 regression and the Efron method for ties³⁵. Models were applied in a staged process in line with
23
24 180 previous studies³⁻⁵ and reported as unadjusted (model one), partially adjusted (model two) and fully
25
26 181 adjusted (model three). Model two adjusted for sociodemographic factors (age, sex, Townsend
27
28 182 score, age of leaving full time education and ethnicity) and model three additionally adjusted for
29
30 183 health and lifestyle factors (diabetes, hypercholesterolemia, BMI, smoking history, alcohol use,
31
32 184 systolic BP, sedentary hours per day, physical activity and psychotropic medication use). The
33
34 185 proportionality of hazard assumption was assessed using Schoenfeld residuals³⁶. We compared our
35
36 186 fully adjusted models with results from competing risk analyses using the Fine and Grey approach³⁷,
37
38 187 incorporating non-cardiovascular deaths as a competing event for cardiovascular events, and non-
39
40 188 stroke deaths for stroke events. The relative excess risk due to interaction (RERI)³⁸ was calculated to
41
42 189 assess for additivity in the risk. All analyses were performed with Stata statistical software, version
43
44 190 12³⁹ with the exception of RERI which was calculated using the Microsoft Excel method of Andersson
45
46 191 and colleagues, which allows for comparison of adjusted outcomes⁴⁰. Presence of multiplicative
47
48 192 interaction was calculated using the likelihood ratio test.⁴¹

54
55 193 Psychotropic medication use was included as a confounding variable because of reports that they
56
57 194 may increase risk of mortality⁴² but we also conducted a sensitivity analysis which excluded
58
59 195 participants who were taking psychotropic medication. Sub-group analyses looking separately at

1
2
3 196 hazard ratios (HR) in male and female groups only was also carried out to assess for any gender
4
5 197 specific differences in light of differing rates of depression and adverse cardiovascular events in each
6
7 198 gender^{43 24}.

9
10
11 199 ***Time-varying coefficients.***

12
13
14 200 In the context of Schoenfeld residuals showing non-proportionality, models with time varying
15
16 201 coefficients were used. In addition, log(-log) plots were carried out to find the time point at which
17
18 202 the proportionality assumption failed. Following this, the data was stratified by time at this time
19
20 203 point, effectively creating two separate survival analyses pre and post the failure time point.

21
22
23
24 204 **Patient involvement**

25
26
27
28 205 Although patients were not directly involved with the design of the specific research questions in
29
30 206 this study, the hypotheses tested were developed in the context of clinical experience that
31
32 207 depression and hypertension may interact to impact on CVD. UK Biobank has an active and ongoing
33
34 208 programme of participant involvement: www.ukbiobank.ac.uk/participants/. The outcome
35
36 209 measures used were those provided by the UK Biobank data collection protocol, the design of which
37
38 210 had input from participants. UK Biobank also has a website and social media streams to disseminate
39
40 211 research findings and hosts an annual scientific meeting, which includes cohort participants.

41
42
43
44
45 212 **RESULTS**

46
47
48 213 The final sample for adverse cardiovascular outcome included 134,860 participants followed for a
49
50 214 median duration of 63 months (702,901.6 person-years follow-up, mean 62.5 months). In total
51
52 215 3,685 (2.73%) participants had a first-episode cardiovascular event during the follow-up period (total
53
54 216 number of all deaths plus non-fatal cardiovascular events = 5,788) and 910 (0.64%) participants had
55
56 217 a first-episode stroke event (total number of all deaths plus non-fatal stroke events = 7,317).

1
2
3 218 Table 1 describes the baseline characteristics of the four groups. In general, the hypertension only
4
5 219 and comorbid hypertension plus MDD groups were older, had higher BMI and were more likely to
6
7 220 have diabetes and hypercholesterolemia. The MDD only and comorbid hypertension plus MDD
8
9 221 groups had a higher proportion of women and were more likely to be current smokers (table 1).
10
11
12 222 Gender-separated descriptive tables are shown in the supplementary content (Supplementary tables
13
14 223 1 and 2).

15
16
17 224 The sample for stroke-specific outcomes included 141,754 participants followed for a median
18
19 225 duration of 63 months (735247.7 person-years follow-up, mean 62.2 months). Table 2 describes the
20
21 226 baseline characteristics of the four groups which display similar characteristics to the adverse CVD
22
23 227 outcome groups. Gender-separated descriptive tables are shown in the supplementary content
24
25 228 (Supplementary tables 3 and 4).

29 229 **Adverse cardiovascular outcomes**

30
31
32 230 Within the main analysis and the female only subgroup analysis, MDD failed the proportional
33
34 231 hazards assumption. Table 3 presents unadjusted and multivariate-adjusted Hazard ratios (aHR) for
35
36 232 adverse cardiovascular outcomes. In the fully adjusted model, relative to the comparator group, the
37
38 233 aHR for adverse cardiovascular outcomes was significantly raised for hypertension only (aHR=1.36,
39
40 234 95%CI 1.22-1.52) and higher still for comorbid hypertension plus MDD (aHR=1.66, 95%CI 1.46-1.9)
41
42 235 but reduced for MDD only (aHR=0.55, 95%CI 0.46-0.76). Although the MDD only HR was noted to
43
44 236 increase over time as a time-varying coefficient. With the exception of MDD, these findings were
45
46 237 robust to sensitivity-analysis excluding those on psychotropic medication (sensitivity analysis
47
48 238 aHR=1.43, 95%CI 1.27-1.62; aHR=1.72, 95%CI 1.49-1.999, aHR=0.74, 95%CI 0.52-1.06 respectively).
49
50 239 Table 4 presents HRs and aHRs for adverse cardiovascular outcomes using the hypertension only
51
52 240 group as comparator. In the fully adjusted model, relative to hypertension, the aHR for adverse
53
54 241 cardiovascular outcomes was significantly raised for comorbid hypertension plus MDD (aHR=1.22,
55
56
57
58
59
60

242 95%CI 1.1-1.35, sensitivity-analysis aHR= 1.20, 95%CI 1.08-1.34). An adjusted survival plot is shown
243 in figure 1.

244 Within the sub-analysis, the male-only model showed a significant increase in HR for hypertension
245 (male aHR 1.29, 95% CI 1.13-1.47) (supplementary table 5) and comorbid MDD and hypertension
246 (male aHR 1.47, 95%CI 1.24-1.74). However, the difference between comorbid disease and
247 hypertension only was not statistically significant (aHR 1.14, 95%CI 0.995-1.3). The female only sub-
248 analysis showed an increase in HR for hypertension (aHR 1.64, 95%CI 1.33-2.02) and a greater
249 increase in comorbid MDD and hypertension (aHR 2.18, 95%CI 1.82-2.92) (table 6 of the
250 supplementary content). The difference between comorbid disease and hypertension only was also
251 statistically significant (aHR 1.33, 95%CI 1.14- 1.56). Sensitivity analysis supported these findings.

252 **Stroke Outcomes**

253 None of the independent variables for stroke outcome failed the proportionality assumption. Table 5
254 presents HRs and aHRs for stroke outcomes. In the fully adjusted model, the aHR for stroke was
255 insignificantly raised for hypertension only (aHR=1.21, 95%CI 0.97-1.51) and depression only
256 (aHR=1.20, 95%CI 0.89-1.63) but significantly raised for comorbid hypertension plus MDD (aHR=1.37,
257 95%CI 1.04-1.79). In the hypertension comparator group, no group was significantly different from
258 hypertension only (table 6). Similar trends were shown in the gender subset analysis but not
259 reaching significance (supplementary Tables 7-8). An adjusted survival plot is shown in figure 2.
260 Again, all results were supported by sensitivity analysis excluding those on psychotropic medication.

261 **Interaction, time stratified analysis and competing risk analysis**

262 Survival analysis stratified by time is described and included within the supplementary content
263 (supplementary tables 9, 10 and figure 3). There was evidence of both additive and multiplicative
264 interaction between hypertension and MDD at baseline for the overall cardiovascular outcome
265 analysis before the 22.5 month time point (additive: RERI=0.563, 95%CI 0.189 - 0.938. Multiplicative:

1
2
3 266 Likelihood ratio p-value 0.0116) and the female only cardiovascular endpoint analysis before the 29
4
5 267 month time point (additive: RERI=0.588, 95%CI 0.074 - 1.103. Multiplicative: Likelihood ratio p-value
6
7 268 0.031). However, after these time points there was no evidence of interaction on either the additive
8
9
10 269 or multiplicative scale. Supplementary table 11 shows the full results for this analysis. Competing risk
11
12 270 analysis showed no significant difference from the main analyses for cardiovascular outcomes or
13
14 271 stroke outcomes (tables 7-8)

17 272

20 273 **DISCUSSION**

23 274 In this large population cohort of middle-aged adults without CVD (adjusted for a broad range of
24
25 275 confounders), individuals with co-morbid hypertension and MDD were at increased risk of CVD when
26
27 276 compared to those with hypertension alone, MDD alone and neither condition. There was some
28
29 277 evidence of additive and multiplicative interaction between hypertension and MDD at baseline, but
30
31 278 not throughout follow-up and only within the female subgroup. Such a finding may suggest a causal
32
33 279 interaction between MDD and hypertension in females only, but suggests that this may be limited
34
35 280 over time leading to a suspected further interaction with a gender specific unmeasured confounder.
36
37 281 Differences between co-morbid disease and either disease alone or no disease were more marked in
38
39 282 females. For stroke outcomes, comorbid depression and hypertension was the only group that
40
41 283 showed significantly increased HRs.

46 284 **Previous research**

48
49
50 285 Our findings expand upon previous research from UK Biobank looking at CVD in those with BD and
51
52 286 MDD²⁷. It was found that there were significantly increased odds of having 'any CVD' (fully adjusted
53
54 287 OR 1.15 CI 1.12–1.19) or hypertension (fully adjusted OR 1.15 CI 1.13–1.18) if depressed, with even
55
56 288 higher odds for stroke (fully adjusted OR 1.26 CI 1.13–1.40). There are distinct differences between
57
58 289 our current paper and the previous publication. Follow-up data within UK-Biobank has been released
59
60

1
2
3 290 to allow meaningful prospective studies be conducted. Thus, the current paper has the benefits of
4
5 291 using hospital records and death certification for outcomes, rather than self-reported data. We are
6
7 292 also able to make inferences about the direction of effect regarding MDD and CVD and assess the
8
9 293 influence of hypertension and MDD over time, both in isolation and when comorbid, and assess for
10
11 294 statistical interaction to inform on whether there may be a biological interaction.
12
13
14

15 295 Other survival analyses in hypertension/MDD comorbidity have focussed primarily on mortality
16
17 296 outcomes. In the National Health and Nutrition Epidemiologic Follow-up Study in the United States³¹
18
19 297 and the Taiwanese Survey of Health and Living Status³², individuals with self-reported hypertension
20
21 298 plus depressive symptoms (compared to a reference group with neither) had increased all-cause
22
23 299 mortality (aHR=1.39, 95%CI 1.14-1.69, aHR=1.54, 95%CI 1.29-1.83, respectively)³⁴ with the former
24
25 300 also showing increased CVD specific mortality (aHR=1.59, 95%CI 1.08-2.34)⁴. Similarly, Hamer and
26
27 301 colleagues⁵ reported a prospective analysis of common mental disorder on mortality outcomes in
28
29 302 individuals with hypertension versus those without hypertension in participants from the Health
30
31 303 Survey for England and the Scottish Health Survey (1994–2004), finding that risk of CVD death was
32
33 304 highest in the group with comorbid disease.
34
35
36
37

