Journal of the American Heart Association

ORIGINAL RESEARCH

Neuroticism, Worry, and Cardiometabolic Risk Trajectories: Findings From a 40-Year Study of Men

Lewina O. Lee, PhD; Kevin J. Grimm, PhD; Avron Spiro, III, PhD; Laura D. Kubzansky, MPH, PhD

BACKGROUND: Anxiety is linked to elevated risk of cardiometabolic disease onset, but the underlying mechanisms remain unclear. We examined the prospective association of 2 anxiety facets, neuroticism and worry, with cardiometabolic risk (CMR) trajectories for 4 decades.

METHODS AND RESULTS: The sample comprised 1561 men from an ongoing adult male cohort. In 1975, healthy men (mean age, 53 years [SD, 8.4 years]) completed the Eysenck Personality Inventory-Short Form neuroticism scale and a Worries Scale. Seven CMR biomarkers were assessed every 3 to 5 years. The CMR score was the number of biomarkers categorized as high-risk based on established cut points or medication use. Using mixed effects regression, we modeled CMR trajectories over age and evaluated their associations with neuroticism and worry. Using Cox regression, we examined associations of neuroticism and worry with risk of having ≥6 CMR high-risk biomarkers through 2015. CMR increased at 0.8 markers per decade from age 33 to 65 years, at which point men had an average of 3.8 high-risk markers, followed by a slower increase of 0.5 markers per decade. Higher neuroticism (B=0.08; 95% CI, 0.02–0.15) and worry levels (B=0.07; 95% CI, 0.001–0.13) were associated with elevated CMR across time, and with 13% (95% CI, 1.03–1.23) and 10% (95% CI, 1.01–1.20) greater risks, respectively, of having ≥6 high-risk CMR markers, adjusting for potential confounders.

CONCLUSIONS: By middle adulthood, higher anxiety levels are associated with stable differences in CMR that are maintained into older ages. Anxious individuals may experience deteriorations in cardiometabolic health earlier in life and remain on a stable trajectory of heightened risk into older ages.

Key Words: anxiety ■ neuroticism ■ cardiometabolic risk ■ aging ■ prospective study

A robust literature, including meta-analytic findings, supports prospective associations of anxiety to elevated risk of incident cardiometabolic disease, including coronary heart disease (CHD),[1] stroke,[2] diabetes,[3] and hypertension.[4] However, mechanisms and trajectories of risk have not been clearly identified. One approach to evaluating the pathogenetic role of anxiety is to examine its association with upstream physiological dysregulation that may occur before cardiometabolic disease onset. Some have speculated that anxious individuals show worsening trajectories of cardiometabolic risk (CMR) as they age (eg, steeper rise in body mass index with age relative to nonanxious individuals),[5] whereas others have suggested that deteriorations in cardiometabolic health occur relatively early in life among anxious individuals who then remain on a stable trajectory of poorer health into older ages.[6] However, empirical support for either pattern is limited. Compared with the conventional approach of studying cardiometabolic disease onset as outcome, examining the trajectory of upstream physiological processes related to cardiometabolic disease additionally informs the developmental period at which exposure to a causative factor is most critical.[7] Few cohort studies have longitudinal data on anxiety and a broad range of cardiometabolic outcomes. However, neuroticism

Correspondence to: Lewina O. Lee, PhD, VA Boston Healthcare System, 150 South Huntington Avenue (116B-4), Boston, MA 02130. E-mail: lewina@bu.edu

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022006

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What is New?

- In a cohort of initially healthy, middle-aged men, higher baseline levels of 2 forms of anxiety, neuroticism and worry, were associated with 10% to 13% greater risk of being classified as high-risk on ≥6 biomarkers of cardiometabolic risk, such as blood pressure and fasting glucose, over 40 years of follow-up.
- The magnitude of cardiometabolic risk difference by baseline neuroticism and worry levels was maintained across the full follow-up period but did not widen with older age.

What are the Clinical Implications?

- Anxiety may affect cardiometabolic health earlier in the life course than previously thought.
- Efforts to prevent cardiometabolic disease have typically targeted screening and lifestyle modifications among middle-aged and older adults; however, findings from this and other studies increasingly suggest that assessment of cardiometabolic and psychological risk factors beginning much earlier in life may be impactful.

Nonstandard Abbreviations and Acronyms

CMR	cardiometabolic risk
EPI-Q	Eysenck Personality Inventory-Short Form
NAS	Normative Aging Study
SBP	systolic blood pressure
VA	US Department of Veterans Affairs

and worry are 2 constructs closely linked to anxiety that were measured in some of the cohort studies that were initiated over 30 years ago. Data on these anxiety-linked constructs can be leveraged to examine how different facets of anxiety relate to changes in subclinical processes that precede disease onset.

Neuroticism is a personality trait characterized by a stable tendency to perceive experiences as threatening, feel that challenges are uncontrollable, and experience frequent and disproportionately intense negative emotions among many situations.[8] Neuroticism is a key causative factor for anxiety and mood disorders.[9,10] Worry, a major facet of anxiety, is a coping mechanism that enables individuals to prepare for future threats. While worry is not necessarily problematic and can be functional, chronic, uncontrollable, and intense worry is a maladaptive and pathological process that underlies anxiety and mood disorders.[9,11,12]

Some work has specifically linked neuroticism and worry to adverse cardiovascular end points. For example, in 2 large US and UK population–based studies, neuroticism was linked to 14% to 27% excess risk of CHD mortality.[13,14] Worry has been associated with 40% to 134% excess risk of developing CHD and stroke in 2 studies with 15 to 20 years of follow-up.[15,16] The associations of neuroticism and worry with metabolic disease are more mixed and less well investigated. For example, Čukić and Weiss[17] reported an association between higher neuroticism and *lower* diabetes incidence among a US national sample. To our knowledge, worry has not been studied in relation to incident diabetes risk. While tracking CMR markers longitudinally can inform the timing of progression from subclinical processes to disease, such data are scarce.[18] Higher neuroticism levels have been linked to unhealthier levels of individual metabolic markers, such as higher overall body mass index across multiple time points[19] and reduced nocturnal blood pressure (BP) dipping 7 years later.[20] However, we know of no studies that have examined worry in relation to metabolic syndrome or markers.

