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Does psychological distress directly increase risk of incident cardiovascular disease? Evidence from a prospective cohort study using a longer-term measure of distress

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ABSTRACT

Objective Cardiovascular disease (CVD) incidence is elevated among people with psychological distress. However, whether the relationship is causal is unclear, partly due to methodological limitations, including limited evidence relating to longer-term rather than single time-point measures of distress. We compared CVD relative risks for psychological distress using single time-point and multi-time-point assessments using data from a large-scale cohort study.

Design We used questionnaire data, with data collection at two time-points (time 1: between 2006 and 2009; time 2: between 2010 and 2015), from CVD-free and cancer-free 45 and Up Study participants, linked to hospitalisation and death records. The follow-up period began at time 2 and ended on 30 November 2017. Psychological distress was measured at both time-points using Kessler 10 (K10), allowing assessment of single time-point (at time 2: high (K10 score: 22–50) vs low (K10 score: <12)) and multi-time-point (high distress (K10 score: 22–50) at both time-points vs low distress (K10 score: <12) at both time-points) measures of distress. Cox regression quantified the association between distress and major CVD, with and without adjustment for sociodemographic and health-related characteristics, including functional limitations.

Results Among 83 906 respondents, 7350 CVD events occurred over 410 719 follow-up person-years (rate: 17.9 per 1000 person-years). Age-adjusted and sex-adjusted rates of major CVD were elevated by 50%–60% among those with high versus low distress for both the multi-time-point (HR=1.63, 95% CI 1.40 to 1.90) and single time-point (HR=1.53, 95% CI 1.39 to 1.69) assessments. HRs for both measures of distress attenuated with adjustment for sociodemographic and health-related characteristics, and there was little evidence of an association when functional limitations were taken into account (multi-time-point HR=1.09, 95% CI 0.93 to 1.27; single time-point HR=1.14, 95% CI 1.02 to 1.26).

Conclusion Irrespective of whether a single time-point or multi-time-point measure is used, the distress–CVD relationship is substantively explained by sociodemographic characteristics and pre-existing physical health-related factors.

Strengths and limitations of this study

- We used data from a large-scale prospective study of people aged 45 years and over living in the general community.
- We were able to use questionnaire data collected at two time-points, allowing us to ascertain a longer-term measure of psychological distress.
- Using questionnaires linked to administrative data allowed for assessment of sociodemographic and health behaviours with virtually complete and objectively measured cardiovascular disease outcomes.
- Despite a large sample size, we observed small numbers of outcome events in some exposure groups, limiting the precision of our estimates.
- Our sample was restricted to participants who completed two questionnaires, and we cannot rule out that loss to follow-up biased our estimates.

INTRODUCTION

Cardiovascular disease (CVD) is a leading contributor to fatal and non-fatal burden of disease internationally and in Australia.[1 2] The burden of CVD is disproportionately high among people who experience symptoms of depression and anxiety.[3 4] Given that symptoms of depression and anxiety commonly co-occur, they are often studied together and collectively referred to as psychological distress. The incidence of ischaemic heart disease (IHD) and stroke is elevated by around 50%[5 6] and CVD mortality is elevated by 72%[7] in those with high compared with low levels of distress.

Reasons for the elevated rates of CVD among people with distress are currently unclear. Multiple linking mechanisms have been proposed, including genetic pleiotropy, reverse causality, a behaviour-related (eg, poor diet) pathway and a direct relationship,

potentially mediated by biological changes resulting from ongoing cognitive factors (eg, excessive worry).[8] However, whether a direct relationship exists remains uncertain,[9] at least in part due to methodological limitations to the evidence.[10 11]

One limitation to the current evidence relates to the way distress is measured.[9–12] Most studies quantifying the distress–incident CVD association assess symptoms of distress once, with measures assessing symptoms in the previous 4 weeks. Single time-point assessments of distress are practical in large-scale cohort studies. However, the course of depression and anxiety is variable: symptoms can remit, reoccur or become chronic, including with fluctuating patterns of severity.[13–15] Given that symptoms of distress experienced for short periods are unlikely to cause disease, an implicit assumption in studies using single time-point assessments is that they can be used as proxies for the longer-term experience of symptoms. Whether this assumption is valid is unclear.

