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1 **Psychological distress and risk of myocardial infarction and stroke in the 45 and Up Study: a**  
2 **prospective cohort study**

3 Short title: Psychological distress and MI and stroke risk

4 Caroline A Jackson (PhD)<sup>\*1,2</sup>, Cathie LM Sudlow (DPhil)<sup>1,3</sup>, Gita D Mishra (PhD)<sup>2</sup>

5 <sup>1</sup>Usher Institute of Population Health Sciences and Informatics  
6 University of Edinburgh  
7 Nine Bioquarter, 9 Little France Road  
8 Edinburgh, EH16 4UX

9  
10 <sup>2</sup>School of Public Health  
11 University of Queensland

12  
13 <sup>3</sup>Centre for Clinical Brain Sciences  
14 University of Edinburgh  
15

16 \*Corresponding author contact details:

17 Email: [caroline.jackson@ed.ac.uk](mailto:caroline.jackson@ed.ac.uk)

18 Tel: +44 (0) 1316517872

19

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22

23 **ABSTRACT**

24 **Background** The interplay between mental and physical health remains poorly understood. We  
25 investigated whether psychological distress is associated with risk of myocardial infarction (MI) and  
26 stroke in a population-based prospective study.

27 **Methods and Results** We included participants without prior stroke/MI from the New South Wales  
28 45 and Up Study. We categorised baseline psychological distress as low, medium, and high/very high  
29 on the 10-item Kessler Psychological Distress Scale and identified stroke and MI through linkage to  
30 hospital admission and mortality records. We obtained sex and age-stratified adjusted and  
31 unadjusted hazard ratios (HRs) for the association between psychological distress and MI and stroke.  
32 We investigated for interaction between psychological distress and each of age and sex.  
33 Among 221,677 participants 16.2% and 7.3% had moderate and high/very high psychological distress  
34 at recruitment, respectively. During  $4.7 \pm \text{SD } 0.98$  years of follow-up, 4573 MIs and 2421 strokes  
35 occurred. Absolute risk of MI and stroke increased with increasing psychological distress level. In  
36 men aged 45-79, high/very high versus low psychological distress was associated with a 30%  
37 increased risk of MI (fully adjusted HRs 1.30, 95% CI 1.12 to 1.51), with weaker estimates in those  
38 aged  $\geq 80$  years. Among women, high/very high psychological distress was associated with an 18%  
39 increased risk of MI (adjusted HR 1.18, 95% CI 0.99, 1.42) with similar findings across age-groups. In  
40 the 45-79 years age group, high/very high psychological distress and male sex had a supra-additive  
41 effect on MI risk. Similar estimates were observed for stroke, with high/very high psychological  
42 distress associated with a 24% and 44% increased stroke risk in men and women, respectively, with  
43 no evidence of interaction with age or sex.

44 **Conclusion** Psychological distress has a strong, dose-dependent, positive association with MI and  
45 stroke in men and women, despite adjustment for a wide range of confounders.

46

47 **INTRODUCTION**

48 Cardiovascular and cerebrovascular disease (collectively referred to here as CVD) are leading causes  
49 of mortality and morbidity worldwide.<sup>1,2</sup> Mental disorders are a similarly important global public  
50 health problem, with depression and anxiety disorders listed second and ninth, respectively, in the  
51 top 20 causes of global years lived with disability.<sup>2</sup> The growing dual burden of CVD and mental  
52 disorders is of particular importance given the increasingly recognised, yet poorly understood,  
53 interplay between the two.<sup>3,4</sup>

54 Common mental disorders such as depression and anxiety, or measures of their symptoms, are  
55 thought to be associated with an increased risk of coronary heart disease and stroke, but meta-  
56 analyses have found substantial heterogeneity between studies and inconsistency in findings.<sup>5-8</sup>  
57 Controversy persists as to whether common mental disorders or their symptoms play an  
58 independent aetiological role in the development of CVD, with the potential for residual  
59 confounding being a recurrent criticism of existing studies. Studies which define depression or  
60 anxiety based on a clinical diagnosis include a selected population, since they include those people  
61 who have sought or have access to healthcare for their mental health problems. An alternative  
62 approach, often used in population-based epidemiological studies, is to measure self-reported  
63 mental health problems, which somewhat reduces this selection bias and may improve  
64 generalisability of findings to the whole population setting. Some measures, such as the Centre for  
65 Epidemiological Studies Depression (CESD) scale seek to measure depressive symptoms only,  
66 whereas others, such as the Kessler psychological distress scale, measure non-specific psychological  
67 distress, but with a focus on depression and anxiety. Few studies have investigated the association  
68 between psychological distress and CVD occurrence and have generally examined CVD mortality<sup>9-13</sup>  
69 and not incidence. Existing studies which have reported on CVD incidence are limited by small size,  
70 incomplete adjustment for potential confounders, heterogeneous psychological distress measures  
71 and inconsistent findings.<sup>14-19</sup> Furthermore, studies have rarely reported sex-specific associations.  
72 The pathophysiology of psychological distress may differ between men and women, with changes in

73 hormone levels throughout the life-course playing a potentially important aetiological role in  
74 women.<sup>20</sup> Also, sex differences in treatment-seeking behaviour for, and/or specific treatment of  
75 psychological distress might lead to differential associations with CVD risk. Similarly, it is unclear  
76 whether the association between psychological distress and CVD risk persists within all age-groups.  
77 It is therefore prudent to explore differential demographic effects when relating psychological  
78 measures to physical disease.  
79 To address these gaps, we investigated the association between psychological distress and incidence  
80 of myocardial infarction (MI) and stroke, by sex and age in a large prospective cohort study.

## 81 **METHODS**

82 The data, analytic methods, and study materials will not be made available to other researchers for  
83 purposes of reproducing the results or replicating the procedure since access to the data is only via  
84 approved application by the study investigators.