38 **Strengths**

39
40
41 306 These observations are broadly consistent with our results but our study has a number of
42
43 307 methodological advantages, including a very large sample size, adjustment of analyses for a more
44
45 308 comprehensive range of confounders, and a focus on first-episode non-fatal and fatal adverse
46
47 309 cardiovascular events. We also used a definition of prior MDD history which was based on
48
49 310 diagnostic criteria within ICD-10 (rather than a threshold score on a depressive symptoms or general
50
51 311 wellbeing scale) and our composite definition of hypertension incorporated past history, baseline
52
53 312 medication and BP measurements. Lifetime MDD is thought to be under-reported in the literature.
54
55 313 However, using current symptom scores may reduce power and precision because a smaller number
56
57 314 of respondents would be identified as having an episode of MDD.⁴⁴ Given that we are assessing
58
59
60

1
2
3 315 outcomes for which risk accumulates over a lifetime, we felt that a primary focus on lifetime
4
5 316 episodes was appropriate. We believe our lifetime definition to be better suited as it offers a view
6
7 317 depression and depressive symptoms over the course of a lifespan as opposed the past week. Also,
8
9
10 318 within our current study we were able to exclude those with previous self-declared or hospital
11
12 319 admission CVD, as previous studies show depression may result from CVD^{45 46} and worsen
13
14 320 prognosis⁴⁶

321 **Limitations**

322 However, some limitations are acknowledged. Recruitment criteria for UK Biobank may lead to
323 selection bias. Specifically, age-restrictions may lead to underrepresentation of early-onset
324 hypertension and those with more severe MDD may be less inclined to attend for assessment. We
325 also acknowledge limitations with our classifications of MDD and hypertension, which were primarily
326 self-report rather than formal diagnostic assessments. Although we have excluded prior
327 cardiovascular events where possible, the MDD plus hypertension sub-type may capture older
328 individuals with a degree of vascular depression, which has an established association with raised
329 BP⁴⁷. In addition, although we adjust for a host of risk factors at baseline such as smoking status, BMI
330 and psychotropic medication, we are limited by the lack of follow-up data, which could show change
331 and modification of said risk factors over time. Similarly, we were unable to assess for medication
332 adherence and transitions from one investigatory group to another. Participants who are aware of or
333 had sought treatment for MDD may also have complicated our findings, however, our sensitivity
334 analysis excluded those using pharmaceutical treatments and was in keeping with our main findings.
335 Such modifications could explain the non-proportional nature of the depression group, which may in
336 itself be a predictor of poor medication adherence⁴⁸. Although adherence to medication was not
337 formally assessed, the number and duration of antihypertensive medications used in the
338 hypertension plus MDD group was the same as for the hypertension only group (supplementary
339 content, table 12). As such, worse outcomes in the MDD plus hypertension group are not explained

1
2
3 340 by less intensive antihypertensive treatment at baseline. The end-points used for stroke and
4
5 341 cardiovascular events also require to be further validated, however are in line with previous
6
7 342 epidemiological studies⁵ and have been suggested in previous papers in UK Biobank³².
8
9
10 343 Cardiovascular endpoints have not, to our knowledge, been validated within UKbiobank, however
11
12 344 we do not feel that this will bias the results towards any particular group. The amelioration of the
13
14 345 aHR suggests other covariates contribute considerably to the risk. This is important in the context of
15
16 346 increased rates of diabetes, hypercholesterolemia and obesity along with lower socio-economic
17
18 347 status in the hypertension only and comorbid groups and as such we may be seeing the summation
19
20 348 of CV risk factors. Finally, the overall recruitment rate to UK Biobank was low (at around 6%);
21
22
23 349 however, the large final cohort size, the depth and diversity of phenotype data collected at baseline,
24
25 350 and the wide sociodemographic representation of participants all make our findings highly relevant
26
27
28 351 to UK primary care settings. While UK Biobank participants cannot be used to provide
29
30 352 representative disease prevalence and incidence rates, valid assessment of exposure-disease
31
32 353 relationships are nonetheless widely generalizable and do not require participants to be
33
34 354 representative of the UK population at large⁴⁹, although findings will not be generalizable to other
35
36 355 countries.

356 **Possible mechanisms**

357 Our finding that a history of MDD, in the context of a current diagnosis of hypertension increased
358 the risk of first-episode CVD is complicated by the time varying risk that MDD conveys to CVD. Sub-
359 sample analysis show this time-varying aspect is gender-specific to females. Within our sample, the
360 MDD group has a slightly reduced BP compared to comparators. Previously, reduced BP has been
361 put forth as being causative of MDD and therefore reducing CVD risk²⁰, but findings from
362 longitudinal studies are inconsistent with regards to direction of effect^{50 51}. Potential menopausal
363 effects are tempting explanations. Common factors for BP and mood such as neuropeptide Y^{52 53} may
364 also influence cardiovascular outcomes. Neuropeptide Y has a complex relationship with oestrogen⁵⁴

1
2
3 365 and both have dampening effect on the SNS⁵⁵. Neuropeptide Y and oestrogen may represent a
4
5 366 biologically plausible interaction between MDD and hypertension, however, this would require
6
7 367 investigation.
8
9

10 368 Personality factors may also play a role. MDD correlates highly with neuroticism which, although
11
12 369 inconsistent, may be protective of CVD⁵⁶. Conscientiousness traits may lead to better outcomes⁵⁷
13
14 370 and it is possible that this trait has been selected for within UK Biobank. Despite this early reduced
15
16 371 risk, due to the time varying nature of MDD, MDD has increased risk in the latter aspects of the time-
17
18 372 stratified analyses for the full and female only analyses (supplementary table 9 and 10). The findings
19
20 373 from our study in this context suggest MDDs role as a risk factor for CVD and its relationship with BP
21
22 374 may be much more complex than initially thought, in particular within female populations however
23
24 375 further investigation is clearly needed.
25
26
27
28

29 376 We can see in the hypertension only baseline models that comorbid hypertension and depression
30
31 377 convey a significantly greater risk than hypertension alone. Individuals with either hypertension or
32
33 378 depression may have increased sympathetic stimulation that is increased further in comorbid states
34
35 379 leading to worse outcomes⁵⁸.
36
37
38

39 380

41 381 **CONCLUSIONS**

42
43
44 382 Overall, our findings may have important implications for routine clinical practice, particularly within
45
46 383 primary care settings and further demonstrate the complex relationship between depression and
47
48 384 hypertension. Although evidence of an interaction is inconsistent, we found that comorbid
49
50 385 hypertension and depression conferred greater hazard than hypertension alone for adverse
51
52 386 cardiovascular outcomes. This significant finding remained after adjustment for factors such as BMI,
53
54 387 smoking status and diabetes and was robust to sensitivity analysis excluding those on psychotropic
55
56 388 medication. One implication is that clinicians should be more aware of the negative long-term
57
58 389 impact on CVD outcomes caused by a history of MDD in the context of hypertension, particularly
59
60

1
2
3 390 within females. Although this work awaits replication and testing in other cohorts and settings,
4
5 391 further work in this field may suggest that future iterations of CVD risk prediction tools, such as
6
7 392 ASSIGN⁵⁹, would benefit from the addition of a question on whether individuals have a past history
8
9 393 of MDD, to facilitate more intensive support to prevent CVD⁶⁰.
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3 395 **ACKNOWLEDGEMENTS**
4
5

6 396 We are grateful to all participants of the UK Biobank cohort. UK Biobank was established by the
7
8 397 Wellcome Trust, the Medical Research Council, Department of Health, Scottish Government and the
9
10 398 Northwest Regional Development Agency. It has also had funding from the Welsh Assembly
11
12 399 Government and the British Heart Foundation. UK Biobank is hosted by the University of Manchester
13
14 400 and supported by the National Health Service (NHS). NG is supported by the Aitchison Family Clinical
15
16 401 Research Fellowship at the University of Glasgow and DJS is supported by a Lister Institute Prize
17
18 402 Fellowship. JC is supported by the Sackler Trust and the Wellcome Trust. Part-funded by the Medical
19
20 403 Research Council Mental Health Data Pathfinder Award (grant reference MC_PC_17217)"
21
22
23
24

25 404 Footnotes
26
27

28 405 **Authors Statement:** Contributors NG, JW, JP, JC, DS, SP and DM, contributed to study design and
29
30 406 writing of the manuscript. JP and DM contributed to data acquisition. NG conducted data processing
31
32 407 and statistical analyses.
33
34
35

36 408 **Funding:** Authors declare no support from any organisation for the submitted work;
37
38
39

40 409 **Competing interests:** All authors have completed the ICMJE uniform disclosure form at
41
42 410 http://www.icmje.org/coi_disclosure.pdf and no financial relationships with any organisations that
43
44 411 might have an interest in the submitted work in the previous three years; no other relationships or
45
46 412 activities that could appear to have influenced the submitted work.
47
48
49

50 413 **Ethics approval:** This study has been conducted using UK Biobank data. UK Biobank has received
51
52 414 ethics approval from the UK Biobank Research Ethics Committee (ref. 11/NW/0382).
53
54

55 415 **Data sharing statement:** The data used in this study are available via a direct application to UK
56
57 416 Biobank.
58
59
60

1
2
3 417 **Transparency statement:** The lead author affirms that this manuscript is an honest, accurate and
4
5 418 transparent account of the study being reported; that no important aspects of the study have been
6
7 419 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have
8
9
10 420 been explained.
11
12

13 421
14
15

16 422 **COMPETING INTERESTS STATEMENTS**
17

18
19 423 All authors have completed the ICMJE uniform disclosure form at
20
21 424 http://www.icmje.org/coi_disclosure.pdf and no financial relationships with any organisations that
22
23 425 might have an interest in the submitted work in the previous three years; no other relationships or
24
25
26 426 activities that could appear to have influenced the submitted work.
27
28