To date, there are limited longitudinal data available for examining anxiety in relation to when and how pathophysiologic alterations associated with cardiometabolic disease might become evident. Using data from a cohort of community-dwelling men followed for 4 decades from middle to late adulthood, we evaluated 2 patterns by which neuroticism and worry levels could be prospectively associated with heightened cardiometabolic risk in adulthood. First, we tested an accelerated risk model, wherein more versus fewer neurotic and worry-prone individuals showed steeper age-related increases in CMR (Figure 1A). Second, we tested a consistent risk model, wherein more versus fewer neurotic and worry-prone individuals had worse CMR at most points in adulthood, but the magnitude of such differences remained stable and did not worsen with age (Figure 1B). Evidence for the consistent risk model may suggest that anxiety affects CMR earlier in life, but such differences in risk stabilize and are maintained from middle adulthood into older ages. Following prior work,[21,22] we used a summary index based on 7 CMR biomarkers to capture information on multiple pathophysiological processes that underlie cardiometabolic disease development. We considered separately the association of neuroticism and worry with CMR. This serves as a conceptual replication to evaluate whether 2 different facets of anxiety relate similarly to CMR. To reduce concerns about possible reverse causation or other sources of confounding, we examined associations among initially healthy individuals and accounted for a range of relevant covariates suggested in prior work.[23] We also considered time-varying health behaviors as covariates that could

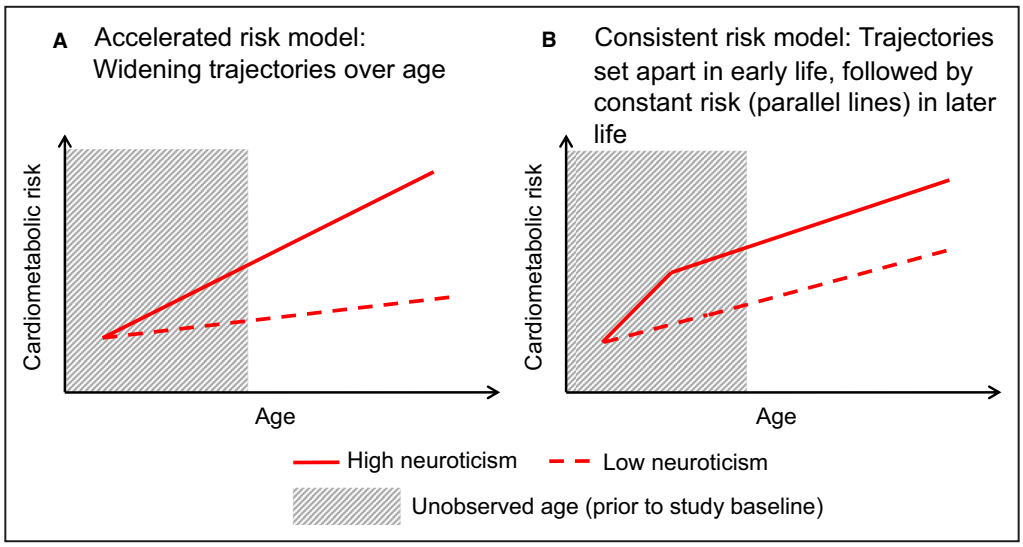

Figure 1. Hypothetical models of cardiometabolic risk (CMR) trajectories by neuroticism levels. (**A**) Depicts a model in which higher neuroticism brings about a steeper increase in CMR among all ages. (**B**) Reflects a model in which neuroticism primarily affects CMR in early life. According to this model, more vs less neurotic individuals show a steeper increase in CMR early in life and thereafter have worse CMR at all points in later adulthood, but the pace of change in CMR throughout adulthood is similar for both groups. Therefore, group differences in CMR as assessed in adulthood manifest as parallel lines in (**B**), as opposed to widening trajectories in (**A**). The shaded area represents ages unobserved for the current sample; nonetheless, examining their CMR trajectories in midlife and old age is useful for testing differing hypotheses regarding the pathogenetic timing of risk associated with neuroticism and worry for CMR.

confound or explain the association of neuroticism or worry with CMR.

METHODS

NAS (Normative Aging Study) data are held by the US Department of Veterans Affairs (VA) and any request for data access requires VA authorization. Therefore, the data and study materials are not made publicly available for purposes of reproducing the results or replicating the procedures. However, study measures, analytic codes, and outputs are available from the corresponding author upon request. The corresponding author has full access to the data used in the current study and is responsible for its integrity and data analysis.

Study Design and Sample

NAS is longitudinal study of aging processes in men established at the VA Boston Outpatient Clinic.[24] Between 1961 and 1970, over 6000 community-dwelling men were screened for the absence of chronic or major physical and mental illnesses, and for geographic stability; 2280 men aged 21 to 80 years were enrolled. Participants provided written informed consent, and the study protocol was approved by the institutional review board of the VA Boston Healthcare System.

Neuroticism and worry were first assessed in 2 mail surveys administered to all active NAS participants in 1975; the earlier of the 2 survey dates serves as the baseline for this study. Biomarkers of CMR were assessed via blood draws and anthropometric assessments as part of onsite physical examinations every 3 to 5 years (every 3 years since 1984). Current medications were reviewed and recorded by a study nurse at each examination. Among 1945 men who participated in at least 1 of the 2 mail surveys, men were excluded if they had missing data on both measures (n=6), prevalent CHD, type II diabetes, a history of stroke, or cancer at baseline (n=288), or did not have any examination since baseline (n=90). This yielded an analytic sample of 1561 men. We considered examination data through December 31, 2015. Only examinations with available data on at least 6 cardiometabolic markers were considered (98.8% of examinations in our sample).