Studies describing change in symptoms find that symptoms of distress are broadly stable over time; however, a proportion of people do show variability.[16–18] One study found that while three-quarters of people reported either consistently low (73%) or consistently high (3%) symptoms of depression over a 12-year period, a quarter had either decreasing (11%), remitting (5%) or increasing (8%) symptoms.[17] These findings indicate that using single assessments to indicate longer-term symptoms of distress is likely to result in a degree of misclassification, potentially biasing estimates of the distress–CVD association. The direction and magnitude of bias are difficult to predict because they depend on whether the misclassification is differential with respect to other characteristics of the respondents.[19]

A small number of studies have quantified the risk of incident CVD associated with duration of symptoms of psychological distress, finding that longer-term symptoms are associated with elevated CVD risk.[20 21] However, no studies have compared the risks of incident CVD associated with longer versus single assessments of distress, making the impact of misclassification bias difficult to assess. Furthermore, studies quantifying the association between longer-term distress and incident CVD do not account for confounding by pre-existing poor physical health. Physical health is another source of bias in estimates of the direct distress–CVD association because people with physical disability are more likely than others to have poor mental health[22] and are also at increased risk of CVD events.[5]

We compare estimates of the association between psychological distress and incident CVD using single time-point and multi-time-point assessments of distress. We also examine the extent to which any distress-related elevation in incident CVD events can be explained by sociodemographic factors and pre-existing physical health.

METHODS

Data sources

Data came from the Sax Institute's 45 and Up Study, a cohort study of more than a quarter of a million men and women aged 45 years and over living in New South Wales (NSW), Australia,[23] with questionnaires linked to hospitalisation and death records. Participants were randomly sampled from the Department of Human Services (formerly Medicare Australia) enrolment database, which provides near complete coverage of the population. Those aged ≥80 years and those living in remote areas were oversampled. Those eligible were mailed an information booklet, a consent form—including consent for follow-up and linkage of their information to administrative databases—and a questionnaire (available from https://www.saxinstitute.org.au/our-work/45-up-study/for-participants/). Participants joined the 45 and Up Study by returning their consent form and completing the baseline questionnaire. Around 18% of those who were mailed an invitation joined the study.

We examine psychological distress at two time-points using questionnaire data as part of the 45 and Up Study. The first questionnaire was the baseline questionnaire (collected between 2006 and 2009) and data for time 2 were drawn from either the Social, Economic and Environmental Factors (SEEF) Study, a substudy of the 45 and Up Study which aimed to investigate how social, economic and environmental factors related to health outcomes over time, or wave 2 of the 45 and Up Study. Questionnaires for the SEEF substudy were distributed in 2010 to the first 100 000 participants enrolled in the study. Of those invited, 60% returned questionnaires. Questionnaires for the second wave of data collection were distributed to all participants between 2012 and 2015; more than 142 000 people responded, including a number who previously completed the SEEF questionnaire. Questionnaires used at time 1 and time 2 surveyed participants on their sociodemographic characteristics, health, health-related behaviours, time use and workforce participation. The questionnaires had a number of survey items in common, including identical measures of psychological distress, physical functioning and diagnoses with medical conditions. Factors which do not change (eg, country of birth) or which change little over time in older adults (eg, education) were measured only at baseline. Questionnaires for the 45 and Up Study are available online: https://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/.

Questionnaire data were linked to four administrative databases: the NSW Admitted Patient Data Collection (APDC); the NSW Registry of Births, Deaths and Marriages (RBDM); the National Death Index (NDI); and the Australian Bureau of Statistics (ABS) mortality data. The APDC database contains information on hospitalisations in NSW, including admission and discharge dates, and diagnostic and procedure codes. Diagnoses were coded using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,

Australian Modification (ICD-10-AM), and procedures were coded using the Australian Classification of Health Intervention codes. NSW RBDM provided date of death, ABS mortality data provided cause of death, and both date and cause of death were available from the NDI. Causes of death were coded using the ICD-10. Data were available and complete from all four databases until 30 November 2017. Data were linked probabilistically by the Centre for Health Record Linkage[24] (APDC and NSW RBDM data) and the Australian Institute of Health and Welfare (ABS mortality and NDI data).