29 427
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

428 **References**

429

- 430 1. Organization. WH. The global burden of disease: 2004 update. Geneva, Switzerland.: WHO press.
431 2008.
- 432 2. Hare DL, Toukhsati SR, Johansson P, et al. Depression and cardiovascular disease: a clinical review.
433 *Eur Heart J* 2014;35(21):1365-72. doi: 10.1093/eurheartj/eh462
- 434 3. Kuo PL, Pu C. The contribution of depression to mortality among elderly with self-reported
435 hypertension: analysis using a national representative longitudinal survey. *J Hypertens*
436 2011;29(11):2084-90. doi: 10.1097/HJH.0b013e32834b59ad [published Online First:
437 2011/09/22]
- 438 4. Axon RN, Zhao Y, Egede LE. Association of depressive symptoms with all-cause and ischemic heart
439 disease mortality in adults with self-reported hypertension. *Am J Hypertens* 2010;23(1):30-7.
440 doi: 10.1038/ajh.2009.199
- 441 5. Hamer M, Batty GD, Stamatakis E, et al. The combined influence of hypertension and common
442 mental disorder on all-cause and cardiovascular disease mortality. *J Hypertens*
443 2010;28(12):2401-6. doi: 10.1097/HJH.0b013e32833e9d7c
- 444 6. Jani BD, Cavanagh J, Barry SJ, et al. Relationship Between Blood Pressure Values, Depressive
445 Symptoms, and Cardiovascular Outcomes in Patients With Cardiometabolic Disease. *Journal*
446 *of clinical hypertension (Greenwich, Conn)* 2016;18(10):1027-35. doi: 10.1111/jch.12813
447 [published Online First: 2016/04/05]
- 448 7. Taylor CB, Youngblood ME, Catellier D, et al. Effects of antidepressant medication on morbidity
449 and mortality in depressed patients after myocardial infarction. *Arch Gen Psychiatry*
450 2005;62(7):792-8. doi: 10.1001/archpsyc.62.7.792 [published Online First: 2005/07/06]
- 451 8. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide
452 data. *Lancet* 2005;365(9455):217-23. doi: 10.1016/S0140-6736(05)17741-1
- 453 9. Lawes CM, Vander Hoorn S, Rodgers A, et al. Global burden of blood-pressure-related disease,
454 2001. *Lancet* 2008;371(9623):1513-8. doi: 10.1016/S0140-6736(08)60655-8
- 455 10. Meng L, Chen D, Yang Y, et al. Depression increases the risk of hypertension incidence: a meta-
456 analysis of prospective cohort studies. *J Hypertens* 2012;30:842 - 51.
- 457 11. Wu EL, Chien IC, Lin CH, et al. Increased risk of hypertension in patients with major depressive
458 disorder: a population-based study. *J Psychosom Res* 2012;73(3):169-74. doi:
459 10.1016/j.jpsychores.2012.07.002
- 460 12. Li Z, Li Y, Chen L, et al. Prevalence of Depression in Patients With Hypertension: A Systematic
461 Review and Meta-Analysis. *Medicine (Baltimore)* 2015;94(31):e1317. doi:
462 10.1097/md.0000000000001317 [published Online First: 2015/08/08]
- 463 13. Johnson AD, Newton-Cheh C, Chasman DI, et al. Association of hypertension drug target genes
464 with blood pressure and hypertension in 86,588 individuals. *Hypertension* 2011;57(5):903-
465 10. doi: 10.1161/HYPERTENSIONAHA.110.158667
- 466 14. Casamassima F HJ, Fava M, Sachs GS, Smoller JW, Cassano GB, Lattanzi L, Fagerness J, Stange JP,
467 Perlis RH. Phenotypic effects of a bipolar liability gene among individuals with major
468 depressive disorder. . *Am J Med Genet B Neuropsychiatr Genet* 2010;153B:303-09.
- 469 15. Green EK, Grozeva D, Jones I, et al. The bipolar disorder risk allele at CACNA1C also confers risk
470 of recurrent major depression and of schizophrenia. *Molecular Psychiatry* 2010;15(10):1016-
471 22. doi: 10.1038/mp.2009.49
- 472 16. Ferreira MA, O'Donovan MC, Meng YA, et al. Collaborative genome-wide association analysis
473 supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat Genet* 2008;40(9):1056-8.
474 doi: 10.1038/ng.209
- 475 17. Consortium WTCC. Identification of risk loci with shared effects on five major psychiatric
476 disorders: a genome-wide analysis. *The Lancet* 2013;381(9875):1371-79.

- 1
2
3 477 18. Scalco AZ, Scalco MZ, Azul JB, et al. Hypertension and depression. *Clinics (Sao Paulo)*
4 478 2005;60(3):241-50. doi: /S1807-59322005000300010
- 5 479 19. Boal AH, Smith DJ, McCallum L, et al. Monotherapy With Major Antihypertensive Drug Classes
6 480 and Risk of Hospital Admissions for Mood Disorders. *Hypertension* 2016;68(5):1132-38. doi:
7 481 10.1161/hypertensionaha.116.08188 [published Online First: 2016/10/14]
- 8 482 20. Licht CM, de Geus EJ, Seldenrijk A, et al. Depression is associated with decreased blood pressure,
9 483 but antidepressant use increases the risk for hypertension. *Hypertension* 2009;53(4):631-8.
10 484 doi: 10.1161/HYPERTENSIONAHA.108.126698
- 11 485 21. Crookes DM, Demmer RT, Keyes KM, et al. Depressive Symptoms, Antidepressant Use, and
12 486 Hypertension in Young Adulthood. *Epidemiology (Cambridge, Mass)* 2018;29(4):547-55. doi:
13 487 10.1097/ede.0000000000000840 [published Online First: 2018/04/10]
- 14 488 22. Diminic-Lisica I, Popovic B, Rebic J, et al. Outcome of treatment with antidepressants in patients
15 489 with hypertension and undetected depression. *Int J Psychiatry Med* 2014;47(2):115-29. doi:
16 490 10.2190/PM.47.2.c [published Online First: 2014/08/03]
- 17 491 23. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the
18 492 causes of a wide range of complex diseases of middle and old age. *PLoS Med*
19 493 2015;12(3):e1001779. doi: 10.1371/journal.pmed.1001779
- 20 494 24. Smith DJ, Nicholl BI, Cullen B, et al. Prevalence and characteristics of probable major depression
21 495 and bipolar disorder within UK biobank: cross-sectional study of 172,751 participants. *PLoS*
22 496 *One* 2013;8(11):e75362. doi: 10.1371/journal.pone.0075362
- 23 497 25. Ong KL, Cheung BM, Man YB, et al. Prevalence, awareness, treatment, and control of
24 498 hypertension among United States adults 1999-2004. *Hypertension* 2007;49(1):69-75. doi:
25 499 10.1161/01.hyp.0000252676.46043.18 [published Online First: 2006/12/13]
- 26 500 26. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of
27 501 hypertension, 1988-2008. *Jama* 2010;303(20):2043-50. doi: 10.1001/jama.2010.650
28 502 [published Online First: 2010/05/27]
- 29 503 27. Martin DJ, Ul-Haq Z, Nicholl BI, et al. Cardiometabolic disease and features of depression and
30 504 bipolar disorder: population-based, cross-sectional study. *Br J Psychiatry* 2016;208(4):343-
31 505 51. doi: 10.1192/bjp.bp.114.157784
- 32 506 28. Ul-Haq Z, Smith DJ, Nicholl BI, et al. Gender differences in the association between adiposity and
33 507 probable major depression: a cross-sectional study of 140,564 UK Biobank participants. *BMC*
34 508 *psychiatry* 2014;14:153-53. doi: 10.1186/1471-244X-14-153
- 35 509 29. Sarkar C, Webster C, Gallacher J. Residential greenness and prevalence of major depressive
36 510 disorders: a cross-sectional, observational, associational study of 94 879 adult UK Biobank
37 511 participants. *The Lancet Planetary Health* 2018;2(4):e162-e73. doi:
38 512 [https://doi.org/10.1016/S2542-5196\(18\)30051-2](https://doi.org/10.1016/S2542-5196(18)30051-2)
- 39 513 30. Hall LS, Adams MJ, Arnau-Soler A, et al. Genome-wide meta-analyses of stratified depression in
40 514 Generation Scotland and UK Biobank. *Translational psychiatry* 2018;8(1):9-9. doi:
41 515 10.1038/s41398-017-0034-1
- 42 516 31. Howard DM, Adams MJ, Shirali M, et al. Genome-wide association study of depression
43 517 phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. *Nature*
44 518 *Communications* 2018;9(1):1470. doi: 10.1038/s41467-018-03819-3
- 45 519 32. Woodfield R, Grant I, Group UKBSO, et al. Accuracy of Electronic Health Record Data for
46 520 Identifying Stroke Cases in Large-Scale Epidemiological Studies: A Systematic Review from
47 521 the UK Biobank Stroke Outcomes Group. *PLOS ONE* 2015;10(10):e0140533. doi:
48 522 10.1371/journal.pone.0140533
- 49 523 33. Townsend P. Deprivation. *Journal of Social Policy* 2009;16(02):125. doi:
50 524 10.1017/s0047279400020341
- 51 525 34. Guo W, Bradbury KE, Reeves GK, et al. Physical activity in relation to body size and composition
52 526 in women in UK Biobank. *Annals of Epidemiology* 2015;25(6):406-13.e6. doi:
53 527 <http://dx.doi.org/10.1016/j.annepidem.2015.01.015>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 528 35. Efron B. The Efficiency of Cox's Likelihood Function for Censored Data. *Journal of the American*
529 *Statistical Association*, 1977;72(359):557-65.
- 530 36. Schoenfeld D. Partial Residuals for the Proportional Hazards Regression-Model. *Biometrika*
531 1982;69(1):239-41. doi: Doi 10.2307/2335876
- 532 37. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk.
533 *Journal of the American Statistical Association* 1999;94(446):496-509. doi: 10.2307/2670170
- 534 38. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology*
535 *(Cambridge, Mass)* 1992;3(5):452-6. [published Online First: 1992/09/01]
- 536 39. Stata Statistical Software, version 12 [program]. College station, Texas.
- 537 40. Andersson T, Alfredsson L, Kallberg H, et al. Calculating measures of biological interaction.
538 *European journal of epidemiology* 2005;20(7):575-9. [published Online First: 2005/08/27]
- 539 41. Marshall SW. Power for tests of interaction: effect of raising the Type I error rate. *Epidemiologic*
540 *Perspectives & Innovations* 2007;4(1):4. doi: 10.1186/1742-5573-4-4
- 541 42. Weich S, Pearce HL, Croft P, et al. Effect of anxiolytic and hypnotic drug prescriptions on
542 mortality hazards: retrospective cohort study. *BMJ* 2014;348:g1996. doi: 10.1136/bmj.g1996
- 543 43. Nichols M, Townsend N, Scarborough P, et al. Cardiovascular disease in Europe 2014:
544 epidemiological update. *European Heart Journal* 2014;35(42):2950-59. doi:
545 10.1093/eurheartj/ehu299
- 546 44. Patten SB. Accumulation of major depressive episodes over time in a prospective study indicates
547 that retrospectively assessed lifetime prevalence estimates are too low. *BMC psychiatry*
548 2009;9:19-19. doi: 10.1186/1471-244X-9-19
- 549 45. Kang HJ, Stewart R, Bae KY, et al. Predictive value of homocysteine for depression after acute
550 coronary syndrome. *Oncotarget* 2016;7(42):69032-40. doi: 10.18632/oncotarget.11966
- 551 46. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis
552 among patients with acute coronary syndrome: systematic review and recommendations: a
553 scientific statement from the American Heart Association. *Circulation* 2014;129(12):1350-69.
554 doi: 10.1161/CIR.0000000000000019
- 555 47. Aizenstein HJ, Baskys A, Boldrini M, et al. Vascular depression consensus report – a critical
556 update. *BMC Medicine* 2016;14(1):161. doi: 10.1186/s12916-016-0720-5
- 557 48. Goldstein CM, Gathright EC, Garcia S. Relationship between depression and medication
558 adherence in cardiovascular disease: the perfect challenge for the integrated care team.
559 *Patient preference and adherence* 2017;11:547-59. doi: 10.2147/PPA.S127277
- 560 49. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related
561 Characteristics of UK Biobank Participants With Those of the General Population. *American*
562 *journal of epidemiology* 2017;186(9):1026-34. doi: 10.1093/aje/kwx246 [published Online
563 First: 2017/06/24]
- 564 50. Hildrum B, Mykletun A, Holmen J, et al. Effect of anxiety and depression on blood pressure: 11-
565 year longitudinal population study. *British Journal of Psychiatry* 2018;193(2):108-13. doi:
566 10.1192/bjp.bp.107.045013 [published Online First: 01/02]
- 567 51. Paterniti S. Low blood pressure and risk of depression in the elderly: A prospective community-
568 based study. *The British Journal of Psychiatry* 2000;176(5):464-67. doi:
569 10.1192/bjp.176.5.464
- 570 52. Zhang P, Qi Y-X, Yao Q-P, et al. Neuropeptide Y Stimulates Proliferation and Migration of Vascular
571 Smooth Muscle Cells from Pregnancy Hypertensive Rats via Y1 and Y5 Receptors. *PLOS ONE*
572 2015;10(7):e0131124. doi: 10.1371/journal.pone.0131124
- 573 53. Morales-Medina JC, Dumont Y, Quirion R. A possible role of neuropeptide Y in depression and
574 stress. *Brain research* 2010;1314:194-205. doi:
575 <https://doi.org/10.1016/j.brainres.2009.09.077>
- 576 54. Pelletier G, Li S, Luu-The V, et al. Oestrogenic Regulation of Pro-Opiomelanocortin, Neuropeptide
577 Y and Corticotrophin-Releasing Hormone mRNAs in Mouse Hypothalamus. *Journal of*
578 *Neuroendocrinology* 2007;19(6):426-31. doi: 10.1111/j.1365-2826.2007.01548.x