### 85 **Study population**

86 We included participants from the Sax Institute's 45 and Up Study, a prospective cohort from the  
87 New South Wales (NSW), Australia, general population aged 45 years or over, recruited in 2006-  
88 2009. Recruitment methods are described in detail elsewhere.<sup>21</sup> Briefly, potential participants were  
89 randomly sampled from the Department of Human Services (formerly Medicare Australia) database  
90 and mailed a self-administered questionnaire and information leaflet. Participants consented to  
91 follow-up, including linkage to routinely collected health datasets. For this study, the cohort was  
92 linked to the NSW Admitted Patient Data Collection, the Australian Capital Territory (ACT) Admitted  
93 Patient Collection and the Australian Bureau of Statistics Death Data, with linkage performed by the  
94 Centre for Health Record Linkage.<sup>22</sup> We excluded participants with a previous hospitalised stroke or  
95 MI record or self-reported stroke, MI or angina at baseline (since participants were asked about  
96 prior MI or angina within a single question).

97 The conduct of the 45 and Up Study was approved by the University of NSW Human Research Ethics  
 98 Committee. Ethical approval for the present study was obtained from the NSW Population and  
 99 Health Services Research Ethics Committee, the ACT Health Human Research Ethics Committee and  
 100 the University of Queensland Institutional Human Research Ethics Committee.

101 **Psychological distress**

102 Psychological distress was measured at baseline using the self-administered 10-item Kessler  
 103 psychological distress (K10) scale<sup>23</sup>, a widely used screening tool that measures symptoms of  
 104 psychological distress in the previous four weeks (Table 1). The K10 scale has high construct and  
 105 factorial validity<sup>23, 24</sup> and has been shown to have high validity when evaluated against the gold  
 106 standard of Structured Clinical Interview for DSM-IV disorders, especially mood and anxiety  
 107 disorders.<sup>25-27</sup> We modelled psychological distress as a categorical variable since K10 scores were  
 108 not normally distributed and heavily skewed, with many people reporting little or no psychological  
 109 distress. We created low (scores of  $\leq 15$ ), moderate (16-21), high (22-29) and very high (30-50)  
 110 distress groups, in line with categorisation used in Australian Bureau of Statistics surveys.<sup>28</sup> We  
 111 combined the two latter categories, given the relatively low numbers in the highest groups.

112 Table 1 Component questions used in the 10-item Kessler Psychological distress scale and  
 113 accompanying scoring system

'During the past 4 weeks, about how often did you feel':	Respondents selected 1 of 5 possible responses for each question: [score given]*
tired out for no good reason?	
nervous?	
so nervous that nothing could calm you down?	None of the time: [1]
hopeless?	A little of the time: [2]
restless or fidgety?	Some of the time: [3]
so restless that you could not sit still?	Most of the time: [4]
depressed?	All of the time: [5]
that everything was an effort?	
so sad that nothing could cheer you up?	
worthless?	
*Minimum total score = 10; maximum total score = 50	

114

115 **Myocardial infarction and stroke**

116 We identified incident MI and stroke from hospital admission discharge records and mortality  
117 records, defining MI using ICD-10 I21 and stroke using I60, I61, I63 and I64. These codes could  
118 appear either in the primary or secondary diagnosis/cause of death fields of hospital admission or  
119 mortality records. For analyses of pathological stroke types, ischaemic stroke was defined using I63  
120 and I64 (since the majority of 'undetermined' strokes coded as I64 will be ischaemic),<sup>29</sup> and  
121 haemorrhagic stroke by I60 and I61.

## 122 **Covariates**

123 Definitions of covariates are given in supplementary Table 1. We adjusted for: sociodemographic  
124 factors (marital status, geographical remoteness, area-based deprivation, highest attained education  
125 level and average annual household income); lifestyle factors (body mass index (BMI); smoking  
126 status; alcohol intake; physical activity; daily fruit and vegetable consumption; and weekly fish  
127 intake); physiological factors and family history (self-reported history of hypertension, heart disease  
128 and diabetes, treated cholesterol in the past month, family history of heart disease or stroke and  
129 baseline physical comorbidity based on a modified Charlson comorbidity index<sup>30</sup> using hospital  
130 admission data in the five years prior to recruitment); and, among women, reproductive factors.

## 131 **Statistical analyses**

132 We performed analyses using Stata version 12. We summarised baseline characteristics by  
133 psychological distress and stroke occurrence and compared characteristics of included versus  
134 excluded participants (i.e., those without complete information on psychological distress).

### 135 *Missing data and multiple imputation*

136 The frequency of missing values was less than 5% for almost all covariates. However, due to wide  
137 dispersion of missingness, overall, 37% of men and 50% of women had missing values for at least  
138 one variable. We therefore used multiple imputation by chained equations to impute missing values  
139 of included covariates, performing 37 imputations for men and 50 for women.<sup>31</sup> We imputed data  
140 separately for men and women since we included sex-specific variables for women in our analyses.

141 *Survival analyses*

142 We created Kaplan-Meier plots of probability of survival free of each of stroke and MI for  
143 psychological distress categories, censoring for date of stroke event, non-stroke death and end of  
144 follow-up (31<sup>st</sup> Dec 2012), using age in years as the time scale. The proportional hazards assumption  
145 was violated for MI among men but not women. Thus, among men, the effect of psychological  
146 distress was not constant by age. As shown in supplementary Figure 1, the effect of moderate or  
147 high/very high psychological distress attenuated among those aged 80 years or over at baseline,  
148 with the gap between the survival curves narrowing. We therefore stratified by baseline age and  
149 report on the association between psychological distress and MI for each age group separately (ages  
150 45-79 and  $\geq 80$ ), after confirming that the proportional hazards assumption was not violated within  
151 these two age groups. There was no violation of the proportional hazards assumption by  
152 psychological distress for the stroke model and no clear violation by any covariate included in the MI  
153 or stroke models.