For this study, follow-up of outcomes through data linkage began at the time when participants completed the second questionnaire (SEEF or wave 2) and ended on 30 November 2017.

Study population

Our study sample included 45 and Up Study participants who completed two questionnaires (baseline at time 1 and SEEF or wave 2 at time 2). If respondents completed both SEEF and wave 2 questionnaires, data from the SEEF questionnaire were used as it was the first questionnaire completed at time 2. We included respondents who did not have a history of CVD (hospital admission with a major CVD diagnosis or related procedure[25] in the 5 years prior to completing the baseline questionnaire or between baseline and follow-up questionnaires, or self-reported history of heart disease, blood clot or stroke on either questionnaire) or a previous cancer diagnosis (other than non-melanoma skin cancer, self-reported on either questionnaire). In order to minimise the amount of missing data on levels of psychological distress, we first performed logical imputation and backfilling (see online supplemental material 1). We then excluded participants if they did not have a valid Kessler 10 (K10) score on questionnaires at both time-points (primary exposure variable), or they did not have a valid functional limitations score (primary confounding variable of interest) at time 2.[26]

Measures of distress

On all questionnaires, psychological distress was measured with K10. K10 requires respondents to indicate how often in the past 4 weeks they felt 10 non-specific symptoms of psychological distress. Scores range from 10 'no distress' to 50 'extreme distress' and have been validated to indicate the increasing likelihood of a mood/anxiety disorder.[27] Nationally representative data from Australia have demonstrated that more than one-third of people with an anxiety disorder and around 50% of people with an affective disorder in the previous 12 months report a K10 score of ≥22 compared with less than 10% of those with no mental disorder.[28] Given this, scores were grouped at both time-points into three categories: low (K10 score: 10–12), mild/moderate (12–22) and high (22–50) distress. The single time-point assessment of distress included low, mild/moderate and high distress, assessed at time 2 (the beginning of the follow-up period). The multi-time-point measure was derived by grouping participants according to their scores at both time-points: always low (K10 score: <12 at both time-points), always high (K10 score: 22–50 both time-points) and mixed levels of distress (other combinations).

Major incident CVD

The outcome was the first fatal or non-fatal major CVD event, measured with a hospital admission with a diagnosis of major CVD or a related procedure, or death where major CVD was the underlying cause. Major CVD was defined as atherosclerotic/thromboembolic CVD and included hospitalisation with a diagnosis of, or death due to, hypertensive diseases (ICD-10-AM: I11–I13), IHD (I20–I25), pulmonary heart disease (I26–I28), cerebrovascular disease (I61–I67, I69), disease of the arteries, arterioles and capillaries (I70–I77), phlebitis and thrombophlebitis (I80), episodic and paroxysmal disorders (G45, G46), and other forms of heart disease (I34–I36, I42, I44, I46–I51).[25] Procedures used to identify major CVD included percutaneous coronary interventions; coronary artery bypass grafting; heart transplant; cardiac defibrillator implants, valve replacement, repair or reconstruction; pacemaker insertion; and carotid endarterectomy.[25]

Other variables

Non-time-varying characteristics measured at time 1 were age (based on date of birth and used as the underlying time variable), sex (male, female), country of birth (Australia/New Zealand, other), highest level of education (no qualifications, certificate/diploma/trade, university degree) and region of residence (major cities, inner regional, outer regional). Body mass index (BMI) was calculated using height measured at time 1 and weight measured at time 2, and grouped into categories (15–18.5 kg/m^2; 18.5–25 kg/m^2; 25–30 kg/m^2; 30–50 kg/m^2). All other characteristics were measured at time 2 and included annual household income (<40 000, 40 000–60 000, 60 000–90 000, ≥90 000), marital status (married/de facto, single/widowed/divorced/separated), smoking (never, former, current), alcohol consumption (standard drinks per week: none, 1–14, ≥15), physical activity (measured in tertiles) and self-reported diabetes (yes/no). Physical functioning limitations, a validated marker of physical comorbidities,[29] were measured with the Medical Outcomes Study Physical Functioning Scale at time 2 and categorised into severe (score: 0–60), moderate (60–90), mild (90–99) or no (100) functional limitations.