- 1
2
3 579 55. Rosano GM, Panina G. Oestrogens and the heart. *Therapie* 1999;54(3):381-5. [published Online
4 580 First: 1999/09/29]
5 581 56. Gale CR, Čukić I, Batty GD, et al. When Is Higher Neuroticism Protective Against Death? Findings
6 582 From UK Biobank. *Psychological Science* 2017;28(9):1345-57. doi:
7 583 10.1177/0956797617709813
8 584 57. Cheng H, Montgomery S, Treglown L, et al. Emotional stability, conscientiousness, and self-
9 585 reported hypertension in adulthood. *Personality and Individual Differences* 2017;115:159-63.
10 586 doi: <https://doi.org/10.1016/j.paid.2016.02.034>
11 587 58. Barton DA, Dawood T, Lambert EA, et al. Sympathetic activity in major depressive disorder:
12 588 identifying those at increased cardiac risk? *J Hypertens* 2007;25(10):2117-24. doi:
13 589 10.1097/HJH.0b013e32829baae7 [published Online First: 2007/09/22]
14 590 59. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to
15 591 cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended
16 592 Cohort (SHHEC). *Heart* 2007;93(2):172-76. doi: 10.1136/hrt.2006.108167
17 593 60. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and
18 594 Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;336(7659):1475-82. doi:
19 595 10.1136/bmj.39609.449676.25
20
21
22
23 596

peer review only

597 Table 1. Baseline characteristics for adverse cardiovascular outcomes

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 50798	N = 56035	N = 15098	N = 12929
Median age (range)*	54 (47 - 61)	61 (55 - 65)	53 (46 - 60)	60 (53 - 64)
Females, N (%)	29228 (57.54%)	25893 (46.21%)	10929 (72.39%)	7676 (59.37%)
Ethnicity, N (%)				
<i>White</i>	46147 (90.84%)	51249 (91.46%)	14247 (94.36%)	12272 (94.92%)
<i>Asian/Asian British</i>	1771 (3.49%)	1696 (3.03%)	261 (1.73%)	179 (1.38%)
<i>Black/ Black British</i>	1323 (2.6%)	1769 (3.16%)	219 (1.45%)	222 (1.72%)
Median Townsend score (range)*	-1.89 (-3.45 - 0.54)	-2.07 (-3.51 - 0.39)	-1.64 (-3.3 - 0.93)	-1.84 (-3.42 - 0.76)
Age at leaving full-time education, N (%)				
<16	5916 (11.65%)	12085 (21.57%)	1725 (11.43%)	2607 (20.16%)
16	10265 (20.21%)	11827 (21.11%)	3178 (21.05%)	2732 (21.13%)
>16	34090 (67.11%)	31480 (56.18%)	10090 (66.83%)	7503 (58.03%)
Total physical activity in metabolic	3.97 (1.68 - 8.03)	3.79 (1.51 - 8.03)	3.89 (1.66 - 8)	3.68 (1.49 - 7.95)
Sedentary time in hours, median (range)*	4 (3 - 6)	4.5 (3.5 - 6)	4.5 (3 - 6)	5 (3.5 - 6)

Diabetes, N (%)	1268 (2.5%)	3777 (6.74%)	380 (2.52%)	929 (7.19%)
Hypercholesterolaemia, N (%)	3011 (5.93%)	9210 (16.44%)	893 (5.91%)	2211 (17.1%)
Systolic BP in mmHg, median (range)*	125.5 (118 - 132)	149.5 (142 - 159.5)	124 (116 - 131)	147.5 (140.5 - 157.)
Body Mass Index, N (%)				
<18.5	389 (0.77%)	142 (0.25%)	103 (0.68%)	34 (0.26%)
18.5 – 25	22549 (44.39%)	13678 (24.41%)	6251 (41.4%)	2874 (22.23%)
25-30	20410 (40.18%)	25216 (45 %)	5936 (39.32%)	5389 (41.68%)
>30	7450 (14.67%)	16999 (30.34%)	2808 (18.6%)	4632 (35.83%)
Smoking status, N (%)				
Never smoked	30626 (60.29%)	31503 (56.22%)	7864 (52.09%)	6454 (49.92%)
Previously smoked	15056 (29.64%)	20140 (35.94%)	5118 (33.9%)	5065 (39.18%)
Current smoker	4970 (9.78%)	4199 (7.49%)	2093 (13.86%)	1381 (10.68%)
Alcohol frequency, N (%)				
Daily or almost daily	9450 (18.6%)	12970 (23.15%)	2736 (18.12%)	2881 (22.28%)
Three or four times a week	12175 (23.97%)	13033 (23.26%)	3253 (21.55%)	2837 (21.94%)
Once or twice a week	13644 (26.86%)	13889 (24.79%)	3880 (25.7%)	2916 (22.55%)

One to three times a month	6052 (11.91%)	5588 (9.97%)	2058 (13.63%)	1512 (11.69%)
Special occasions only	5534 (10.89%)	6330 (11.3%)	1904 (12.61%)	1729 (13.37%)
Never	3924 (7.72%)	4199 (7.49%)	1262 (8.36%)	1048 (8.11%)
Psychotropic medication, N (%)	1341 (2.64%)	1795 (3.2%)	2844 (18.84%)	2522 (19.51%)

598 All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value
 599 of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is
 600 an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households,
 601 households not owner-occupied and unemployment.

603 Table 2 Baseline characteristics for stroke outcomes

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 52502	N = 59724	N = 15581	N = 13947
Median age (range)*	54 (47 - 61)	61 (55 - 65)	54 (47 - 61)	60 (53 - 64)
Females, N (%)	29684 (56.54%)	26937 (45.1%)	11143 (71.52%)	8090 (58.01%)
Ethnicity, N (%)				
White	47697 (90.85%)	54578 (91.38%)	14697 (94.33%)	13212 (94.73%)
Asian/Asian British	1857 (3.54%)	1889 (3.16%)	280 (1.8%)	209 (1.5%)
Black/ Black British	1355 (2.58%)	1854 (3.1%)	223 (1.43%)	246 (1.76%)
Median Townsend score (range)*	-1.89 (-3.45 - 0.55)	-2.04 (-3.49 - 0.44)	-1.56 (-3.28 - 1.15)	-1.74 (-3.4 - 0.93)
Age at leaving full-time education, N (%)				
<16	6446 (12.28%)	13396 (22.43%)	1884 (12.09%)	2945 (21.12%)
16	10590 (20.17%)	12507 (20.94%)	3270 (20.99%)	2953 (21.17%)
>16	34914 (66.5%)	33114 (55.45%)	10317 (66.22%)	7947 (56.98%)
Total physical activity in metabolic	3.96 (1.67 - 8.02)	3.75 (1.5 - 8)	4.13 (1.67 - 8.36)	3.66 (1.45 - 7.83)
Sedentary time in hours, median (range)*	4 (3 - 6)	5 (3.5 - 6)	5 (3.5 - 6.5)	5 (4 - 7)

Diabetes, N (%)	1454 (2.77%)	4502 (7.54%)	449 (2.88%)	1163 (8.34%)
Hypercholesterolaemia, N (%)	3592 (6.84%)	10768 (18.03%)	1049 (6.73%)	2620 (18.79%)
Systolic BP in mmHg, median (range)*	125.5 (118 - 132)	149.5 (142 - 159.5)	127 (120.5 - 133)	147.5 (140.5 - 156.5)
Body Mass Index, N (%)				
<18.5	395 (0.75%)	151 (0.25%)	104 (0.67%)	38 (0.27%)
18.5 – 25	22967 (43.75%)	14242 (23.85%)	6374 (40.91%)	3017 (21.63%)
25-30	21185 (40.35%)	26817 (44.9%)	6149 (39.46%)	5769 (41.36%)
>30	7953 (15.15%)	18514 (31.%)	2954 (18.96%)	5123 (36.73%)
Smoking status, N (%)				
Never smoked	31318 (59.65%)	32982 (55.22%)	8052 (51.68%)	6834 (49%)
Previously smoked	15851 (30.19%)	22019 (36.87%)	5340 (34.27%)	5560 (39.87%)
Current smoker	5170 (9.85%)	4501 (7.54%)	2163 (13.88%)	1519 (10.89%)
Alcohol frequency, N (%)				
Daily or almost daily	9760 (18.59%)	13751 (23.02%)	2817 (18.08%)	3085 (22.12%)
Three or four times a week	12563 (23.93%)	13827 (23.15%)	3335 (21.4%)	3020 (21.65%)
Once or twice a week	14089 (26.84%)	14719 (24.65%)	3993 (25.63%)	3125 (22.41%)

One to three times a month	6220 (11.85%)	5971 (10%)	2122 (13.62%)	1627 (11.67%)
Special occasions only	5744 (10.94%)	6794 (11.38%)	1978 (12.69%)	1885 (13.52%)
Never	4102 (7.81%)	4630 (7.75%)	1330 (8.54%)	1199 (8.6%)
Psychotropic medication, N (%)	1408 (2.68%)	1996 (3.34%)	2976 (19.1%)	2778 (19.92%)

604 All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value
 605 of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is
 606 an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households,
 607 households not owner-occupied and unemployment.

609 Table 3: Risk of adverse cardiovascular event by clinical group: unadjusted, partially adjusted and fully adjusted models.

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.60	(2.39 - 2.82)	3.31x10 ⁻¹¹³	1.72	(1.57 - 1.88)	1.99x10 ⁻³³	1.36	(1.22 - 1.52)	2.92x10 ⁻⁸
MDD only	0.69	(0.51 - 0.94)	0.02	0.82	(0.6 - 1.13)	0.23	0.75	(0.54 - 1.04)	0.08
Hypertension and MDD	2.84	(2.55 - 3.17)	6.31x10 ⁻⁷⁷	2.27	(2.02 - 2.55)	2.75x10 ⁻⁴⁴	1.66	(1.45 - 1.9)	7.48x10 ⁻¹⁴
Time varying Variables									
MDD only	1.01	(1.004 - 1.02)	2.38x10 ⁻³	1.01	(1.004 - 1.02)	3.19x10 ⁻³	1.01	(1.004 - 1.02)	3.03x10 ⁻³

610

611 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of
612 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
613 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

615 Table 4: Risk of adverse cardiovascular event by clinical group: unadjusted, partially adjusted and fully adjusted models with hypertension as the
616 comparator

Group	Unadjusted			Model 1 - Sociodemographic			Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
<i>Hypertension only</i>	1(ref)			1(ref)			1(ref)		
<i>No Hypertension - No MDD</i>	0.38	(0.35 - 0.42)	3.31x10 ⁻¹¹³	0.58	(0.53 - 0.63)	1.99x10 ⁻³³	0.73	(0.66 - 0.82)	2.92x10 ⁻⁸
<i>MDD only</i>	0.27	(0.2 - 0.36)	1.14x10 ⁻¹⁷	0.48	(0.35 - 0.66)	4.91x10 ⁻⁶	0.55	(0.4 - 0.76)	3.23x10 ⁻⁴
<i>Hypertension and MDD</i>	1.09	(0.996 - 1.2)	0.06	1.32	(1.2 - 1.46)	3.07x10 ⁻⁸	1.22	(1.1 - 1.35)	1.30x10 ⁻⁴
Time varying Variables									
<i>MDD only</i>	1.01	(1.004 - 1.02)	0.002	1.01	(1.004 - 1.02)	3.19x10 ⁻³	1.01	(1.004 - 1.02)	3.03x10 ⁻³