Neuroticism and Worry Assessment

Neuroticism was assessed in a 1975 mail survey with 9 dichotomous items of the EPI-Q,[25] a short form of the Eysenck Personality Inventory.[26] Item scores were summed (range: 0–9). The EPI-Q has demonstrated excellent construct validity.[27] It has acceptable internal consistency (Kuder-Richardson Formula 20=0.74) and moderate temporal stability (10-year correlation: 0.59; 28-year correlation: 0.55 [both $P<0.0001$]) in our sample.

Worry was assessed using a content-based paper-and-pencil scale asking participants to rate how much they worry about various issues using 20 items on a scale of 0 (never) to 4 (all the time). Participants could also rate an item as "does not apply"; these items were coded as missing. To avoid confounding with health outcomes, we removed 2 items querying worry about one's illness and dying. An overall worry score was computed as the mean score among applicable items, with higher scores reflecting higher worry levels. The scale has good internal consistency (Cronbach α=0.84) and moderate temporal stability (9-year correlation: 0.56; $P<0.0001$) in our sample. In prior work with this measure, the overall score was associated with increased risk of CHD.[15]

Neuroticism and worry were operationalized as both continuous *z* scores and categorical variables (using terciles for neuroticism and quartiles for worry). In this sample, the correlation of neuroticism and worry was $r=0.30$ ($P<0.0001$). See Data S1 for details on handling item-level missing data for neuroticism and worry.

Cardiometabolic Risk Assessment

Because individual biomarkers representing the physiological integrity of different bodily systems interact in a nonlinear manner, summary indices are more effective than individual biomarkers in capturing the multiple pathophysiological processes that underlie disease development.[21,22,28] Therefore, we quantified CMR using 7 established biological risk indicators of cardiovascular disease and metabolic syndrome, drawing on both direct measures and reports of relevant medication use. These include systolic BP (SBP) and diastolic BP as indicators of hypertension, fasting total cholesterol and fasting triglycerides as indicators of dyslipidemia, body mass index as an indicator of obesity, fasting glucose as an indicator of hyperglycemia, and erythrocyte sedimentation rate (ESR) as an indicator of unhealthy levels of inflammation. Laboratory measurements and assay procedures for these biomarkers have been described elsewhere.[29,30] When individuals indicated use of medications that target or have known effects on any of these risk indicators (ie, antihypertensives for SBP and diastolic BP, statins for fasting cholesterol and triglycerides, anti-inflammatory medications for ESR, and antidiabetics for fasting glucose), we assigned individuals to the high-risk category for that indicator. For example, having an SBP level >130 mm Hg or endorsing use of any antihypertensive would result in SBP being coded as high risk at that study visit. To define the high-risk categories, for all biomarkers except ESR, we used clinical cut points established by the Third Adult Treatment Panel of the National Cholesterol Education Program and International Diabetes Federation.[31,32] Lacking a clinical cut point for ESR, we defined high risk as the top quartile. Cut points are summarized in Table S1. We handled missing biomarker data (maximum of 1 missing biomarker value per study visit; observed in 21% of included study visits) by generating maximum likelihood estimates of missing values based on all available biomarker data, demographics, medication use, and time-varying health behaviors.[33]

Following prior work,[34,35] we first operationalized CMR as a count score summing the number of biomarkers categorized as reflecting high risk, defined according to the cut point for each biomarker or current use of relevant medications. Similar count scores of high-risk markers have been used to track CMR change over age[36] and predict risks of cardiovascular disease onset and premature mortality.[34] To assess time to developing cardiometabolic dysregulation, we dichotomized the count score using a threshold of ≥6 high-risk markers, chosen to capture physiologic dysregulation in at least 4 of 5 components (hypertension, hyperglycemia, dyslipidemia, obesity, and inflammation) and because the sample had on average 2.9 high-risk markers at baseline.

We also quantified CMR as a continuous *z* score, which has greater variability than the count score. We first computed a *z* score for each biomarker at each time point, referenced against the sample's baseline values and adjusted for current medications (see Data S1 for details). Next, we computed a CMR *z* score as the mean at each time point among the 7 biomarker *z* scores.

Covariate Assessment

Demographic variables assessed by questionnaires at NAS entry in 1961 to 1970 include race (White versus other) and childhood socioeconomic status (SES) as measured by paternal occupation (unskilled/semiskilled/skilled and foreman/white collar/semiprofessional/professional, managerial, and proprietary). Adult SES was assessed in 1973 and measured by education (in years) and annual family income. Age (continuous) and marital status (married versus not married) were assessed in 1975. Family history of CHD was assessed with a questionnaire item administered as part of recurring NAS examinations; the value from the earliest examination available was used.

For health behaviors, smoking status (current/former/never) was queried by study staff during examinations. At each examination via self-report on a survey, alcohol consumption was assessed with an item asking whether one usually drinks ≥2 alcoholic drinks daily (yes/no), and physical activity was assessed with an item asking whether one finds it impossible to have regular daily exercise (yes/no). We used time-varying values of smoking, drinking, and physical activity assessed at each examination. Past-year physician visit

was assessed with an item (yes/no) administered concurrently with worry in 1973.

Statistical Analysis

We generated descriptive statistics and examined distributions of demographic factors and health behaviors by neuroticism and worry categories using 1-way ANOVA and chi-square test. On verifying that the CMR score was distributed normally, we characterized trajectories of CMR using mixed effects linear regression with chronological age as the temporal axis. We conducted multilevel linear regression using SAS PROC MIXED (SAS Institute Inc) to estimate several candidate models of CMR change over age: no change, linear change (ie, linear increase in CMR score with age), quadratic change, cubic change, and spline models comprising 2 linear slopes joined at a knot point. All models included fixed and random effects of the intercept and age polynomials. Among all models, the intercept was specified at age 53, the mean age of the sample at the first examination. For ease of interpretation, age was specified in 10-year units. In spline models, a knot point represents an age at which CMR score increases or decreases more (or less) steeply with age. We considered spline models with varying knot points at 5-year increments from ages 50 to 80 years. Models were evaluated using Akaike information criterion,[37] Bayes information criterion,[38] and the likelihood ratio test, calculated as the difference in –2 log-likelihood relative to the difference in parameters between 2 models.