154 We used Cox regression to obtain sex-specific unadjusted and serially adjusted hazard ratios (HRs)  
155 with 95% confidence intervals (CIs) for the association between psychological distress and each of  
156 MI and stroke.

157 The primary analysis was performed following multiple imputation. We also performed a complete-  
158 case analysis (presented in supplementary material). As depicted simplistically in part A of Figure 1,  
159 there are multiple pathways through which psychological distress might lead to an increased risk of  
160 CVD. A number of these factors might also confound the association (as shown in part B of Figure 1).  
161 Since the K10 scale asks about psychological distress in the past four weeks, with information on  
162 covariates collected at baseline only, we treated all covariates as common sources (confounders) in  
163 our analyses and adjusted for them. Since some of these covariates might actually lie on a possible  
164 causal pathway between psychological distress and CVD, we acknowledge that this assumption may  
165 not be valid and discuss the implications of this in our discussion.



166 We investigated for interaction between psychological distress and sex on MI and stroke risk among  
167 participants aged 45-79 and 80 years or over at baseline. Within men and women separately, we  
168 also investigated for interaction between psychological distress and age on MI and stroke risk. We  
169 investigated interaction on the multiplicative scale by adding interaction terms to the age-adjusted  
170 models. Since additive (i.e. biological) interaction is more important for understanding population  
171 health, we also investigated interaction on the additive scale, by calculating the relative excess risk  
172 of interaction (RERI) and synergy index with accompanying 95% CIs.<sup>32</sup>  
173 In subgroup analyses, we stratified by pathological stroke type.  
174 This article was written in accordance with the STROBE statement.<sup>33</sup>

## 175 **RESULTS**

176 Among 267,019 participants, 248,462 were eligible for inclusion. After excluding those with missing  
177 information on psychological distress, we included 221,677 participants (Figure 2). Compared to  
178 included participants, excluded participants were older and more likely to be: female; of lower SES;  
179 and less healthy (supplementary Table 2). We included 102,039 men and 119,638 women (mean age  
180  $62.2 \pm 10.5$  and  $60.2 \pm 10.2$ , respectively). Psychological distress was more common in women than  
181 men (17.3% versus 14.8% for moderate distress and 8.1% versus 6.3% for high/very high distress,  
182 respectively;  $p < 0.001$ ) and more common in younger age groups for both men and women ( $p < 0.001$   
183 for both sexes). Increasing psychological distress was also associated with lower SES, poorer lifestyle,  
184 clinical stroke risk factors, and among women, reproductive factors (Table 2). Similarly, most  
185 characteristics were associated with MI and stroke occurrence. Cross-tabulations of baseline  
186 characteristics and psychological distress stratified by sex and of baseline characteristics by MI and  
187 stroke are given in supplementary Tables 3-5.

### 188 **Psychological distress and absolute risk of MI and stroke**

189 The follow-up period was almost identical for the stroke and MI analyses. During a mean follow-up  
190 of 4.70 ( $\pm$  SD 0.98) years, 4573 MIs and 2421 strokes occurred. Absolute age standardised MI and

191 stroke risk was generally higher among men than women and increased with increasing  
192 psychological distress level (Table 3). When stratifying by age, this pattern persisted for MI incidence  
193 among men aged under 80 years at baseline, but not those aged 80 years or over (Figure 3a). In the  
194 latter group, MI incidence was broadly similar across levels of psychological distress. In contrast,  
195 among women, MI incidence increased with increasing psychological distress levels irrespective of  
196 age at baseline (Figure 3b). Similar sex and age patterns were observed for stroke (Figures 3c and  
197 3d).

### 198 **Psychological distress and relative risk of MI**

199 Among men aged 45-79 years at baseline, moderate and high/very high distress were associated  
200 with 28% and 60% increased risk of MI after adjustment for sociodemographic factors, (HRs 1.28,  
201 95% CI 1.15 to 1.43 and 1.60, 95% CI 1.39, 1.86, respectively; Table 4, model 2). Similar results were  
202 observed for women, although the effect estimate for moderate versus low/no psychological  
203 distress was not statistically significant (Table 4, model 2). Additional adjustment for lifestyle,  
204 disease history and clinical risk factors attenuated estimates further and in some instances estimates  
205 were no longer statistically significant. However, even in the fully adjusted models, a significant  
206 association or trend towards an association persisted (Table 4; models 3 and 4).

207 Among men aged 80 years or over the effect of psychological distress on MI risk was weaker (Table  
208 4), with evidence of interaction on both the multiplicative scale (p-value for age-by-distress  
209 interaction: 0.003) and additive scales.

210 There was no evidence of any interaction between age and psychological distress among women,  
211 with effect estimates broadly similar across both age groups.

212 We did find evidence of interaction on the additive scale between sex and psychological distress in  
213 the 45-79 years age group, with high/very high psychological distress and male sex having a supra-  
214 additive effect on MI risk. Essentially, the joint effect of high/very high psychological distress and  
215 male sex on MI risk was greater than we would expect based on their separate effects on MI risk. All  
216 interaction results are provided in supplementary Table 6.

## 217 **Psychological distress and relative risk of stroke**

218 There was a similar dose-dependent association between psychological distress and stroke, although  
219 point estimates were larger in women than men. After adjusting for sociodemographic factors,  
220 moderate and high/very high distress were associated with 14% and 37% increased risk of stroke  
221 among men (HR 1.14, 95% CI 0.98 to 1.32 and 1.37, 95% CI 1.10 to 1.69, respectively) and 31% and  
222 81% increased risk of stroke among women (HR 1.31, 95% CI 1.11 to 1.55 and 1.81, 95% CI 1.46 to  
223 2.23; Table 5, model 2). Effect estimates were similar across younger and older age groups. There  
224 was no clear evidence of interaction between psychological distress and sex or between  
225 psychological distress and age on stroke risk (supplementary Table 7), although as with MI, effect  
226 estimates among men aged 80 years or over were weaker than in younger ages.