617 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of
618 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
619 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

621 Table 5: Risk of stroke event by clinical group: unadjusted, partially adjusted and fully adjusted models.

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension- No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.55	(2.16 - 3.02)	3.84x10 ⁻²⁸	1.64	(1.38 - 1.96)	3.35x10 ⁻⁸	1.21	(0.97 - 1.51)	0.09
MDD only	1.14	(0.86 - 1.52)	0.37	1.37	(1.02 - 1.84)	0.037	1.20	(0.89 - 1.63)	0.24
Hypertension and MDD	2.67	(2.13 - 3.34)	9.79x10 ⁻¹⁸	2.05	(1.63 - 2.58)	1.08x10 ⁻⁹	1.37	(1.04 - 1.79)	0.02

622 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of
623 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
624 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

625

627 Table 6: Risk of stroke event by clinical group: unadjusted, partially adjusted and fully adjusted models with hypertension as the comparator

Group	Unadjusted			Model 1 - Sociodemographic			Model 2 - Model 1 + Health/ Lifestyle		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
<i>Hypertension only</i>	1(ref)			1(ref)			1(ref)		
<i>No Hypertension - No MDD</i>	0.39	(0.33 - 0.46)	3.84x10 ⁻²⁸	0.61	(0.51 - 0.73)	3.35x10 ⁻⁸	0.82	(0.66 - 1.03)	0.09
<i>MDD only</i>	0.45	(0.34 - 0.58)	1.43x10 ⁻⁹	0.83	(0.63 - 1.1)	0.19	0.99	(0.73 - 1.35)	0.95
<i>Hypertension and MDD</i>	1.05	(0.86 - 1.27)	0.64	1.25	(1.03 - 1.52)	0.03	1.13	(0.92 - 1.39)	0.26

628 *Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). †Additionally adjusted for history of
 629 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
 630 psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval.

631

632 Table 7: Fully adjusted HR compared with results from competing risks analysis for cardiovascular endpoints

 6 Fully adjusted non-competing risks Fully adjusted competing risks model
 7 analysis

Group	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.36	(1.22- 1.52)	2.92x10 ⁻⁸	1.37	(1.22-1.53)	4 x10 ⁻⁸
MDD only	0.75	(0.54- 1.04)	0.08	0.76	(0.55-1.03)	0.08
Hypertension and MDD	1.66	(1.45- 1.9)	7.48x10 ⁻¹⁴	1.67	(1.45-1.91)	2.2 x10 ⁻¹³
tvc						
MDD only	1.01	(1.004- 1.02)	3.03x10 ⁻³	1.01	(1.004-1.02)	0.003

633 Adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking

634 history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder,

635 aHR = Adjusted hazard ratio, C.I. = Confidence interval.

636 Table 8: Fully adjusted HR compared with results from competing risks analysis for stroke endpoints

Fully adjusted non-competing risks analysis Fully adjusted competing risks model

Group	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.21	(0.97- 1.51)	0.09	1.21	(0.96- 1.52)	0.1
MDD only	1.20	(0.89- 1.63)	0.24	1.20	(0.88- 1.64)	0.25
Hypertension and MDD	1.37	(1.04- 1.79)	0.02	1.36	(1.03- 1.8)	0.031

637 Adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking
 638 history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder,
 639 aHR = Adjusted hazard ratio, C.I. = Confidence interval.

640

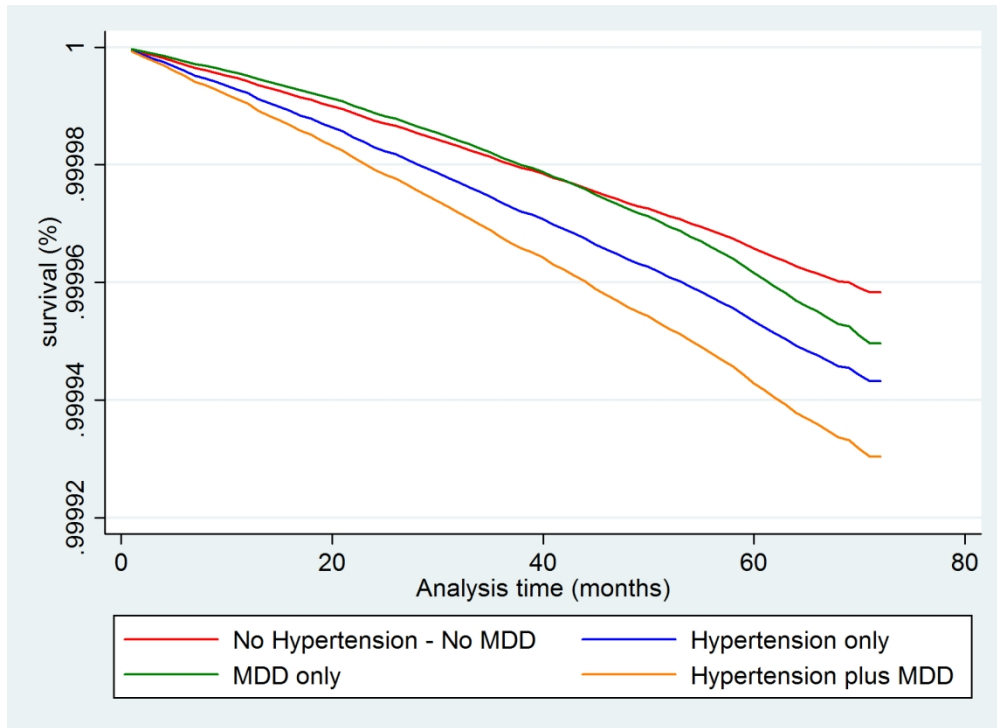
641 Figure 1: Adjusted survival analysis graph for adverse cardiovascular outcome showing greatest hazard for the comorbid group. MDD appears protective compared to the
 642 comparator group initially, however, shows increased hazard after 41 months. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and
 643 ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and
 644 psychotropic medication use (MDD = Major Depressive disorder)

645
 646 Figure 2: Adjusted survival analysis graph for stroke outcomes showing significantly increased hazard for comorbid Hypertension and MDD, with similar insignificant
 647 increased hazard trends for hypertension only and MDD only. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of
 648 diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic
 649 medication use. (MDD = Major Depressive disorder)

1
2
3 650
4 651
5 652
6 653
7 654
8 655

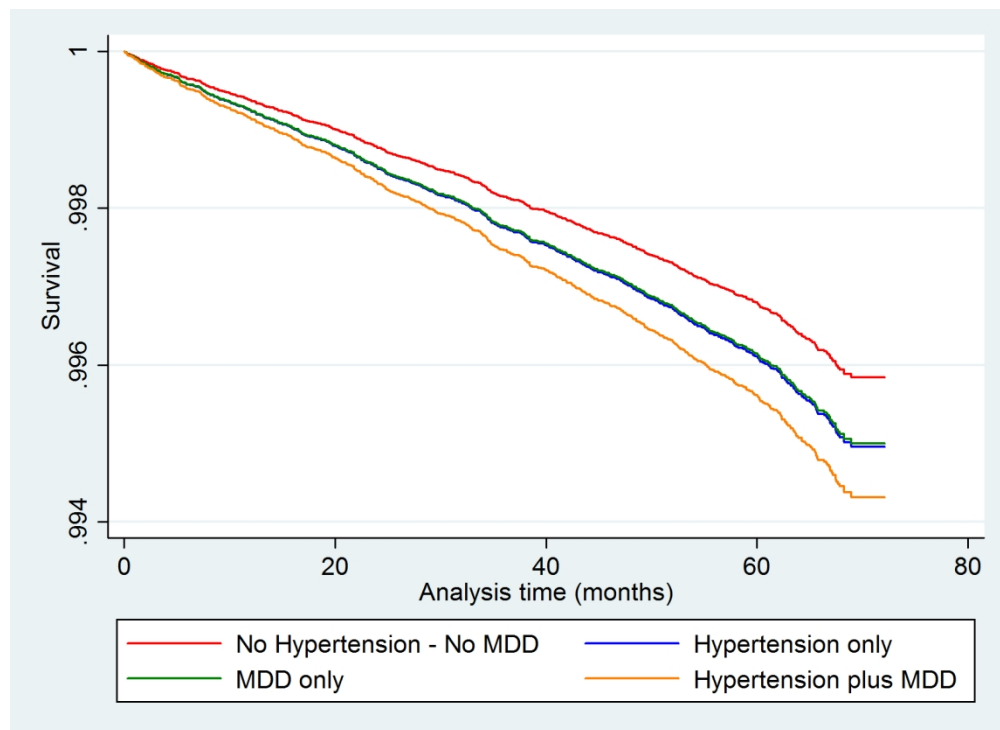
Figure 3: Log (-log) plot showing non-proportionality of MDD only survival over time. Paths between the comparator group and the MDD group cross at the 22.5 month mark. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. (MDD = Major Depressive disorder)

For peer review only



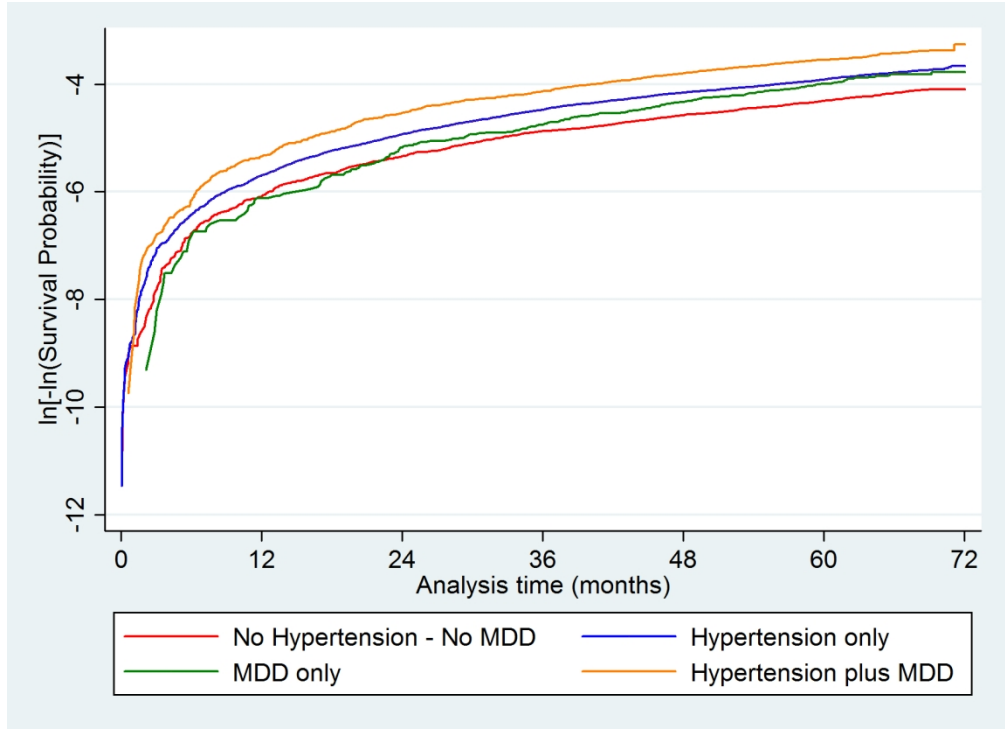
Adjusted survival analysis graph for adverse cardiovascular outcome showing greatest hazard for the comorbid group. MDD appears protective compared to the comparator group initially, however, shows increased hazard after 41 months. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use (MDD = Major Depressive disorder)