Using the best age trajectory model of CMR, we examined continuous scores of neuroticism and worry in relation to CMR levels at the model intercept (ie, age 53) and to change over age, modeled as main effects and interactions with age slopes. For neuroticism and worry, we evaluated 3 models: model 1 adjusted for baseline age; model 2 added childhood SES, baseline demographic factors, and family history of CHD as potential confounders; and model 3 further considered health behaviors during follow-up as potential confounders and/or intermediate variables. To adjust for the possibility that healthier men are more likely to return for an examination (ie, revisits), we used a propensity score, which indicated one's probability of having a subsequent visit, given all relevant factors at a given visit (see Data S1 for details). This revisit propensity score was used in all subsequent regression analyses.[39]

Given that findings from the age trajectory analyses showed increases in CMR score over age, we conducted secondary analyses using Cox proportional hazards regression to further quantify associations of baseline neuroticism and worry levels with risk of having ≥6 CMR markers exceeding high-risk cut points during follow-up. A higher hazard ratio (HR) represents greater risk of developing multisystem physiologic dysregulation during follow-up. For neuroticism and worry, we considered models 1 to 3 as described above. Because preliminary analyses suggested a significant baseline age-by-time interaction ($P<0.05$), indicating a violation of the proportional hazards assumption, all Cox models were stratified by baseline age quartiles.

In sensitivity analyses, we repeated the multilevel regression and Cox models using categorical variables of worry and neuroticism to evaluate potential threshold effects. We also repeated the multilevel regression analyses using the continuous CMR score in place of the count score as the outcome. In a final set of sensitivity analyses, we conducted influence diagnostics to identify the extent to which study follow-up status and data outliers might bias our findings. Specifically, we considered the influence of 3 subsets of participants: (1) those who survived the entire follow-up; and those who were 3 SDs above or below the mean on (2) Cook's distance or (3) likelihood distance in the best-fitting CMR trajectory model. We re-ran analyses to estimate the best-fitting CMR trajectory model and evaluate the association of neuroticism and worry with CMR trajectories after eliminating each of the 3 subsets of participants and comparing the results with those based on the entire sample.

RESULTS

Sample Description

At baseline, the analytic sample was an average age of 53 years (SD, 8.4 years; range, 33–84 years); 91% were married and 97% were of White race. Median family income was $15 000 to $19 999 (in 1973 US dollars) and average education was 16.2 years (SD, 5.1 years). During follow-up from 1975 to 2015, men had on average of 6.6 examinations (SD, 3.4; range, 1–15); 1067 (67%) men died. The mean follow-up time was 22.9 years (SD, 11.2 years) and 219 (14%) men were seen within 3 years (ie, 1 study visit cycle) of the end of follow-up. Table 1 shows the distribution of demographic factors and health behaviors by neuroticism terciles and worry quartiles. In bivariate analyses, higher neuroticism levels were substantially associated with fewer years of education; lower paternal occupational status; higher prevalence of CHD family history; and higher levels of current smoking, regular drinking, and not having regular exercise; and weakly associated with younger age. Men in the highest worry quartile had lower family income than those in the 2 middle quartiles. Higher worry levels were also associated with greater likelihood of a past-year physician visit and not exercising regularly.

Table 1. Descriptive Statistics of the Analytic Sample at Baseline, By Neuroticism Score Tercile (n=1462) and Total Worry Score Quartile (n=1475)

Mean (SD) or %	Neuroticism terciles (tercile 1=lowest)			Worry quartiles (quartile 1=lowest)			
	Tercile 1 (n=436)	Tercile 2 (n=451)	Tercile 3 (n=575)	Quartile 1 (n=351)	Quartile 2 (n=367)	Quartile 3 (n=364)	Quartile 4 (n=393)
No. of examinations	6.9 (3.6)	6.7 (3.5)	6.6 (3.1)	6.6 (3.3)	6.8 (3.5)	7.0 (3.3)	6.4 (3.3)
Demographics							
Age, y	*53.7 (9.2)*	*52.7 (8.0)*	*52.4[a] (7.8)*	52.7 (8.3)	52.1 (7.8)	53.2 (8.0)	53.7 (8.8)
White race	96	96	98	96	97	98	97
Father's occupation	2.0 (1.4)*	2.0 (1.5)*	1.8[a,b] (1.3)*	2.0 (1.4)	1.9 (1.4)	2.0 (1.4)	1.9 (1.4)
Education, y	16.7 (5.2)*	16.5 (5.2)*	15.6[a,b] (5.0)*	16.0 (5.0)	16.0 (5.1)	16.7 (5.3)	16.0 (5.1)
Family income	6.6 (1.6)	6.6 (1.5)	6.5 (1.5)	6.5 (1.6)*	6.7 (1.4)*	6.7 (1.5)*	6.4[b,c] (1.6)*
Married	91	91	91	91	94	89	90
Family history of CHD	15*	22*	23*	19	18	21	19
Health behaviors							
Had past-y physician visit	68	68	70	60*	68*	68*	70*
Smoking status: current	33*	34*	39*	35	38	35	39
Smoking status: former	34*	45*	41*	38	43	40	36
Smoking status: never (reference)	33*	21*	20*	27	19	25	25
Drinking (have ≥2 drinks daily)	19*	23*	28*	21	27	24	25
No regular daily exercise	22*	32*	46*	17*	23*	26*	34*

CHD indicates coronary heart disease. To compare each variable by neuroticism and worry categories, we used 1-way ANOVA for continuous variables and chi-square test for categorical variables. *P<0.05. Italics indicate 0.05≤P<0.10 for the overall association of a variable with neuroticism or worry. For continuous variables, [a], [b], [c], [d], and [e] denote statistical significance (P<0.05) Tukey-adjusted pairwise comparison against tercile 1 and tercile 2 (for worry), and quartile 1, quartile 2, and quartile 3 (for neuroticism), respectively. Father's occupation: 0=unskilled, 1=semiskilled, 2=skilled and foreman, 3=white collar, 4=semiprofessional, and 5=professional/managerial/proprietary. Family income (in 1973 US dollars): 0=<$3000 to 9=≥$25 000.