## 227 **Sensitivity analyses**

228 The association between psychological distress and stroke was similar for ischaemic and  
229 haemorrhagic stroke, although smaller numbers of haemorrhagic stroke decreased precision  
230 (supplementary Figure 2).

231 Results of the complete-case analyses for MI and stroke are given in supplementary Tables 8 and 9.

## 232 **DISCUSSION**

233 Psychological distress has a strong, dose-dependent, positive association with MI and stroke risk in  
234 both men and women. There was some indication of possible sex differences. Among those aged 45-  
235 79, we observed a supra-additive interaction between psychological distress and male sex on MI risk  
236 (i.e. the joint effect of psychological distress and male sex on MI risk was greater than we would  
237 expect). Among women the magnitude of effect of psychological distress appeared greater for  
238 stroke than for MI. Furthermore, associations generally persisted despite adjustment for a wide  
239 range of confounding factors. To our knowledge, this is by far the largest study of psychological  
240 distress and incident CVD, including more than four times the number of MIs<sup>16-18</sup> and double the  
241 number of strokes included in previous published studies combined.<sup>14, 15, 19</sup> It is also one of just a  
242 handful of studies to examine whether the effect of psychological distress differs by sex and age.

243 There is a paucity of prospective studies relating psychological distress to subsequent risk of CVD  
244 and to our knowledge none have used the K10 to measure psychological distress. However, despite  
245 some inconsistencies with previous studies, our findings concur with the view that high  
246 psychological distress is independently associated with increased CVD risk, even after controlling for  
247 a wide range of covariates. Consistent with our findings for MI, two previous small studies reporting  
248 on psychological distress and MI risk with stratification by sex reported a greater magnitude of effect  
249 in men than women.<sup>16, 18</sup> Contrastingly, a third study found no clear evidence of an association  
250 between psychological distress and MI risk when those with coronary heart disease at baseline were  
251 excluded.<sup>16</sup> Our findings are somewhat consistent with results from previous studies linking  
252 measures of psychological distress to stroke risk<sup>14, 15, 19</sup>, although two studies found significant  
253 associations with fatal but not non-fatal<sup>15</sup> or hospitalised<sup>14</sup> stroke. The only study of stroke which  
254 stratified by sex reported a consistent association between psychological distress and stroke among  
255 both men and women, which concurs with our findings.<sup>19</sup>

256 The findings from our study, along with those from the broader literature, suggest that psychological  
257 distress might operate partly through lifestyle behaviours, but also support the view that other  
258 mechanisms may exist. Disorders such as depression and anxiety are thought to induce patho-  
259 physiologic changes, including: alteration of the hypothalamic-pituitary-adrenal axis of the  
260 neuroendocrine system; activation of inflammatory processes (e.g. through release of pro-  
261 inflammatory cytokines); platelet hyperactivity; and endothelial dysfunction.<sup>34-37</sup> It is reasonable to  
262 postulate that symptoms of psychological distress might operate through the same mechanisms to  
263 increase CVD risk. Interestingly, although a different construct, psychosocial stress has been linked  
264 to increased amygdalar activity, which in turn was associated with increased cardiovascular  
265 (including stroke) event risk, potentially through increased bone-marrow activity (and release of  
266 inflammatory cells) and arterial inflammation.<sup>38</sup> Our finding of a consistent association between  
267 psychological distress and both ischaemic and haemorrhagic stroke suggests that the underlying  
268 mechanism(s) are likely to cause pathophysiologic changes common to both pathological stroke

269 types. It is interesting that, consistent with some previous studies, the association between  
270 psychological distress and MI risk appears stronger in men than women. Whilst common mental  
271 disorders and psychological distress are more common in women than men, women are more likely  
272 than men to seek primary care for mental (as well as physical) health problems. Women might  
273 therefore address their mental health concerns more constructively than men, thereby partially  
274 negating the physical disease consequences of psychological distress. Somewhat paradoxically, we  
275 didn't find the same sex difference for stroke, with the risk perhaps slightly stronger in women than  
276 men. Effect estimates in women were however certainly larger for stroke than MI, raising the  
277 possibility of different pathways between psychological distress and types of CVD in women.  
278 Alternatively, these findings might reflect divergent protective effects of hormone levels on coronary  
279 heart disease as compared to cerebrovascular disease risk in women.<sup>39</sup> The apparent moderating  
280 effect of older age on the association between psychological distress and CVD risk in men may be  
281 more likely to be due to survival bias rather than a true counteraction of risk by older age. Men who  
282 survive into their 80s (and with symptoms of psychological distress) are perhaps a somewhat  
283 selected resilient sub-group. One might also query the role of non-CVD death as a potential  
284 competing risk in our analyses, which might affect/prevent the outcomes of interest being observed.  
285 However, in line with guidance on accounting for competing risks when addressing aetiological  
286 research questions, we did not calculate sub-distribution HRs to examine the role of non-stroke/non-  
287 MI death as a competing risk.<sup>40, 41</sup> As recommended, we additionally calculated cause-specific hazard  
288 ratios for non-stroke and non-MI death (data available on request). As expected, increased  
289 psychological distress was associated with increased risk of non-CVD death.