152x110mm (300 x 300 DPI)



Adjusted survival analysis graph for stroke outcomes showing significantly increased hazard for comorbid Hypertension and MDD, with similar insignificant increased hazard trends for hypertension only and MDD only. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. (MDD = Major Depressive disorder)

152x110mm (300 x 300 DPI)



Log (-log) plot showing non-proportionality of MDD only survival over time. Paths between the comparator group and the MDD group cross at the 22.5 month mark. Analysis adjusted for age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. (MDD = Major Depressive disorder)

152x110mm (300 x 300 DPI)

1
2
3 **Supplementary information for Impact of major depression on cardiovascular outcomes for**
4 **individuals with hypertension: prospective study in UK Biobank. Graham et al**
5
6
7

8 **METHODS**
9

10
11 **New-onset cardiovascular outcomes**
12

13
14 Date and cause of death were obtained from death certificates held by the National Health Service
15 (NHS) Information Centre for participants from England and Wales and the NHS Central Register
16 Scotland for participants from Scotland. Date and cause of hospital admissions were identified via
17 record linkage to Health Episode Statistics (HES) records for England, the Patient Episode Database
18 for Wales (PEDW) and to the Scottish Morbidity Records (SMR) for Scotland. Detailed information
19 about the record linkage procedure is available online ^{1,2}. At the time of analysis, mortality data were
20 available up to 31st January 2016 for England and Wales and 11th November 2015 for Scotland.
21
22

23
24 Hospital admission data were available for the Scottish, English and Welsh participants until the 31st
25 August 2014, 31st March 2015, and 28th February 2015 respectively. Therefore, for new
26 cardiovascular events, end of follow up was classified as the hospital admission dates unless
27 preceded by the date of death or the date of first cardiovascular event. New onset cardiovascular
28 events were defined as an ICD 10 code of G45, G46, I20- I25, or I6 recorded on a death certificate or
29 hospital admission. Deaths that predated the assessment date were excluded from analysis as
30 presumed errors as were those in which data had only recorded a death date but no cause of death
31 or a cause of death but no death date. Participants that had hospital admissions prior to the
32 assessment date due to the aforementioned ICD10 codes were excluded as were not first episode. In
33 addition, ICD-9 codes 430-438, 410-414, 429 and 429.2 were also excluded. hospital records are not
34 available for the entire lifetime of study individuals, potentially missing some early cardiovascular
35 events, as such those with self-declared prior cardiovascular disease at baseline were also excluded.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56

57
58 **Blood Pressure**
59
60

1
2
3 Blood pressure was measured in a sitting position partway through the interview and at the end of
4 the interview using a digital blood pressure monitor (Omron HEM-7015IT.). Full protocol is available
5
6 online <https://biobank.ctsu.ox.ac.uk/crystal/docs/Bloodpressure.pdf>
7
8
9

10 11 12 13 **Depression definition**

14
15 The criteria for lifetime MDD were created via the the following questions via touchscreen
16 questionnaire were: *"Looking back over your life, have you ever had a time when you were feeling*
17 *depressed or down for at least a whole week?"* (depression); *"Have you ever had a period of time*
18 *lasting at least two days when you were so irritable that you found yourself shouting at people or*
19 *starting fights or arguments?"* (irritability); *"How many weeks was the longest period when you were*
20 *feeling depressed or down?"* (duration); *"Have you ever seen a general practitioner (GP) for nerves,*
21 *anxiety, tension or depression?"* (consulted GP); *"Have you ever seen a psychiatrist for nerves,*
22 *anxiety, tension or depression?"* (consulted psychiatrist). Participants were classified as having a
23 history of MDD if they reported at least one episode which comprised of depression and/or
24 irritability, with a duration of at least two weeks, plus had consulted with either a general
25 practitioner or psychiatrist for mental ill-health.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 **Physical activity**

42
43 Physical activity was based on self-report, utilising the short form International Physical Activity
44 Questionnaire (IPAQ). Participants reported the frequency and duration of moderate and vigorous
45 activity along with walking undertaken in a typical week ³. Data were analysed in accordance with
46 the IPAQ scoring protocol ⁴ and total physical activity was computed as the sum of walking,
47 moderate and vigorous activity, measured as metabolic equivalents (MET-hours/week). Physical
48 activity was used in analyses as a continuous variable. Participants who reported greater than 24
49 hours a day doing all activity were classified as missing.
50
51
52
53
54
55
56
57
58
59
60

Sedentary behaviour

Sedentary behaviour duration was derived from the sum of self-reported time spent driving, using computer and watching television. Those stating that they had performed “less than an hour” of sedentary activities were coded as 0.5hrs to allow use of a continuous variable. Participants who reported greater than 24 hours a day doing all activity were classified as missing.

Socio-demographic and other covariates

Self-report on taking antihypertensive medication was taken from a question specific to cardiovascular medications, where antihypertensive medication was an option to respond. Area-based socioeconomic status was derived from postcode of residence, utilising the census-derived Townsend deprivation index scored on housing, employment, social class and car availability where a negative score represents greater affluence^{5 6}. Age was calculated from dates of birth and baseline assessment date. Smoking status was categorised into never, former and current smoking based on self-report, those who wished not to answer were coded as missing. Drink frequency was categorised into daily, three or four times a week, once or twice a week, one to three times a month, special occasions only, and never based on self-report. Those who wished not to answer were coded as missing. Medical history of diabetes and high cholesterol was collected from the self-completed, baseline assessment questionnaire of medical conditions. Ethnicity was categorised as Caucasian, black/mixed and Asian/mixed based on self-report. Other ethnicities coded as missing due to small numbers. Age at completing full-time education was categorised as (<16, 16, >16). Height and body weight were measured by trained nurses during the initial assessment centre visit. Body mass index (BMI) was calculated as (weight/height²) and the WHO criteria⁷ to classify BMI into: underweight <18.5, normal weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.0 kg.m⁻². Psychotropic medication use was defined by the presence of pharmaceuticals from British National Formulary (BNF) chapters 4.1.1 to 4.3.4⁸ on self-report medication lists at baseline. Duration of hypertension was calculated utilising age and age of hypertension diagnosis. Antihypertensive medication count

1
2
3 was calculated as the absolute number of ACE inhibitors, angiotensin II receptor antagonists, calcium
4 channel blockers, beta-blockers and thiazide diuretics prescribed to an individual. Generic
5 medication names were sought and cross-referenced with the BNF chapters 2.2.1, 2.4, 2.5.5 and
6
7
8
9
10 2.6.2⁸.

11 12 13 14 15 **Statistical analysis:**

16
17
18 A best-fit multivariable regression spline model (stata command “mvr”) was used to find the best
19 model to adjust for non-linear covariates. For the adverse cardiovascular outcomes, A single knot
20 was fitted for age at age 50 and two knots were fitted for total physical activity at 1.65 and 8.062
21 metabolic equivalent hours. In the male subgroup analysis two knots were fitted for total physical
22 activity at 1.7 and 8.507 metabolic equivalent hours, in the female subgroup two knots were fitted
23 for total physical activity at 1.57 and 3.75 and two knots were fitted at systolic blood pressure 121.5
24 and 147.5. No bends were noted in any models for the stroke outcomes.
25
26
27
28
29
30
31
32

33 34 35 **Model selection and covariate adjustment**

36
37
38 All variables were tested against outcome measures (cardiovascular outcomes and stroke outcomes)
39 using univariate analysis to assess appropriateness for inclusion in the final model. All covariates
40 were significantly associated with the outcomes. and were Two continuous variables, age and total
41 physical activity, expressed non-linearity within the main analysis and male subgroup analysis for
42 cardiovascular outcomes and as such regression splines were used with two and three knots
43 respectively. Two knots were included within the female subgroup analysis for physical activity. For
44 stroke outcome there were no bends in the main or sex-specific models.
45
46
47
48
49
50
51
52

53
54 Within the main analysis for cardiovascular outcomes, the groups of depression only, Asian/Asian
55 British ethnicity and BMI<18.5 covariates failed the proportionality assumption and as such, were
56 incorporated into the model as a time varying coefficients. Within the sex specific models depression
57
58
59
60

1
2
3 only failed the PH test within the female only analysis and ethnicity and BMI failed within the male
4
5 only analysis. For the stroke outcomes gender and BMI class failed the proportionality assumption
6
7 within the main analysis, with no failures within the sex-specific analysis. Analysis was repeated with
8
9 the hypertension only as the comparator group to assess for any significant difference between the
10
11 co-morbid group and the hypertension only group.
12
13

14 15 **Time varying covariates**

16
17
18 Due to the finding of MDD failing the proportionality assumption in the cardiovascular outcome in
19
20 the primary analysis a series of further analyses have been performed to find when the assumption
21
22 was not met. A log (-log) plot (fig 3) showed the proportionality assumption was broken at 22.5
23
24 months in the fully adjusted model in the primary analysis. As such, separate models were
25
26 performed prior to and after these points. Prior to 22.5 months the HR for MDD shows a trend that is
27
28 reduced but insignificant (HR 0.82, 95%CI 0.6 - 1.13), becoming significantly increased after the 22.5
29
30 time point. (HR 1.27, 95%CI 1.06 - 1.52) (Table 9 supplementary digital content). Both stratified
31
32 models passed the proportionality assumption using Schoenfeld residuals. Similar to the major
33
34 analysis, the female model showed the MDD only group failing the proportionality assumption,
35
36 although this was at the 29 month time point. (tables 6 and 10 of the supplementary digital
37
38 content).
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. Palmer LJ. UK Biobank: bank on it. *Lancet* 2007;369(9578):1980-2. doi: 10.1016/S0140-6736(07)60924-6
2. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *Plos Medicine* 2015;12(3) doi: 10.1371/journal.pmed.1001779
3. Guo W, Bradbury KE, Reeves GK, et al. Physical activity in relation to body size and composition in women in UK Biobank. *Annals of Epidemiology* 2015;25(6):406-13.e6. doi: <http://dx.doi.org/10.1016/j.annepidem.2015.01.015>
4. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Medicine and science in sports and exercise* 2003;35(8):1381-95. doi: 10.1249/01.mss.0000078924.61453.fb [published Online First: 2003/08/06]
5. Townsend P. Deprivation. *Journal of Social Policy* 2009;16(02):125. doi: 10.1017/s0047279400020341
6. Townsend P, Phillimore M, Beattie A. Health and Deprivation: Inequality and the North. London: Croom Helm Ltd 1988.
7. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;894:i-xii, 1-253.
8. COMMITTEE. JF. British National Formulary. 67 ed. London: BMJ Group and Pharmaceutical Press 2014.