Baseline distribution of the CMR count score and its components are shown in Table S1. In general, higher neuroticism and worry levels were associated with higher CMR scores. Considering individual biomarkers, higher neuroticism levels were strongly associated with higher ESR and weakly associated with higher SBP and body mass index. Higher levels of both neuroticism and worry were weakly associated with higher fasting triglycerides levels.

Trajectories of CMR Over Age

Among candidate models of CMR trajectories over age, a spline model with a knot point at age 65 provided the best fit to our data (see Table S2 for fit indices from model comparisons). According to the best-fitting model, by age 65, men had on average 3.78 (95% CI, 3.70–3.86) cardiometabolic markers in the high-risk category. From ages 33 to 65, the number of high-risk markers increased at a rate of 0.80 (95% CI, 0.74–0.86) per decade. After age 65, the number of high-risk markers continued to increase, but at a slower rate of 0.5 marker per decade (95% CI, 0.44–0.56).

Association of Neuroticism and Worry With CMR Trajectories

Higher neuroticism levels were associated with higher CMR levels among all ages. Adjusted for baseline age (Table 2; upper panel, model 1), each additional SD of neuroticism was associated with a 0.10-point (95% CI, 0.01–0.07) higher CMR score pooled among all ages. This association was slightly attenuated to 0.08 (95% CI, 0.02–0.15) after further adjusting for baseline demographics and family history of CHD, and remained even after accounting for health behaviors. Among covariates, younger age at baseline (B=–0.05; 95% CI, –0.06 to –0.04), family history of CHD (B=0.35; 95% CI, 0.18–0.51), being a former smoker (relative to never-smokers, B=0.19; 95% CI, 0.08–0.29), consuming ≥2 alcohol drinks daily (B=0.18; 95% CI, 0.08–0.29), not exercising daily (B=0.08; 95% CI, 0.0002–0.15), and having a past-year physician visit at baseline (B=0.21; 95% CI, 0.07–0.35) were associated with higher CMR levels. Among all models, the interaction terms of neuroticism with the 2 age slopes (before and after the age-65 knot point) were not statistically significant (all

Table 2. Prospective Association Between Continuous Neuroticism and Worry Scores in 1975 and CMR Trajectories Between 1975 and 2015 (Neuroticism: n=1462, Observations=9818; Worry: n=1475, Observations=9830)

	Model 1 (age-adjusted)		Model 2 (+ demographics, family history of CHD)		Model 3 (+ health behaviors)	
	B	95% CI	B	95% CI	B	95% CI
Neuroticism main effect (*z* score)	0.10*	0.03 to 0.16*	0.08*	0.02 to 0.15*	0.07*	0.003 to 0.13*
CMR change per 10 y, age ≤65 y	0.81*	0.75 to 0.87*	0.81*	0.75 to 0.87*	0.78*	0.72 to 0.84*
CMR change per 10 y, age >65 y	0.50*	0.44 to 0.57*	0.51*	0.44 to 0.57*	0.49*	0.43 to 0.56*
Worry main effect (*z* score)	*0.06*	*−0.0003* to *0.13*	0.07*	0.001 to 0.13*	*0.06*	*−0.01* to *0.12*
CMR change per 10 y, age ≤65 y	0.80*	0.74 to 0.86*	0.80*	0.74 to 0.86*	0.77*	0.71 to 0.83*
CMR change per 10 y, age >65 y	0.50*	0.44 to 0.56*	0.50*	0.44 to 0.57*	0.49*	0.43 to 0.56*

CHD indicates coronary heart disease. CMR, cardiometabolic risk as measured by the count score of biomarkers exceeding high-risk cut-points. Results were weighted with inverse probability of revisits. Among all models, interaction terms of neuroticism with CMR 10-year change (2 slope terms shown above) and interaction terms of with CMR 10-year change were nonsignificant and therefore removed from the models. Model 1 adjusted for baseline age. Model 2 additionally adjusted for baseline demographic factors, including race, father's occupation, education, family income, marital status, and family history of heart disease. Model 3 further adjusted for health behaviors, including time-varying smoking, alcohol consumption, and physical activity, and past-year physician visit at baseline. *$P<0.05$. Italics indicate $0.05 \le P < 0.10$.

$P>0.17$), suggesting that neuroticism was not associated with accelerated (or decelerated) change in CMR score over age.

Findings for worry and CMR were similar, albeit somewhat weaker. In the baseline age-adjusted model (Table 2; lower panel, model 1), each additional SD of worry was associated with a 0.06-point (95% CI, −0.0003 to 0.13) higher CMR score. This association was maintained after adjusting for baseline demographics and family history of CHD (model 2: B=0.07; 95% CI, 0.001 to 0.13), and slightly attenuated after adding health behaviors (model 3: B=0.06; 95% CI, −0.01 to 0.12). As with neuroticism, among all models, the interaction terms of worry with the 2 age slopes were not statistically significant (all $P>0.60$).