290 Whilst evidence from human and animal studies provide some support for a causal association  
291 between psychological distress and physical diseases such as MI and stroke, this remains a complex  
292 and contentious area. Alternative explanations for the observed associations include residual  
293 confounding, reverse causation, and common cause(s) leading to a spurious association. Whilst  
294 some degree of residual confounding is always possible, particularly by unknown confounders, the

295 magnitude of the observed associations in the present study, even after adjusting for confounding  
296 factors (some of which may actually lie on the causal pathway) suggests that residual confounding is  
297 unlikely to fully explain the observed associations. The association may be due to reverse causation,  
298 whereby psychological distress as a result of subclinical disease manifests prior to stroke event.  
299 Future research should address the issue of reverse causation using data from studies in which  
300 psychological distress is measured early in life with repeat measurement over the life-course along  
301 with the reliable recording of CVD events. Finally, psychological distress and CVD might be different  
302 manifestations of the same underlying mechanism, with psychological distress manifesting prior to  
303 CVD occurrence (i.e. the 'common soil' hypothesis). Human and animal studies demonstrate that  
304 chronic stress for example may lead to both psychiatric and physical illness.<sup>34</sup>

### 305 **Strengths and limitations**

306 Our study benefits from key strengths. It included a large CVD-free study population and a large  
307 number of incident CVD events during follow-up, providing sufficient power to stratify by sex and  
308 age. We also identified CVD events objectively through hospital and mortality records. Furthermore,  
309 studies of psychological distress in relation to stroke risk are less than common than cardiovascular  
310 disease and so our study makes a large contribution to this area. Psychological distress was  
311 measured with a highly reliable and valid tool, which performs well when evaluated against present-  
312 state DSM-IV disorders, especially mood and anxiety disorders.<sup>23-27, 42</sup> K10 also out-performs the  
313 GHQ-12 questionnaire.<sup>25, 43</sup> Lastly, we were able to adjust for a wide range of potential confounders,  
314 including those less commonly adjusted for in previous studies on this topic.

315 Our study has some limitations. The participation rate in the 45 and Up Study is about 18% and given  
316 the nature of the 'healthy cohort effect', it's unlikely to be representative of the general NSW  
317 population aged 45 and over.<sup>21</sup> However, importantly, the cohort is very large and heterogeneous  
318 across collected variables. Thus, whilst people with psychological distress may well be under-  
319 represented in this cohort, it is unlikely to have impacted internal comparisons of exposure and  
320 outcomes.<sup>21</sup> Information on psychological distress was missing for some participants, but exclusion

321 of these may, if anything, have underestimated the associations between psychological distress and  
322 CVD risk. Whilst record linkage to hospital admissions and mortality records facilitated robust  
323 outcome ascertainment, we may not have identified all CVD events. We would have missed events  
324 occurring outside NSW and the ACT or Australia itself, although these are likely to be few in number.  
325 We would have also missed non-hospitalised CVD events, which is more likely to have impacted on  
326 stroke, rather than MI, ascertainment. Based on Australian stroke incidence studies, around 15% of  
327 all strokes are not hospitalised, with the number likely to be higher among older people.<sup>44</sup> However,  
328 this would only have impacted the hazard ratios if hospitalisation for stroke was differentially  
329 associated with baseline psychological distress level, which is unlikely. It is possible that some non-  
330 strokes may have been misclassified as strokes and vice-versa, both within hospital and mortality  
331 records. A recent world-wide review of the accuracy of hospital and mortality records suggests that  
332 the use of appropriately selected, stroke-specific codes yields positive predictive values of greater  
333 than 70% in most studies and greater than 90% in some studies.<sup>29</sup> Again, misclassification of stroke  
334 diagnosis would only bias our findings if misdiagnosis was associated with baseline psychological  
335 distress level, which is unlikely. Finally, since we do not have time-varying information on  
336 psychological distress and covariates, we cannot be certain that the covariates are indeed  
337 confounders and not mediators in the relationship between psychological distress and CVD. We may  
338 therefore have over-adjusted our analyses by including possible mediators, thereby underestimating  
339 the association between psychological distress and CVD risk.

#### 340 **Implications**

341 In the absence of clinical trials designed to examine long-term CVD outcomes among those treated  
342 for psychological distress symptoms (or indeed for diagnosed common mental disorders), further  
343 observational epidemiological research is needed in this area. Future research using studies with  
344 time-varying measures of psychological distress and covariates is needed to establish the  
345 contribution of potential mediating factors, including lifestyle factors and other less well-

346 understood, physiological mechanisms. This understanding would inform the design and success of  
347 preventive approaches aimed at reducing CVD risk in those suffering from psychological distress.  
348 Irrespective of the causal nature of the association between psychological distress and CVD, the  
349 growing evidence supports the need for renewed efforts: to encourage people with symptoms of  
350 psychological distress to seek medical help; for more active screening of, and better treatment for,  
351 psychological distress (and diagnosed common mental disorders); and to encourage screening for  
352 traditional cardiovascular risk factors in people with symptoms of psychological distress or  
353 diagnosed common mental disorders.

### 354 **Conclusion**

355 Psychological distress has a strong, dose-dependent, positive association with CVD risk in both men  
356 and women, but possible sex differences exist which deserve further investigation and replication in  
357 future studies. Confounding is unlikely to account for the observed associations, but further research  
358 is needed to determine causality and underlying mechanisms.