Statistical approach

For each measure of distress, we estimated the rates of major CVD events age-standardised and sex-standardised to the 2010 NSW population, and proportions within each category of distress with moderate-severe functional limitations. We used Cox proportional hazard regression to estimate HRs quantifying the association between distress and major CVD. Participants were followed from the day they completed their second questionnaire (at

time 2) until they experienced the outcome, died from any cause or reached the end of the follow-up period (30 November 2017). For each measure of distress, three models were used. HRs were first adjusted for age and sex (model 1), then for additional sociodemographic and behaviour-related factors (model 2: education, income, country of birth, region of residence, marital status, smoking, physical activity, alcohol consumption, BMI and diabetes). The final model (model 3) was additionally adjusted for functional limitations. For each model, the log likelihood ratio (LR) test was used to assess whether the measure of distress made a significant contribution to the model.

We performed three supplementary analyses. First, we re-estimated the results using an alternative measure of longer-term distress: early-onset depression and/or anxiety.[30 31] At time 2, participants were asked if they had ever been diagnosed with depression/anxiety, and if so at what age. Participants were categorised as never diagnosed, later life onset (diagnosed at ≥30 years old) or early onset (diagnosed <30 years old). Second, we assessed the potential selection bias resulting from restricting analyses to participants who completed two questionnaires. We estimated the associations between distress (K10 scores measured with the baseline questionnaire) and major CVD stratified by participants who did and did not complete the follow-up questionnaire. Finally, we assessed the extent to which excluding those with missing data on psychological distress impacted our results by re-estimating the main analyses, first by setting all those with missing data to low distress and second by setting all those with missing data to high distress.

Analyses were performed separately for the two measures of distress, using the least distressed group as the reference category. Missing data on covariates were included as a separate category and included in the analysis. The proportional hazards assumption was checked using Schoenfeld residuals for each model, using an *a priori* significance value of 0.0001. Data were accessed through the Secure Unified Research Environment and all analyses were conducted using Stata 16.0.

Patient and public involvement

Patients were not involved in the development of this study.

RESULTS

After excluding respondents who were <45 years of age at baseline (n=7), had linkage errors (n=265) or did not complete a follow-up questionnaire (n=103 680), there were 162 593 potentially eligible participants. Of these, we excluded participants with prior CVD (n=46 439) or cancer (n=21 339) diagnosis. A further 10 892 respondents were sequentially excluded because they did not have a valid K10 score on both questionnaires (n=8178, 8.6%) or a functional limitations score at time 2 (n=2714, 2.9%), leaving a sample of 83 906 participants. Of these, 5.5% (n=4617) had high distress at time 2 and 2.3% (n=1925) had high distress at both time-points. Almost three-quarters (73.4%) of respondents with high distress at time 2 had either moderate (31.8%, n=1466) or high (41.7%, n=1925) distress at time 1 (online supplemental table 1).

Compared with respondents who never had high distress, a greater proportion of respondents who experienced high distress at time 1 and/or time 2 had lower levels of education and income (table 1). A greater proportion smoked, were obese and had lower levels of physical activity and diabetes. Around two-thirds with high distress at time 1 and/or time 2 had moderate-severe functional limitations compared with less than one in four respondents with low distress (table 2).

There were 7350 incident major CVD events over 410 719 person-years (median follow-up time: 4.7 years, rate=17.9 per 1000 person-years). Age-adjusted and sex-adjusted rates of major CVD were elevated by 53% among those with high versus low psychological distress at time 2 (single time-point measure, HR=1.53, 95% CI 1.39 to 1.69) and were similarly elevated among those with low compared with high distress at both time-points (multi-time-point measure), where rates of major CVD were elevated by 63% (HR=1.63, 95% CI 1.40 to 1.90) (table 2).