In the Cox models, higher neuroticism and worry levels were linked to greater risk of having ≥6 CMR markers exceeding high-risk cut points during follow-up, adjusting for demographics and family history of CHD (Table S3). Specifically, each additional SD of neuroticism was associated with 13% greater risk (95% CI, 1.03–1.23), whereas each additional SD of worry was associated with 10% greater risk (95% CI, 1.01–1.20) of having ≥6 high-risk CMR markers, adjusting for baseline age, demographics, and family history of CHD.

Sensitivity Analysis

Assessing Potential Threshold Effects of Neuroticism and Worry

Table S4 summarizes findings on the associations of neuroticism terciles and worry quartiles with CMR trajectories. After adjusting for demographics and family history of CHD (top panel, model 2), relative to those in the lowest tercile, men in the middle and highest neuroticism terciles had 0.29 (95% CI, 0.12–0.45) and 0.21 (95% CI, 0.05–0.37) higher CMR scores among all ages, respectively. Associations were slightly attenuated but remained evident after further adjusting for health behaviors in model 3. Figure 2 (top) depicts the expected trajectory of CMR by neuroticism terciles. Adjusting for demographics and family history of CHD, men in the 2 highest versus the bottom quartiles of worry had somewhat higher CMR scores (Table S4; lower panel) (model 2, quartile 3: B=0.18 [95% CI, −0.03 to 0.36]; quartile 4: B=0.17 [95% CI, −0.01 to 0.35]). Associations were somewhat attenuated after further adjusting for health behaviors (model 3, quartile 3: B=0.16 [95% CI, −0.03 to 0.34]; quartile 4: B=0.14; 95% CI, −0.04 to 0.32). Given that CMR scores were similar between the 2 lowest (quartile 1≈quartile 2) and 2 highest (quartile 3≈quartile 4) worry quartiles, we plotted the expected trajectory of CMR by a median split in worry scores (Figure 2, bottom).

In Cox models adjusting for demographics and family history of CHD, men in the middle (tercile 2) and highest (tercile 3) versus the lowest neuroticism terciles had higher risks of having ≥6 high-risk CMR markers (Table S3; top panel) (model 2, tercile 2 versus tercile 1: HR, 1.49 [95% CI, 1.18–1.87]; tercile 3 versus tercile 1: HR, 1.35 [95% CI, 1.08–1.69]). When examined as a categorical variable, worry scores were not strongly associated with increased risk of having ≥6 high-risk CMR markers, although associations were in the expected direction (Table S3; bottom panel) (model 2,

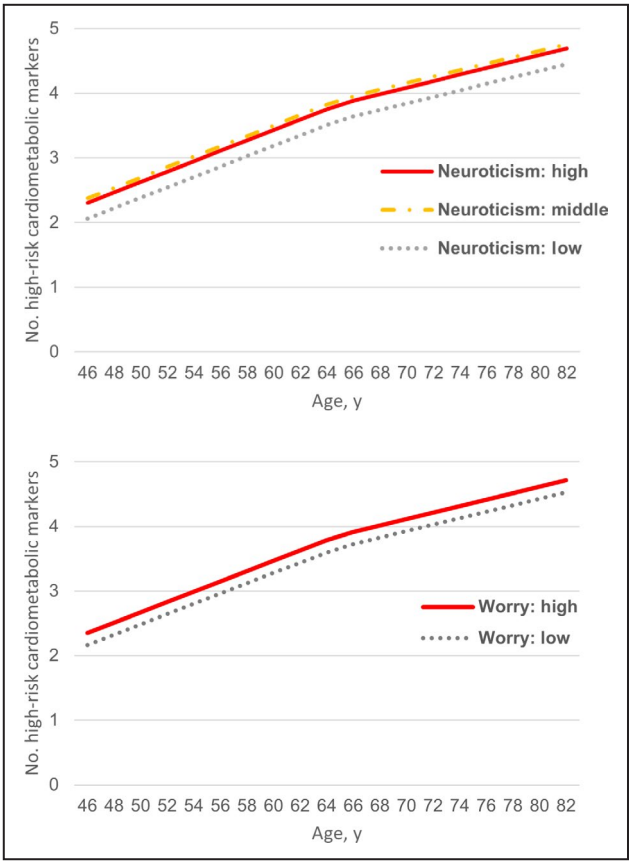

Figure 2. Estimated trajectory of high-risk cardiometabolic markers by neuroticism terciles (top) and a median split in total worry score (bottom).

quartile 4 versus quartile 1 [lowest worry]: HR, 1.25 [95% CI, 0.97–1.61]; quartile 3 versus quartile 1: HR, 1.13 [95% CI, 0.87–1.46]; quartile 2 versus quartile 1: HR, 1.00 [95% CI, 0.77–1.30]).

Considering Continuous CMR Scores

When quantifying CMR as a continuous (*z*) score, we observed a similar pattern of association between higher levels of neuroticism and worry to higher CMR, but associations were somewhat weaker. For example, in the age-adjusted models, higher neuroticism levels were weakly associated with higher CMR (B=0.01; 95% CI, 0.00–0.02), and the estimate for worry was in the same direction but even less precise (B=0.03; 95% CI, −0.03 to 0.10).

Assessing the Influence of Data Outliers and Follow-Up Status

In a series of sensitivity analyses, we removed 3 subsets of participants: 219 men who completed the entire study follow-up, and men identified as outliers based on Cook's distance or likelihood distance from the best-fitting CMR trajectories model. Results indicate that removal of these participants minimally influenced the estimates of CMR trajectories over age and their association with neuroticism and anxiety (Data S2).