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369 **DISCLOSURES**

370 None

371

372 **REFERENCES**

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500 **Figure legends**

501 Figure 1 Diagram depicting, in part A, possible pathways through which psychological distress might  
502 affect risk of cardiovascular disease and, in part B, potential confounders of the psychological  
503 distress-CVD association and the potential overlap between mediators and confounders

504 Figure 2 Flow diagram of included participants from the 45 and Up Study

505 Figure 3 Age-standardised incidence rates of MI among (a) men and (b) women and rates of stroke  
506 among (c) men and (d) women, by psychological distress level, stratified by age-group

507 Table 2 Baseline characteristics, by level of psychological distress, for all participants\*

Characteristic	Psychological distress		
	Low	Medium	High/very high
	(N = 169,735) %	(N = 35,821) %	(N = 16,121) %
Age, years (mean ± SD)	61.8 ± 10.4	59.2 ± 10.2	58.2 ± 9.9
Categorical age, years			
40-59	48.4	61.0	66.1
60-69	29.8	23.4	21.2
70-79	14.6	10.0	7.6
80+	7.2	5.7	5.1
Female	52.6	57.7	59.9
Marital status			
Married/de facto	78.5	73.2	63.7
Divorced/separated/Widowed	16.0	19.3	25.7
Single	5.0	7.0	9.9
Geographical remoteness			
Major cities of Australia	49.5	49.8	50.1
Inner regional Australia	29.0	28.9	29.3
Outer regional Australia	6.8	7.2	7.4
Remote/very remote Australia	0.2	0.2	0.3
SEIFA index of relative disadvantage			
1 (least deprived)	21.6	18.5	13.9
2	19.8	20.0	19.3
3	20.0	20.1	20.4
4	19.9	20.8	21.9
5 (most deprived)	18.7	20.6	24.4
Education			
College/university degree	26.3	24.9	18.7
Certificate/diploma/trade or apprenticeship	32.8	32.4	30.4
High school certificate	9.9	9.9	10.0
School certificate	21.1	20.5	22.1



No qualifications	8.8	11.1	(17.2
Average household annual income per year (AUD)			
≥70,000	(28.1	25.2	16.6
50,000-69,999	11.7	11.6	9.2
40,000-49,999	7.7	7.6	6.9
30,000-39,999	8.3	8.0	7.4
20,000-29,999	9.1	9.6	9.7
≤19,999	15.2	19.3	29.8
BMI, kg/m <sup>2</sup> (mean ± SD)	26.9 ± 4.6	27.3 ± 5.2	27.9 ± 5.8
<i>Missing</i>	6.7	7.2	8.3
Smoking status			
Never	58.9	54.3	48.
Former	34.6	35.8	34.0
Current	6.0	9.4	16.9
Alcohol intake			
Moderate	38.0	36.6	31.0
None/rarely	29.4	33.0	41.1
Hazardous	24.8	22.1	17.3
Harmful	6.6	6.8	7.9
Physical activity			
Sufficiently active	80.1	74.7	66.4
Insufficiently active	14.2	17.7	21.2
Sedentary	3.1	4.7	8.2
Fruit and vegetable intake			
< 5 portions/week	66.2	69.4	69.5
Fish intake			
≥ twice/week	48.2	45.1	42.5
Once/week	40.3	40.9	39.3
Never	7.3	9.2	12.2
History of hypertension	33.0	33.5	35.7
History of heart disease	8.5	9.1	9.8
History of diabetes mellitus	7.1	8.4	11.3
Family history of stroke or heart disease	56.6	58.0	58.0

Treated for high cholesterol	13.2	14.3	16.2
Charlson comorbidity index			
0	92.0	89.7	86.8
1	4.5	5.8	7.9
2	1.8	2.2	2.5
≥3	1.7	2.3	2.8
<b>WOMEN ONLY</b>			
Menopausal status			
Pre-menopause	18.2	23.0	21.3
Post-menopause	51.0	44.0	40.6
Hysterectomy only	18.4	18.6	20.7
Bilateral oophorectomy post-menopause	1.6	1.6	1.6
Bilateral oophorectomy (surgical menopause)	6.1	6.8	8.0
Current HRT use	10.0	10.9	11.9
Current OCP use	0.3	0.3	0.4

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508 AUD = Australian dollars; BMI = body mass index; HRT = hormone replacement therapy; OCP = oral  
509 contraceptive; SD = standard deviation  
510 \*Please see supplementary Table 3 for proportion of patients with missing information on each variable

Table 3 Sex-specific age-standardised incidence rates (per 1000 person-years) for myocardial infarction (MI) and stroke, by psychological distress level

Psychological distress	Men (N = 102,039)			Women (N = 119,638)		
	Person-years	MI events, n	MI rate, per 1000 person-years* (95% CI)	Person-years	MI events, n	MI rate, per 1000 person-years* (95% CI)
Low	376,443	2347	5.77 (5.53, 6.02)	420,984	1117	3.68 (3.42, 3.93)
Moderate	71,015	482	7.19 (6.52, 7.86)	97,951	244	4.09 (3.50, 4.68)
High/very high	29,549	242	9.28 (8.04, 10.53)	44,994	141	5.70 (4.60, 6.81)
Psychological distress	Stroke rate, per 1000			Stroke rate, per 1000		
	Person-years	Stroke events, n	person-years* (95% CI)	Person-years	Stroke events, n	person-years* (95% CI)
Low	377,895	1134	2.75 (2.58, 2.92)	421,217	704	2.64 (2.41, 2.87)
Moderate	71,391	204	3.34 (2.86, 3.82)	97,947	178	3.37 (2.80, 3.93)
High/very high	29,802	96	3.96 (3.11, 4.82)	45,028	105	5.07 (3.97, 6.17)

\*Standardised to the sex-specific Australian Standard Population  
 CI = confidence interval; MI = myocardial infarction; n = number of MI/stroke events

Table 4 Serially adjusted hazard ratios for associations between moderate and high/very high psychological distress versus low distress and myocardial infarction, stratified by sex and age