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Supplementary Tables and figures

Supplementary Table1: Descriptive analysis for adverse cardiovascular outcome – males only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N= 21570	N = 30142	N = 4169	N = 5253
Median age (range)*	54 (47 - 61)	61 (54 - 65)	53 (46 - 60)	59 (52 - 64)
Ethnicity, N (%)				
White	19562 (90.69%)	27808 (92.26%)	3923 (94.1%)	5001 (95.2%)
Asian/Asian British	863 (4.%)	969 (3.21%)	87 (2.09%)	86 (1.64%)
Black/ Black British	559 (2.59%)	780 (2.59%)	52 (1.25%)	54 (1.03%)
Median Townsend score (range)*	-1.87 (-3.47 - 0.59)	-2.08 (-3.53 - 0.41)	-1.58 (-3.3 - 1.07)	-1.81 (-3.44 - 0.78)
Age at leaving full-time education, N (%)				
<16	2517 (11.67%)	6328 (20.99%)	464 (11.13%)	1005 (19.13%)
16	4473 (20.74%)	6235 (20.69%)	859 (20.6%)	1096 (20.86%)
>16	14344 (66.5%)	17257 (57.25%)	2807 (67.33%)	3118 (59.36%)
Total physical activity in metabolic	4.15 (1.75 - 8.51)	3.99 (1.65 - 8.51)	4.15 (1.7 - 8.36)	3.76 (1.54 - 7.97)

Sedentary time in hours, median (range)*	4.5 (3.5 - 6)	5 (3.5 - 6.5)	5 (3.5 - 6.5)	5 (4 - 7)
Diabetes, N (%)	721 (3.34%)	2401 (7.97%)	159 (3.81%)	477 (9.08%)
Hypercholesterolaemia, N (%)	1614 (7.48%)	5585 (18.53%)	363 (8.71%)	1056 (20.1%)
Systolic BP in mmHg, median (range)*	128 (121.5 - 133.5)	149.5 (142 - 159)	127.5 (120.5 - 133)	148 (141 - 157)
Body Mass Index, N (%)				
<18.5	74 (0.34%)	35 (0.12%)	22 (0.53%)	12 (0.23%)
18.5 – 25	7607 (35.27%)	5842 (19.38%)	1394 (33.44%)	890 (16.94%)
25-30	10594 (49.11%)	15114 (50.14%)	2019 (48.43%)	2532 (48.2%)
>30	3295 (15.28%)	9151 (30.36%)	734 (17.61%)	1819 (34.63%)
Smoking status, N (%)				
Never smoked	12038 (55.81%)	15145 (50.25%)	1999 (47.95%)	2268 (43.18%)
Previously smoked	6777 (31.42%)	12125 (40.23%)	1447 (34.71%)	2295 (43.69%)
Current smoker	2688 (12.46%)	2776 (9.21%)	716 (17.17%)	686 (13.06%)
Alcohol frequency, N (%)				
Daily or almost daily	4822 (22.36%)	8653 (28.71%)	969 (23.24%)	1503 (28.61%)
Three or four times a week	5718 (26.51%)	7913 (26.25%)	1022 (24.51%)	1323 (25.19%)

Once or twice a week	5932 (27.5%)	7546 (25.03%)	1063 (25.5%)	1178 (22.43%)
One to three times a month	2193 (10.17%)	2392 (7.94%)	440 (10.55%)	479 (9.12%)
Special occasions only	1554 (7.2%)	2154 (7.15%)	328 (7.87%)	423 (8.05%)
Never	1343 (6.23%)	1473 (4.89%)	345 (8.28%)	345 (6.57%)
Psychotropic medication, N (%)	398 (1.85%)	670 (2.22%)	678 (16.26%)	879 (16.73%)

All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.

bmjopen-2018-024443 on 30 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Supplementary Table 2: Descriptive analysis for adverse cardiovascular outcome – females only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N= 29228	N = 25893	N = 10929	N = 7676
Median age (range)*	54 (47 - 61)	61 (55 - 65)	53 (47 - 60)	60 (53 - 64)
Ethnicity, N (%)				
White	26585 (90.96%)	23441 (90.53%)	10324 (94.46%)	7271 (94.72%)
Asian/Asian British	908 (3.11%)	727 (2.81%)	174 (1.59%)	93 (1.21%)
Black/ Black British	764 (2.61%)	989 (3.82%)	167 (1.53%)	168 (2.19%)
Median Townsend score (range)*	-1.90 (-3.44 - 0.51)	-2.06 (-3.5 - 0.38)	-1.66 (-3.3 - 0.84)	-1.87 (-3.4 - 0.74)
Age at leaving full-time education, N (%)				
<16	3399 (11.63%)	5757 (22.23%)	1261 (11.54%)	1602 (20.87%)
16	5792 (19.82%)	5592 (21.6%)	2319 (21.22%)	1636 (21.31%)
>16	19746 (67.56%)	14223 (54.93%)	7283 (66.64%)	4385 (57.13%)
Total physical activity in metabolic	3.87 (1.65 - 7.71)	3.51 (1.37 - 7.59)	3.79 (1.65 - 7.91)	3.65 (1.45 - 7.93)
Sedentary time in hours, median (range)*	4 (3 - 5)	4 (3 - 5.5)	4 (3 - 5.5)	4.5 (3 - 6)

Diabetes, N (%)	547 (1.87%)	1376 (5.31%)	221 (2.02%)	452 (5.89%)
Hypercholesterolaemia, N (%)	1397 (4.78%)	3625 (14.%)	530 (4.85%)	1155 (15.05%)
Systolic BP in mmHg, median (range)*	123.5 (115.5 - 130.5)	149.5 (142 - 160)	122.5 (114.5 - 130)	147.5 (140.5 - 157)
Body Mass Index, N (%)				
<18.5	315 (1.08%)	107 (0.41%)	81 (0.74%)	22 (0.29%)
18.5 – 25	14942 (51.12%)	7836 (30.26%)	4857 (44.44%)	1984 (25.85%)
25-30	9816 (33.58%)	10102 (39.01%)	3917 (35.84%)	2857 (37.22%)
>30	4155 (14.22%)	7848 (30.31%)	2074 (18.98%)	2813 (36.65%)
Smoking status, N (%)				
Never smoked	18588 (63.6%)	16358 (63.18%)	5865 (53.66%)	4186 (54.53%)
Previously smoked	8279 (28.33%)	8015 (30.95%)	3671 (33.59%)	2770 (36.09%)
Current smoker	2282 (7.81%)	1423 (5.5%)	1377 (12.6%)	695 (9.05%)
Alcohol frequency, N (%)				
Daily or almost daily	4628 (15.83%)	4317 (16.67%)	1767 (16.17%)	1378 (17.95%)
Three or four times a week	6457 (22.09%)	5120 (19.77%)	2231 (20.41%)	1514 (19.72%)
Once or twice a week	7712 (26.39%)	6343 (24.5%)	2817 (25.78%)	1738 (22.64%)

One to three times a month	3859 (13.2%)	3196 (12.34%)	1618 (14.8%)	1033 (13.46%)
Special occasions only	3980 (13.62%)	4176 (16.13%)	1576 (14.42%)	1306 (17.01%)
Never	2581 (8.83%)	2726 (10.53%)	917 (8.39%)	703 (9.16%)
Psychotropic medication, N (%)	943 (3.23%)	1125 (4.34%)	2166 (19.82%)	1643 (21.4%)

All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.

Supplementary Table 3: Descriptive analysis for stroke outcome – males only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 22816	N = 32787	N = 4438	N = 5857
Median age (range)*	55 (47 - 62.)	61 (54 - 65)	54 (47 - 61)	60 (53 - 64)
Ethnicity, N (%)				
White	20699 (90.72%)	30219 (92.17%)	4173 (94.03%)	5569 (95.08%)
Asian/Asian British	932 (4.08%)	1116 (3.4%)	102 (2.3%)	105 (1.79%)
Black/ Black British	576 (2.52%)	820 (2.5%)	53 (1.19%)	59 (1.01%)
Median Townsend score (range)*	-1.88 (-3.47 - 0.59)	-2.05 (-3.5 - 0.46)	-1.56 (-3.28 - 1.15)	1.74 (-3.4 - 0.93)
Age at leaving full-time education, N (%)				
<16	2900 (12.71%)	7256 (22.13%)	558 (12.57%)	1193 (20.37%)
16	4702 (20.61%)	6704 (20.45%)	909 (20.48%)	1222 (20.86%)
>16	14960 (65.57%)	18471 (56.34%)	2930 (66.02%)	3397 (58.%)
Total physical activity in metabolic	4.12 (1.74 - 8.48)	3.96 (1.65 - 8.44)	4.13 (1.67 - 8.36)	3.66 (1.45 - 7.83)
Sedentary time in hours, median (range)*	5 (3.5 - 6)	5 (4 - 7)	5 (3.5 - 6.5)	5 (4 - 7)

Diabetes, N (%)	873 (3.83%)	2951 (9.%)	208 (4.69%)	635 (10.84%)
Hypercholesterolaemia, N (%)	2045 (8.96%)	6736 (20.54%)	457 (10.3%)	2293 (22.08%)
Systolic BP in mmHg, median (range)*	128 (121.5 - 133.5)	149 (142 - 159)	127 (120.5 - 133)	147.5 (140.5 - 156.5)
Body Mass Index, N (%)				
<18.5	79 (0.35%)	39 (0.12%)	22 (0.5%)	12 (0.2%)
18.5 – 25	7867 (34.48%)	6215 (18.96%)	1452 (32.72%)	960 (16.39%)
25-30	11203 (49.1%)	16341 (49.84%)	2142 (48.26%)	2780 (47.46%)
>30	3667 (16.07%)	10192 (31.09%)	822 (18.52%)	2105 (35.94%)
Smoking status, N (%)				
Never smoked	12502 (54.79%)	16054 (48.96%)	2094 (47.18%)	2469 (42.15%)
Previously smoked	7399 (32.43%)	13603 (41.49%)	1582 (35.65%)	2610 (44.56%)
Current smoker	2836 (12.43%)	3013 (9.19%)	754 (16.99%)	770 (13.15%)
Alcohol frequency, N (%)				
Daily or almost daily	5085 (22.29%)	9309 (28.39%)	1021 (23.01%)	1645 (28.09%)
Three or four times a week	6039 (26.47%)	8556 (26.1%)	1077 (24.27%)	1450 (24.76%)
Once or twice a week	6264 (27.45%)	8161 (24.89%)	1121 (25.26%)	1305 (22.28%)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

One to three times a month	2307 (10.11%)	2642 (8.06%)	478 (10.77%)	538 (9.19%)
Special occasions only	1666 (7.3%)	2394 (7.3%)	355 (8.%)	503 (8.59%)
Never	1444 (6.33%)	1711 (5.22%)	383 (8.63%)	414 (7.07%)
Psychotropic medication, N (%)	429 (1.88%)	793 (2.42%)	735 (16.56%)	1025 (17.5%)

*All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.*

Supplementary Table 4: Descriptive analysis for stroke outcome – females only

	Comparator group	Hypertension only	MDD only	Hypertension plus MDD
	N = 29684	N = 26937	N = 11143	N = 8090
Median age (range)*	54 (47 - 61)	61 (56 - 65)	53 (47 - 60)	60 (54 - 64)
Ethnicity, N (%)				
White	26998 (90.95%)	24359 (90.43%)	10524 (94.44%)	7643 (94.47%)
Asian/Asian British	925 (3.12%)	773 (2.87%)	178 (1.6%)	104 (1.29%)
Black/ Black British	779 (2.62%)	1034 (3.84%)	170.00 (1.53%)	187 (2.31%)
Median Townsend score (range)*	-1.90 (-3.44 - 0.52)	-2.03 (-3.48 - 0.43)	-1.66 (-3.29 - 0.86)	-1.83 (-3.38 - 0.85)
Age at leaving full-time education, N (%)				
<16	3546 (11.95%)	6140 (22.79%)	1326 (11.9%)	1752 (21.66%)
16	5888 (19.84%)	5803 (21.54%)	2361 (21.19%)	1731 (21.4%)
>16	19954 (67.22%)	14643 (54.36%)	7387 (66.29%)	4550 (56.24%)
Total physical activity in metabolic	3.85 (1.65 - 7.7)	3.49 (1.35 - 7.57)	3.79 (1.65 - 7.89)	3.61 (1.41 - 7.87)