DISCUSSION

In a longitudinal cohort of initially healthy men, higher neuroticism and worry levels at baseline were associated with elevated CMR during the next 4 decades, with associations of similar strength and magnitude evident at every assessment. These associations were maintained after adjusting for demographics and family history of CHD, and only weakly attenuated by adjustment for time-varying health behaviors during follow-up. Findings were replicated among 2 facets of anxiety and demonstrate a robust association of anxiety with pathophysiological processes that precede cardiometabolic disease onset. Our findings have implications for understanding when potentially health deteriorative effects of anxiety may become apparent, suggesting it could be earlier in the life course than previously appreciated. Repeated biomarker assessment during a lengthy follow-up period in this study provided a rare opportunity to characterize age-related changes in CMR. When quantified as a count score of biomarkers exceeding high-risk cut points, CMR increased at 0.8 marker per decade from the mid-30s to 65 years of age, at which point this sample of initially healthy men had on average of 3.8 high-risk markers, followed by a slower increase of 0.5 marker per decade after age 65.

Our findings do not support the hypothesis that neuroticism and worry would be associated with an accelerated trajectory of CMR in middle and later adulthood; thus, there is not strong support for causal effects of neuroticism and worry on CMR during the ages at which our sample was observed. Instead, being in the highest versus lowest category of neuroticism and worry was consistently associated with 0.17 to 0.21 additional cardiometabolic marker exceeding the high-risk cutoffs among the follow-up period. To provide some context, the magnitude of these associations is similar to that for long-term heavy drinking (B=0.18) on CMR levels. There was suggestive evidence for threshold effects whereby differences were substantially more pronounced among those in the top two thirds of the neuroticism score distribution and top half of the worry score distribution versus those in the lower levels. Even at study baseline, men who were above these thresholds of neuroticism and worry already carried higher CMR relative to those below the thresholds, and the risk differentials were maintained as they aged. Noteworthy is that although men were initially free of major diseases at the time neuroticism

and worry were first assessed, they had an average of 2.9 cardiometabolic markers (of a maximum of 7) exceeding the high-risk cutoffs at an average age of 53, suggesting that subclinical processes were already in motion.

Each SD difference in neuroticism and worry levels at baseline was associated with 10% to 13% greater risks of having ≥6 cardiometabolic markers exceeding the high-risk cutoffs during the course of follow-up, indicating dysregulation in ≥4 pathophysiological components that precede cardiometabolic disease onset. Given strong evidence linking these markers of physiologic dysregulation to excess lifetime risks for cardiometabolic disease,[40] our findings highlight the potential for neuroticism and worry as targets for primordial intervention to prevent the development of risk factors for cardiometabolic disease.[41] Of note, this study examines baseline levels of neuroticism and worry in relation to subsequent trajectories of CMR, thus the influence of our exposures is considered to be invariant over time. Our data indicate that both neuroticism and worry were moderately stable over time; nonetheless, it may be fruitful for future studies to evaluate whether the persistence, exacerbation, or resolution of anxiety symptoms may influence subsequent CMR.

Our findings are also consistent with the interpretation that potential deleterious effects of neuroticism and worry on CMR occurred earlier (ie, the shaded area in Figure 1B), whereby the CMR trajectories of high versus low neurotic and worry-prone individuals diverged before midlife. Evidence from other studies[6,42] supports this interpretation. For example, in a Finnish cohort of children followed from ages 6 to 48 years, differences in BP by SES were evident by the late 20s and maintained into midlife.[42] Although early life data were not available in our study, our findings do not contradict growing evidence suggesting childhood as a sensitive period during which stress-related exposures can have a lifelong "programming" effect by setting off trajectories of pathogenetic mechanisms that culminate in chronic diseases.[43] Alternatively, prior common causes of anxiety and CMR risk (eg, genetic factors) or co-occurrence of anxiety and CMR, may also explain the current findings.

Anxiety-related traits could influence development of cardiometabolic disease via biological, behavioral, and psychosocial pathways. Anxiety stimulates acute responses in the autonomic nervous system and hypothalamic-pituitary-adrenal axis, such as an exaggerated hemodynamic response and excessive cortisol output.[44] Among anxiety-prone individuals, frequent activation of acute physiological responses and insufficient opportunities for recovery to baseline can result in an accrual of physiological insults that give rise to chronic diseases over time.[45,46]

Poor engagement in healthy behaviors has been reliably linked to both anxiety[47] and cardiometabolic conditions.[48] However, in the present study, adjustment for health behaviors only mildly attenuated the associations between anxiety facets and CMR. While these findings support a role for health behaviors, they do not fully account for the observed associations. Psychosocial characteristics associated with neuroticism and worry, such as tendencies to perceive and interpret situations as threatening, and to avoid mildly stressful experiences,[9] may also influence cardiometabolic disease risk through poor adherence to medical regimens and ineffective coping with stressors. Neuroticism and worry are causative factors for psychiatric conditions.[9–12] Our study design does not allow us to evaluate psychiatric conditions as potential mediators of the association between anxiety and CMR. Nonetheless, given the availability of effective treatments for psychiatric conditions, a useful study design is to consider whether interventions to reduce anxiety and the associated psychiatric conditions may lower subsequent CMR.

Our study has several limitations. Because our sample was limited to healthy, primarily White men of higher SES, results may not generalize to women, racial or ethnic minorities, and more socioeconomically disadvantaged populations. Although research has documented racial and socioeconomic disparities in anxiety[49] and cardiometabolic conditions,[50] little work has directly evaluated race and SES as modifiers of the association between anxiety and cardiometabolic disease. Second, as noted, despite our lengthy follow-up period, the sample was on average middle-aged at baseline, thus we were unable to examine the associations of interest in childhood and younger adulthood. Third, although we adjusted for childhood and adulthood demographic factors and family history of CHD, residual confounding by unmeasured variables is possible. For example, unmeasured health behaviors, such as diet quality, are potential confounders and may lie on the pathway linking anxiety to CMR. Related, our measure of physical activity is limited in scope and likely does not fully capture true activity levels. Fourth, reverse causality is possible, whereby higher levels of CMR predisposed men to higher levels of neuroticism and worry at baseline. However, our primary analyses excluded men with prevalent CHD, type II diabetes, and history of stroke at baseline, and we considered an outcome upstream to the onset of cardiometabolic disease. Finally, ESR is not a standard measure of CMR in research studies. This limits the comparability of our findings to studies using other inflammatory markers, such as C-reactive protein. Nonetheless, similar to C-reactive protein, ESR is a nonspecific and widely used marker of systemic inflammation in clinical practice.[51,52] The availability of ESR data during the

lengthy follow-up also offsets the limitation of using a less commonly used inflammatory marker.