The elevated rate of incident major CVD associated with both measures of distress attenuated after adjustment for additional sociodemographic and behaviour-related risk factors (model 2, table 2). However, for both the single time-point and multi-time-point measures, distress remained a significant contributor to the model (single time-point measure LR test χ=53.8, p<0.001; multi-time-point measure LR test χ=30.3, p<0.001). After further adjustment for functional limitations (model 3, table 2), the single time-point assessment of distress remained a significant contributor to the model (LR test χ=6.25, p=0.04), although the HR attenuated to 1.14 (95% CI 1.02 to 1.26). With adjustment for functional limitations, the multi-time-point measure was no longer a significant contributor to the model (LR test χ=1.26, p=0.53): the HR associated with high compared with low distress both at time 1 and time 2 was 1.09 (95% CI 0.93 to 1.27).

Associations between early-onset depression/anxiety and major CVD were similar to those using the K10 (online supplemental table 2). Those with early-onset depression and/or anxiety had elevated rates of major CVD compared with those who had never been diagnosed (HR=1.33, 95% CI 1.12 to 1.58). However, relative risks attenuated with adjustment for additional sociodemographic and behaviour-related risk factors, and after adjustment for functional limitations there was little evidence of an association between early-onset depression/anxiety and major incident CVD (HR=1.14, 95% CI 0.96 to 1.36).

Higher levels of distress assessed at time 1 were associated with higher rates of major CVD among those who did and did not go on to complete the follow-up questionnaire (online supplemental table 3). However,

Table 1 Characteristics of the sample for the multi-time-point and single time-point measures of psychological distress