	Psychological distress HR (95% CI)					
	All ages*		Aged 45-79 <sup>†</sup>		Aged ≥80 <sup>‡</sup>	
	Moderate	High/very high	Moderate	High/very high	Moderate	High/very high
<b>MEN</b>						
Model 1 <sup>§</sup>	-	-	1.35 (1.21, 1.50)	1.84 (1.59, 2.12)	0.99 (0.78, 1.26)	1.11 (0.77, 1.60)
Model 2 <sup>  </sup>	-	-	1.28 (1.15, 1.43)	1.60 (1.39, 1.86)	0.99 (0.78, 1.26)	1.12 (0.77, 1.62)
Model 3 <sup>#</sup>	-	-	1.23 (1.10, 1.37)	1.39 (1.20, 1.62)	0.97 (0.76, 1.24)	1.09 (0.75, 1.58)
Model 4 <sup>**</sup>	-	-	1.18 (1.06, 1.32)	1.30 (1.12, 1.51)	0.95 (0.74, 1.21)	1.02 (0.70, 1.49)
<b>WOMEN</b>						
Model 1 <sup>§</sup>	1.16 (1.01, 1.34)	1.63 (1.37, 1.94)	1.18 (1.00, 1.40)	1.79 (1.45, 2.20)	1.11 (0.86, 1.43)	1.35 (0.97, 1.89)
Model 2 <sup>  </sup>	1.11 (0.97, 1.28)	1.48 (1.23, 1.77)	1.12 (0.95, 1.33)	1.54 (1.25, 1.91)	1.09 (0.84, 1.41)	1.34 (0.95, 1.88)
Model 3 <sup>#</sup>	1.05 (0.91, 1.21)	1.28 (1.07, 1.21)	1.05 (0.89, 1.25)	1.30 (1.05,1.61)	1.05 (0.81, 1.36)	1.24 (0.88, 1.75)
Model 4 <sup>**</sup>	0.99 (0.86, 1.14)	1.18 (0.99, 1.42)	0.99 (0.84, 1.17)	1.19 (0.96, 1.47)	1.00 (0.77, 1.30)	1.18 (0.83, 1.66)

\*Hazard ratios for all ages combined not reported for men since proportional hazards assumption violated

†number of myocardial infarctions / total, N: men = 2427 / 94,071; women = 1041 / 112,480

‡number of myocardial infarctions / total, N: men = 644 / 7968; women = 461 / 7158

§Adjusted for age

|| Model 1 + adjustment for marital status, education, SIEFA index of disadvantage, household income, remoteness

#Model 2 + adjustment for smoking, alcohol intake, BMI, physical activity, fruit & vegetable intake, fish consumption

\*\*Model 3 + adjustment for hypertension, diabetes, family history of stroke or heart disease and Charlson comorbidity index (in women, also adjusted for OCP use, HRT use and menopausal status)

HR = hazard ratio; CI = confidence interval

Table 5 Serially adjusted hazard ratios for associations between moderate and high/very high psychological distress versus low distress and stroke, stratified by sex and age

	Psychological distress HR (95% CI)					
	All ages		Aged 45-79*		Aged ≥80 <sup>†</sup>	
	Moderate	High/very high	Moderate	High/very high	Moderate	High/very high
<b>MEN</b>						
Model 1 <sup>‡</sup>	1.18 (1.02, 1.37)	1.50 (1.22, 1.85)	1.27 (1.06, 1.51)	1.65 (1.30, 2.09)	0.98 (0.73, 1.32)	1.16 (0.74, 1.80)
Model 2 <sup>§</sup>	1.14 (0.98, 1.32)	1.37 (1.10, 1.69)	1.20 (1.01, 1.43)	1.44 (1.13, 1.84)	0.97 (0.72, 1.31)	1.12 (0.72, 1.74)
Model 3 <sup>  </sup>	1.11 (0.95, 1.29)	1.27 (1.03, 1.57)	1.17 (0.98, 1.39)	1.32 (1.04, 1.69)	0.95 (0.71, 1.28)	1.09 (0.69, 1.70)
Model 4 <sup>#</sup>	1.07 (0.92, 1.25)	1.19 (0.96, 1.48)	1.13 (0.94, 1.34)	1.24 (0.97, 1.59)	0.93 (0.69, 1.26)	1.01 (0.65, 1.59)
<b>WOMEN</b>						
Model 1 <sup>‡</sup>	1.34 (1.13, 1.58)	1.89 (1.54, 2.32)	1.31 (1.06, 1.63)	1.83 (1.39, 2.40)	1.37 (1.06, 1.78)	1.99 (1.45, 2.73)
Model 2 <sup>§</sup>	1.31 (1.11, 1.55)	1.81 (1.46, 2.23)	1.28 (1.03, 1.58)	1.68 (1.27, 2.22)	1.36 (1.05, 1.77)	1.96 (1.42, 2.71)
Model 3 <sup>  </sup>	1.25 (1.06, 1.48)	1.64 (1.33, 2.03)	1.23 (0.99, 1.52)	1.52 (1.15, 2.02)	1.27 (0.97, 1.66)	1.75 (1.26, 2.43)
Model 4 <sup>#</sup>	1.20 (1.02, 1.42)	1.56 (1.26, 1.93)	1.18 (0.95, 1.46)	1.44 (1.09, 1.92)	1.22 (0.93, 1.59)	1.66 (1.20, 2.31)

\* number of strokes / total, N: men = 1007 / 94,071; women = 590 / 112,480

<sup>†</sup> number of strokes / total, N: men = 427 / 7968; women = 397 / 7158

<sup>‡</sup> Adjusted for age

<sup>§</sup> Model 1 + adjustment for marital status, education, SIEFA index of disadvantage, household income, remoteness

<sup>||</sup> Model 2 + adjustment for smoking, alcohol intake, BMI, physical activity, fruit & vegetable intake, fish consumption

<sup>#</sup> Model 3 + adjustment for hypertension, diabetes, family history of stroke or heart disease and Charlson comorbidity index (in women, also adjusted for OCP use, HRT use and menopausal status)