Sedentary time in hours, median (range)*	4.0 (3 - 5)	4.0 (3 - 5.5)	4.0 (3 - 5.5)	4.5 (3 - 6)
Diabetes, N (%)	581 (1.96%)	1551 (5.76%)	241 (2.16%)	528 (6.53%)
Hypercholesterolaemia, N (%)	1547 (5.21%)	4032 (14.97%)	592 (5.31%)	1327 (16.4%)
Systolic BP in mmHg, median (range)*	123.5 (115.5 - 131)	149.5 (142 - 160)	122.5 (114.5 - 130)	147.0 (140.5 - 157)
Body Mass Index, N (%)				
<18.5	316 (1.06%)	112 (0.42%)	82 (0.74%)	26 (0.32%)
18.5 – 25	15100 (50.87%)	8027 (29.8%)	4922 (44.17%)	2057 (25.43%)
25-30	9982 (33.63%)	10476 (38.89%)	4007 (35.96%)	2989 (36.95%)
>30	4286 (14.44%)	8322 (30.89%)	2132 (19.13%)	3018 (37.31%)
Smoking status, N (%)				
Never smoked	18816 (63.39%)	16928 (62.84%)	5958 (53.47%)	4365 (53.96%)
Previously smoked	8452 (28.47%)	8416 (31.24%)	3758 (33.73%)	2950 (36.46%)
Current smoker	2334 (7.86%)	1488 (5.52%)	1409 (12.64%)	749 (9.26%)
Alcohol frequency, N (%)				

Daily or almost daily	4675 (15.75%)	4442 (16.49%)	1796 (16.12%)	1440 (17.8%)
Three or four times a week	6524 (21.98%)	5271 (19.57%)	2258 (20.26%)	1570 (19.41%)
Once or twice a week	7825 (26.36%)	6558 (24.35%)	2872 (25.77%)	1820 (22.5%)
One to three times a month	3913 (13.18%)	3329 (12.36%)	1644 (14.75%)	1089 (13.46%)
Special occasions only	4078 (13.74%)	4400 (16.33%)	1623 (14.57%)	1382 (17.08%)
Never	2658 (8.95%)	2919 (10.84%)	947 (8.5%)	785 (9.7%)
Psychotropic medication, N (%)	979 (3.3%)	1203 (4.47%)	2241 (20.11%)	1753 (21.67%)

All data presented as N (%) and has chi-squared p-value of <0.001 except * which are median values (interquartile range) and have a Kruskal-Wallis p-value of 0.0001. Data presented as MET-hrs (hours spent doing exercise adjusted for multiples of basal metabolic rate in accordance with IPAQ). Townsend score is an area based measure based on census statistics. It is a calculation based on the number of: households without a car, overcrowded households, households not owner-occupied and unemployment.

Supplementary Table 5: Risk of adverse cardiovascular event by clinical group, in males only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension- No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.21	(2.00-2.45)	2.28x10 ⁻⁵³	1.62	(1.46-1.83)	5.80x10 ⁻¹⁹	1.29	(1.13-1.47)	1.35x10 ⁻⁴
MDD only	1.17	(0.95-1.56)	0.12	1.18	(0.95-1.46)	0.12	1.12	(0.9-1.39)	0.3
Hypertension and MDD	2.46	(2.13-2.84)	3.12x10 ⁻³⁴	1.95	(1.68-2.27)	2.81x10 ⁻¹⁸	1.47	(1.24-1.74)	8.71x10 ⁻⁶

*Adjusted for sociodemographic factors (age, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I.= confidence interval

Supplementary Table 6: Risk of adverse cardiovascular event by clinical group, in females only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.75	(2.38 - 3.18)	6.16x10 ⁻⁴³	1.86	(1.6-2.17)	1.43x10 ⁻¹⁵	1.64	(1.33-2.02)	4.36x10 ⁻⁶
MDD only	0.67	(0.42-1.08)	0.10	0.72	(0.45-1.17)	0.19	0.68	(0.42-1.1)	0.12
Hypertension and MDD	3.68	(3.1-4.38)	5.62x10 ⁻⁴⁹	2.78	(1.58-3.29)	4.62x10 ⁻²⁹	2.18	(1.82-2.62)	4.76x10 ⁻¹¹
Time varying Variables									
MDD only	1.02	(1.006-1.03)	2.45x10 ⁻³	1.02	(1.005-1.03)	4.00x10 ⁻³	1.02	(1.004-1.03)	6.19x10 ⁻³

*Adjusted for sociodemographic factors (age, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = Confidence interval

Supplementary Table 7: Risk of stroke event by clinical group, in males only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.43	(1.95 - 3.03)	1.92x10 ⁻¹⁵	1.74	(1.38 - 2.19)	2.58x10 ⁻⁶	1.19	(0.9 - 1.5)	0.22
MDD only	1.45	(0.96 - 2.2)	0.07	1.65	(1.09 - 2.5)	0.02	1.49	(0.97 - 2.29)	0.07
Hypertension and MDD	2.39	(1.74 - 3.27)	7.34x10 ⁻⁸	1.87	(1.35 - 2.6)	1.55x10 ⁻⁴	1.20	(0.83 - 1.74)	0.33

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = confidence interval

bmjopen-2018-024433 on 30 September 2019. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Supplementary Table 8: Risk of stroke event by clinical group, in females only.

Group	Model one (unadjusted)			Model two (partially adjusted)*			Model three (fully adjusted) †		
	HR	95% C.I.	p-value	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)			1(ref)		
Hypertension only	2.38	(1.84 - 3.09)	6.50x10 ⁻¹¹	1.51	(1.14 - 1.99)	3.63x10 ⁻³	1.25	(0.88 - 1.79)	0.21
MDD only	1.09	(0.73 - 1.62)	0.67	1.15	(0.76 - 1.75)	0.51	0.99	(0.64 - 1.53)	0.98
Hypertension and MDD	3.05	(2.22 - 4.21)	8.71x10 ⁻¹²	2.22	(1.59 - 3.08)	2.27x10 ⁻⁶	1.62	(1.08 - 2.42)	0.02

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity). † Additionally adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use. MDD = Major depressive disorder, HR = Hazard ratio, aHR = Adjusted hazard ratio, C.I. = confidence interval

Supplementary Table 9: Time stratified analysis by moment of proportional hazards failure for adverse cardiovascular outcomes (stratified at 22.5 months)

Group	Fully adjusted* model pre-22.5 months			Fully adjusted* model post-22.5 months		
	aHR	95% C.I.	p-value	aHR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.36	(1.12 - 1.66)	0.002	1.36	(1.19 -1.55)	5.06x10 ⁻⁶
MDD only	0.82	(0.60 - 1.13)	0.22	1.27	(1.06 -1.52)	0.01
Hypertension and MDD	1.75	(1.39 - 2.21)	2.62x10 ⁻⁶	1.62	(1.38 - 1.90)	5.72x10 ⁻⁹

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.

MDD = Major depressive disorder, aHR =adjusted hazard ratio, C.I.= Confidence interval

bmjopen-2018-024443 on 30 September 2019. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Supplementary Table 10: Time stratified analysis by moment of proportional hazards failure for adverse cardiovascular outcomes (females only - stratified at 29 months)

Group	Fully adjusted* model pre-29 months			Fully adjusted* model post-29 months		
	HR	95% C.I.	p-value	HR	95% C.I.	p-value
No Hypertension - No MDD	1(ref)			1(ref)		
Hypertension only	1.49	(1.06 - 2.08)	0.02	1.75	(1.33 - 2.30)	5.56x10 ⁻⁵
MDD only	0.73	(0.48 - 1.10)	0.13	1.58	(1.19 - 2.09)	0.002
Hypertension and MDD	1.80	(1.24 - 2.62)	0.002	2.47	(1.83 - 3.33)	2.89x10 ⁻⁹

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.

MDD = Major depressive disorder, aHR =adjusted hazard ratio, C.I.= Confidence interval

Supplementary Table 11: Relative excess risk due to interaction results on fully adjusted* models

Analysis	RERI	95% C.I.	LR test p-value
Adverse cardiovascular outcome before 22.5 months	0.563	(0.189 - 0.938)	0.0116
Adverse cardiovascular outcome after 22.5 months	-0.009	(-0.293 - 0.275)	0.563
Adverse cardiovascular outcome (males only)	0.058	(-0.240 - 0.357)	0.899
Adverse cardiovascular outcome (females only)before 29 months	0.588	(0.074 - 1.103)	0.031
Adverse cardiovascular outcome (females only)after 29 months	0.142	(-0.447 - 0.732)	0.5173
Stroke outcome	-0.047	(-0.485 - 0.391)	0.7271
Stroke outcome (males only)	-0.480	(-1.195 - 0.234)	0.1376
Stroke outcome (females only)	0.372	(-0.216 - 0.959)	0.314

*Adjusted for sociodemographic factors (age, sex, Townsend score, age of leaving full time education and ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, systolic blood pressure, sedentary hours per day, physical activity and psychotropic medication use.

RERI = Relative excess risk due to interaction (additive interaction), C.I.= Confidence interval, LR test = likelihood ratio test (multiplicative interaction)

Supplementary Table 12: Comparison of additional hypertension factors (medication and diagnosis duration) across groups

	No Hypertension – No MDD	Hypertension only	MDD only	Hypertension and MDD
Antihypertensive medication prescription, N (%)	1,265 (2.49)	19,045 (33.99)	476 (3.04)	5,037 (37.34)
Number of antihypertensive medications, N (range)*	1 (1-1)	1 (1-2)	1 (1-1)	1 (1- 2)
Reported a duration of hypertension, N (%)	1,376 (2.71)	16,709 (29.82)	678 (4.42)	4,525 (33.55)
Duration of hypertension in years, median (range)*	6 (2-14)	8 (4-13)	6 (3-14)	8 (4 - 14)

*Median quantity of antihypertensive medications and median duration of hypertensive diagnosis presented for those on antihypertensive medications and supplied an age of hypertension diagnosis, respectively. MDD = Major Depressive disorder

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7

1		#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
2				
3				
4	Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
5				
6				
7				
8				
9				
10	Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-8
11				
12				
13				
14				
15				
16				
17				
18	Bias	#9	Describe any efforts to address potential sources of bias	6
19				
20	Study size	#10	Explain how the study size was arrived at	6
21				
22				
23	Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	See note 1
24				
25				
26				
27				
28	Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8-9
29				
30				
31				
32		#12b	Describe any methods used to examine subgroups and interactions	See note 2
33				
34				
35				
36		#12c	Explain how missing data were addressed	6-7
37				
38		#12d	If applicable, explain how loss to follow-up was addressed	1
39				
40				
41		#12e	Describe any sensitivity analyses	9
42				
43	Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	10
44				
45				
46				
47				
48				
49				
50				
51		#13b	Give reasons for non-participation at each stage	6,7
52				
53		#13c	Consider use of a flow diagram	n/a
54				
55				
56	Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	10
57				
58				
59				
60				

		confounders. Give information separately for exposed and unexposed groups if applicable.	
	#14b	Indicate number of participants with missing data for each variable of interest	See note 3
	#14c	Summarise follow-up time (eg, average and total amount)	10
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	6
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
	#16b	Report category boundaries when continuous variables were categorized	n/a
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	See note 4
Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

Author notes

1. 6,7,8,9, supplementary

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

- 1 2. 8-9, supplementary
- 2
- 3 3. n/a (supplementary)
- 4
- 5 4. 11-12, supplemental
- 6

7 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License
8 CC-BY. This checklist was completed on 25. May 2018 using <http://www.goodreports.org/>, a tool
9 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60