	Level of psychological distress at single time-point (time 2)			Level of psychological distress at two time-points (time 1 and time 2)		
	Low	Mild/moderate	High	Low–low	Mixed	High–high
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Total	44.8 (37 575)	49.7 (41 714)	5.5 (4617)	29.5 (24 724)	68.2 (57 257)	2.3 (1925)
Sex						
Male	44.8 (16 849)	40.3 (16 791)	36.9 (1705)	45.8 (11 325)	40.7 (23 294)	37.7 (726)
Female	55.2 (20 726)	59.8 (24 923)	63.1 (2912)	54.2 (13 399)	59.3 (33 963)	62.3 (1199)
Age groups (years)						
45–54	17.6 (6613)	24.2 (10 109)	29.2 (1346)	14.7 (3629)	24.2 (13 849)	30.7 (590)
55–64	43.0 (16 162)	45.8 (19 095)	49.9 (2302)	40.9 (10 116)	46.2 (26 429)	52.7 (1014)
65–74	29.6 (11 108)	22.4 (9348)	16.0 (737)	32.7 (8073)	22.5 (12 859)	13.6 (261)
75–84	8.3 (3114)	6.1 (2555)	3.9 (179)	9.9 (2440)	5.9 (3364)	2.3 (44)
85+	1.5 (578)	1.5 (607)	1.2 (53)	1.9 (466)	1.3 (756)	0.8 (16)
Marital status						
Married/de facto	80.5 (30 263)	77.4 (32 286)	65.2 (3008)	80.4 (19 871)	77.8 (44 515)	60.8 (1171)
Single	18.9 (7099)	22.0 (9193)	33.9 (1567)	19.1 (4714)	21.7 (12 404)	38.5 (741)
Country of birth						
Australia/New Zealand	79.0 (29 664)	79.4 (33 134)	79.4 (3666)	78.9 (19 501)	79.3 (45 409)	80.7 (1554)
Other	20.5 (7709)	20.1 (8363)	20.1 (929)	20.5 (5078)	20.2 (11 560)	18.9 (363)
Highest qualification						
No school certificate	5.8 (2187)	5.7 (2376)	11.3 (520)	6.0 (1476)	5.9 (3356)	13.0 (251)
Certificate/diploma/trade	61.3 (23 022)	60.5 (25 250)	64.0 (2955)	62.2 (15 367)	60.5 (34 631)	63.8 (1229)
Tertiary	32.1 (12 057)	33.1 (13 799)	23.7 (1094)	31.0 (7663)	32.9 (18 863)	22.0 (424)
Household income/year						
<$40 000	9.6 (3609)	11.4 (4761)	18.5 (855)	10.2 (2515)	11.0 (6270)	22.9 (440)
$40 000–$60 000	13.4 (5021)	14.1 (5873)	14.3 (661)	13.7 (3377)	13.8 (7898)	14.6 (280)
$60 000–$90 00	21.0 (7890)	22.5 (9375)	17.8 (821)	20.3 (5028)	22.3 (12 763)	15.3 (295)
$90 000+	19.7 (7394)	19.4 (8073)	10.9 (505)	18.5 (4571)	19.6 (11 238)	8.5 (163)
Region of residence						
Major cities	49.6 (18 633)	49.1 (20 487)	48.4 (2233)	49.4 (12 209)	49.3 (28 220)	48.0 (924)
Inner regional	33.9 (12 735)	34.1 (14 236)	34.2 (1580)	34.2 (8445)	33.9 (19 434)	34.9 (672)
More remote	10.0 (3759)	10.3 (4283)	11.2 (516)	10.2 (2518)	10.2 (5821)	11.4 (219)
Body mass index						
Underweight	1.0 (362)	1.1 (469)	1.4 (65)	1.0 (255)	1.1 (608)	1.7 (33)
Healthy weight	37.1 (13 930)	34.9 (14 555)	29.0 (1337)	37.6 (9283)	35.0 (20 011)	27.4 (528)
Overweight	37.5 (14 088)	35.8 (14 922)	32.9 (1521)	37.8 (9340)	36.0 (20 613)	30.0 (578)
Obese	17.6 (6623)	21.2 (8825)	28.3 (1305)	16.8 (4142)	20.9 (11 986)	32.5 (625)
Smoking status						
Never	63.8 (23 981)	60.7 (25 336)	52.5 (2426)	64.5 (15 958)	60.9 (34 882)	46.9 (903)
Former	31.8 (11 958)	33.6 (13 994)	34.8 (1606)	31.4 (7768)	33.3 (19 092)	36.3 (698)
Current	3.6 (1359)	5.0 (2092)	11.8 (546)	3.3 (814)	5.0 (2876)	16.0 (307)
Physical activity groups						
Lowest	24.3 (9127)	28.0 (11 688)	33.6 (1549)	23.0 (5685)	27.8 (15 941)	38.3 (738)
Middle	34.6 (13 001)	34.9 (14 562)	31.7 (1462)	34.3 (8483)	34.9 (19 971)	29.7 (571)
Highest	39.5 (14 844)	35.7 (14 890)	33.2 (1533)	40.9 (10 115)	35.9 (20 562)	30.7 (590)

Continued

Table 1 Continued

	Level of psychological distress at single time-point (time 2)			Level of psychological distress at two time-points (time 1 and time 2)		
	Low	Mild/moderate	High	Low–low	Mixed	High–high
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Alcohol intake (drinks/week)						
None	27.3 (10 238)	28.3 (11 803)	40.2 (1855)	27.6 (6813)	28.4 (16 241)	43.7 (842)
1–14	57.2 (21 508)	56.3 (23 475)	44.2 (2041)	57.0 (14 098)	56.2 (32 147)	40.5 (779)
15+	14.1 (5295)	14.2 (5916)	13.8 (638)	13.9 (3439)	14.2 (8145)	13.8 (265)
Diabetes	6.2 (2337)	6.8 (2818)	10.7 (493)	6.3 (1546)	6.7 (3845)	13.4 (257)
Functional limitations						
None	3.5 (1321)	9.3 (3886)	26.6 (1226)	3.3 (814)	8.7 (4992)	32.6 (627)
Minor	18.9 (7112)	29.7 (12 402)	34.3 (1585)	18.3 (4516)	27.8 (15 918)	34.6 (665)
Moderate	37.9 (14 241)	35.4 (14 767)	22.5 (1037)	37.7 (9313)	35.6 (20 355)	19.6 (377)
Severe	39.7 (14 901)	25.6 (10 659)	16.7 (769)	40.8 (10 081)	27.9 (15 992)	13.3 (256)