HR = hazard ratio; CI = confidence interval

Figure 1

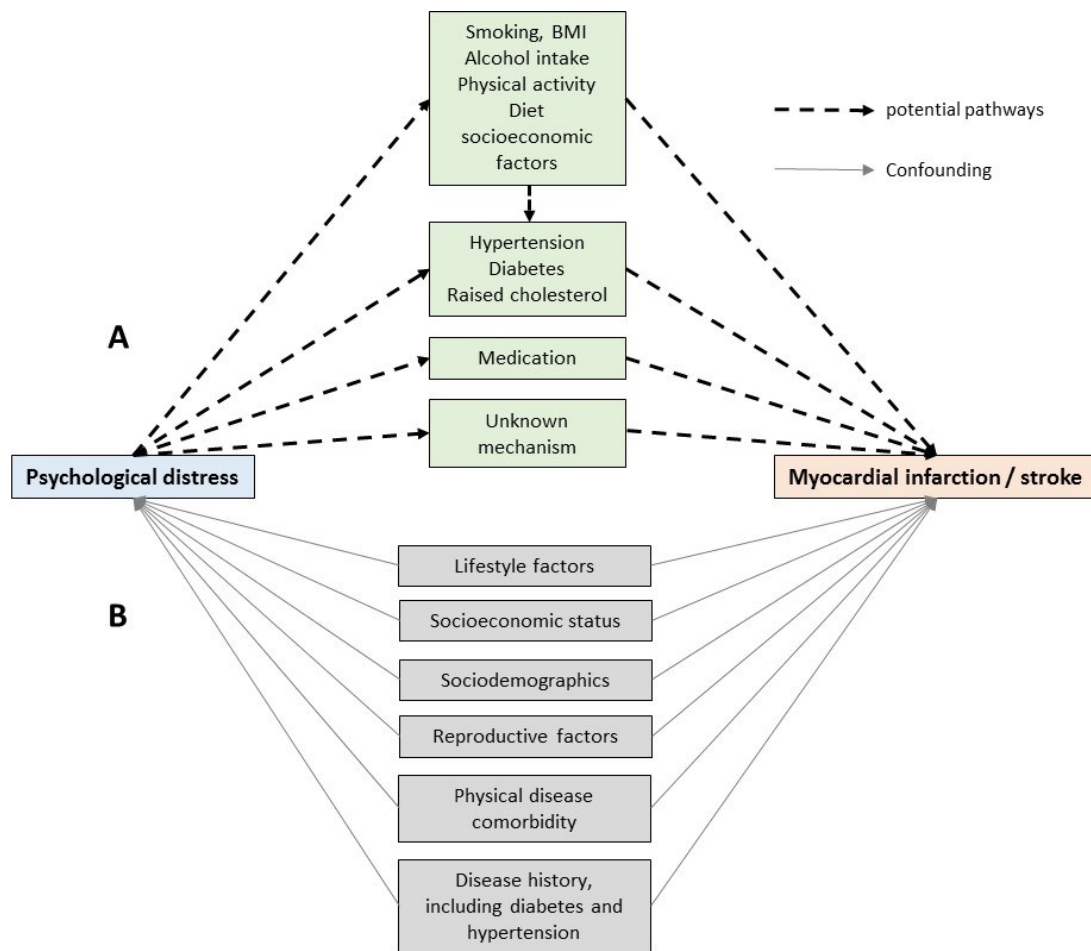


Figure 2

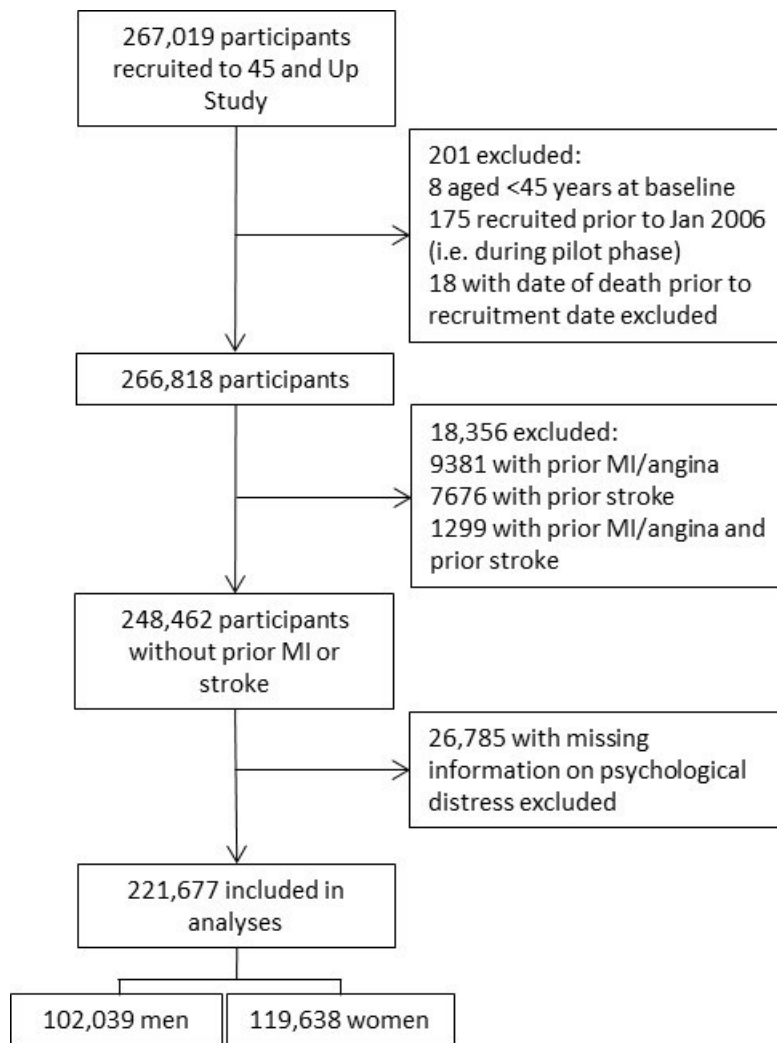




Figure 3