Missing cases, % (n): marital status: 0.6 (490); country of birth: 0.5 (441); education: 0.8 (646); income: 34.6 (29 068); region of residence: 6.5 (5444); body mass index: 7.0 (5904); smoking: 0.7 (608); physical activity: 1.5 (1250); alcohol intake: 1.4 (1137).

effect sizes were larger among those who completed the follow-up questionnaire. HRs did not vary substantially when including those with missing K10 scores as either all low distress or all high distress (online supplemental table 4). There were no violations of the proportional hazards assumption for psychological distress in any of the models.

DISCUSSION

People with high psychological distress at two time-points had rates of incident major CVD around 60% higher than those who had low distress at both time-points. Relative risks associated with this multi-time-point assessment of distress were similar to those of the single assessment. However, behaviour-related risk factors were common among those with longer-term symptoms of distress and up to two-thirds of these respondents had moderate or severe functional limitations. Relative risks for CVD associated with distress attenuated by around 75% for the single time-point measure and more than 85% for the multi-time-point measure with adjustment for behaviour-related risk factors and functional limitations, such that there was little evidence that distress, including longer-term distress, was independently associated with incident CVD. Residual confounding, reflecting unmeasured confounders and imperfectly measured covariates, may

Table 2 HR (95% CI) for incident major cardiovascular disease in relation to the multi-time-point and single time-point measures of psychological distress

	% with limitations	Events/ person-years	Age-standardised and sex-standardised rate	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Single time-point assessment of distress (time 2)						
Low	22.4	3327/187	19.8 (19.0 to 20.6)	1.00	1.00	1.00
Mild/moderate	39.1	3576/202	22.8 (21.9 to 23.7)	1.17 (1.11 to 1.22)	1.14 (1.09 to 1.20)	1.04 (0.99 to 1.09)
High	60.9	447/22	29.1 (25.8 to 32.9)	1.53 (1.39 to 1.69)	1.39 (1.26 to 1.54)	1.14 (1.02 to 1.26)
Multi-time-point assessment (time 1 and time 2)						
Always low distress	21.6	2351/122	19.8 (18.9 to 20.7)	1.00	1.00	1.00
Mixed levels of distress	36.5	4822/279	22.4 (21.6 to 23.1)	1.15 (1.10 to 1.21)	1.12 (1.07 to 1.18)	1.02 (0.97 to 1.07)
Always high distress	67.1	177/9	29.2 (23.2 to 36.7)	1.63 (1.40 to 1.90)	1.40 (1.19 to 1.63)	1.09 (0.93 to 1.27)

% with limitations refers to those with moderate or severe functional limitations at the time of the follow-up questionnaire. Rates are per 1000 person-years.
Model 1 is adjusted for age and sex. Model 2 is additionally adjusted for education, income, region of residence, country of birth, marital status, smoking status, physical activity, alcohol intake, body mass index and diabetes. Model 3 is further adjusted for functional limitations.

account for at least part of the small remaining association between the single time-point assessment of distress and incident major CVD.

Until now, the extent to which exposure misclassification resulting from single time-point assessments of distress biased estimates of the distress–incident CVD association has been unclear. While our two time-point measures of distress are unlikely to perfectly capture those experiencing long-term distress, our findings suggest that single assessments of distress are unlikely to substantially bias estimates of the distress–CVD association. This is consistent with findings from studies demonstrating stability in symptoms of distress over time.[16 17 32] Although there is some variability in distress, most people with high distress remain moderately or highly distressed and most people with low levels of distress continue to experience low levels of symptoms.[18]

Although single time-point and multi-time-point measures of distress conferred a similar elevation in CVD risk, information regarding duration of symptoms remains an important component of the distress–CVD association. People with high distress at two or more time-points are more likely to have detectable calcification of the coronary arteries compared with respondents who never report distress or who report distress at one time-point.[33–35] A small number of studies have examined CVD risks associated with repeated measures of distress, finding evidence of a dose–response relationship between number of occasions of high distress and risk of CVD.[20 21] This suggests that while repeated measures of distress are likely to provide more precise estimates of the distress–CVD association, single time-point assessments are unlikely to alter the conclusions of studies examining the distress-CVD relationship.

Our finding that for each measure of distress the distress–CVD association was substantively explained by confounding factors is consistent with previous findings based on single distress measures. People with distress have more comorbid chronic physical health conditions, including conditions associated with elevated risk of CVD such as chronic kidney disease[36] and diabetes.[22] People with higher compared with lower distress also have a poorer CVD risk factor profile, and as a result are almost twice as likely to have high absolute risk for a primary CVD event.[37] Most studies using single assessments of distress report a reduction in the distress–CVD association once behaviour-related risk factors are taken into account,[38] and studies which consider physical morbidity show that they effectively explain the remaining association.[5 21 39 40] These findings indicate that from a clinical perspective, the most effective way to reduce incidence of CVD among people with distress is to address traditional CVD risk factors, that is, factors on the behaviour-related pathway, and to support people to manage comorbid chronic health conditions. They also indicate that, from a public health point of view, distress may be most helpfully viewed as a marker of CVD risk rather than a risk factor for the disease.[41]

Strengths and limitations

This large-scale, population-based study had a number of strengths, including repeated measures of psychological distress. Use of administrative data allowed us to reliably exclude people with prior CVD and independently measure CVD events with virtually complete follow-up. Prospective questionnaire data allowed assessment of sociodemographic and behaviour-related risk factors often not available when using administrative data. The large-scale nature of the study allowed us to capture a relatively large number of outcome events over a relatively short period. However, even with this large sample the precision of our estimates was limited. Like most population-based cohort studies, the 45 and Up Study sample is healthier than the general population.[23] Furthermore, we restricted our sample to respondents who completed at least two questionnaires. Supplementary analyses demonstrated that higher distress was associated with elevated CVD incidence among respondents who did and did not complete the follow-up questionnaire and we observed a similar pattern of attenuation after adjustment for potential confounders. Loss to follow-up from non-participation in the 45 and Up Study has been shown to have minimal impact on effect estimates with outcomes defined using linked data,[42] and relative effect estimates are expected to remain valid in the absence of confounding and effect modification.[43 44] However, we cannot rule out that loss to follow-up biased our estimates. Finally, while K10 scores are correlated with the presence of a depressive or anxiety disorder, validation studies report that between one-third and half of those with high distress will not meet clinical criteria.[27] Given that the magnitude of the association between distress and CVD is typically stronger in studies using measures of diagnosed conditions relative to those measuring symptoms, it is possible that the estimates presented in this study are an underestimate of the associations between depressive and/or anxiety disorders and CVD. However, they remain relevant to studies of the association between symptoms of distress and CVD.

CONCLUSION

People who experience psychological distress, including those with longer-term symptoms, have an elevated risk of having a major CVD event. Relative risks associated with longer-term symptoms of distress were similar to risks associated with single assessments of distress, reflecting stability in symptoms over time. However, the association between both measures of distress and CVD was largely explained by differences in sociodemographic characteristics and pre-existing poorer physical health.

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Contributors JW, RJK and EB designed the study. JW performed the analyses. GJ and PB advised on the analyses. JW drafted the manuscript. JW, GJ, EB, PB, LS and RJK interpreted the findings and provided input to the manuscript.

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Data availability statement Data may be obtained from a third party and are not publicly available. Access to the 45 and Up Study data set and cohort is available to any bona fide researcher who has a scientifically sound and feasible research proposal, has ethics approval for the proposal and data custodian approval for access to linked data, if required for the project, and can meet 45 and Up Study licence and SURE changes. Having the required funds in hand, however, is not a precondition for submission of an expression of interest. For more information, see https://www.saxinstitute.org.au/our-work/45-up-study/for-researchers/.

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