These limitations notwithstanding, our study provides novel evidence on the prospective associations of 2 anxiety facets, namely, neuroticism and worry, to elevated levels of CMR evident in midlife and maintained through older age in a sample of initially healthy men followed for 4 decades. Replication of these associations among 2 distinct but related facets of anxiety lends insights into the timing and potential mechanisms by which anxiety contributes to cardiometabolic dysregulation over the life course. While efforts to prevent cardiometabolic disease have typically targeted screening and lifestyle modifications among middle-aged and older adults, findings from the current study and other investigations increasingly suggest that population surveillance of cardiometabolic and psychological risk factors beginning much earlier in the life course may be fruitful. Such work may provide a better understanding of disease pathogenesis and development of primordial interventions to improve population health.

ARTICLE INFORMATION

Received July 1, 2021; accepted November 9, 2021.

Affiliations

National Center for Posttraumatic Stress Disorder at VA Boston Healthcare System, Boston, MA (L.O.L.); Department of Psychiatry, Boston University School of Medicine, Boston, MA (L.O.L.); Department of Psychology, Arizona State University, Tempe, AZ (K.J.G.); Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, Boston, MA (A.S.); Department of Epidemiology, Boston University School of Public Health, Boston, MA (A.S.); Department of Social and Behavioral Sciences (L.D.K.) and Lee Kum Sheung Center for Health and Happiness, Harvard T.H. Chan School of Public Health, Boston, MA (L.D.K.).

Sources of Funding

This study was supported by grants from the National Institutes of Health (K08-AG048221, RF1-AG064006, UL1-TR001430) and a Senior Research Career Scientist Award from the Office of Research and Development, US Department of Veterans Affairs. NAS is a research component of the Massachusetts Veterans Epidemiology Research and Information Center and is supported by the VA Cooperative Studies Program/Epidemiological Research Centers. The views expressed in this article are those of the authors and do not necessarily represent the views of the support institutions.

Disclosures

None.

Supplemental Material

Data S1–S2
Tables S1–S4

REFERENCES

1. Batelaan NM, Seldenrijk A, Bot M, van Balkom AJ, Penninx BW. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. *Br J Psychiatry*. 2016;208:223–231. doi: 10.1192/bjp.bp.114.156554
2. Pérez-Piñar M, Ayerbe L, González E, Mathur R, Foguet-Boreu Q, Ayis S. Anxiety disorders and risk of stroke: a systematic review and meta-analysis. *Eur Psychiatry*. 2017;41:102–108. doi: 10.1016/j.eurpsy.2016.11.004
3. Smith KJ, Deschênes SS, Schmitz N. Investigating the longitudinal association between diabetes and anxiety: a systematic review and meta-analysis. *Diabet Med*. 2018;35:677–693. doi: 10.1111/dme.13606
4. Pan Y, Wenpang C, Cheng Q, Dong W, An T, Yan J. Association between anxiety and hypertension: a systematic review and meta-analysis of epidemiological studies. *Neuropsychiatr Dis Treat*. 2015;11:1121–1130. doi: 10.2147/NDT.S77710
5. Kubzansky L, Bordelois P, Jun HJ, Roberts AL, Cerda M, Bluestone N, Koenen KC. The weight of traumatic stress: a prospective study of posttraumatic stress disorder symptoms and weight status in women. *JAMA Psychiatry*. 2014;71:44–51. doi: 10.1001/jamapsychiatry.2013.2798
6. Winning A, Glymour MM, McCormick MC, Gilsanz P, Kubzansky LD. Psychological distress across the life course and cardiometabolic risk: findings from the 1958 British Birth Cohort Study. *J Am Coll Cardiol*. 2015;66:1577–1586. doi: 10.1016/j.jacc.2015.08.021
7. Berkman LF. Social epidemiology: social determinants of health in the United States: are we losing ground? *Annu Rev Public Health*. 2009;30:27–41. doi: 10.1146/annurev.publhealth.031308.100310
8. Lahey BB. Public health significance of neuroticism. *Am Psychol*. 2009;64:241. doi: 10.1037/a0015309
9. Barlow DH, Sauer-Zavala S, Carl JR, Bullis JR, Ellard KK. The nature, diagnosis, and treatment of neuroticism: back to the future. *Clinical Psychol*. 2014;2:344–365. doi: 10.1177/2167702613505532
10. Kendler KS, Gardner CO, Gatz M, Pedersen NL. The sources of comorbidity between major depression and generalized anxiety disorder in a Swedish national twin sample. *Psychol Med*. 2007;37:453–462. doi: 10.1017/S0033291706009135
11. McEvoy PM, Watson H, Watkins ER, Nathan P. The relationship between worry, rumination, and comorbidity: evidence for repetitive negative thinking as a transdiagnostic construct. *J Affect Disord*. 2013;151:313–320. doi: 10.1016/j.jad.2013.06.014
12. Olatunji BO, Broman-Fulks JJ, Bergman SM, Green BA, Zlomke KR. A taxometric investigation of the latent structure of worry: dimensionality and associations with depression, anxiety, and stress. *Behav Ther*. 2010;41:212–228. doi: 10.1016/j.beth.2009.03.001
13. Jokela M, Pulkki-Råback L, Elovainio M, Kivimäki M. Personality traits as risk factors for stroke and coronary heart disease mortality: pooled analysis of three cohort studies. *J Behav Med*. 2014;37:881–889. doi: 10.1007/s10865-013-9548-z
14. Shipley BA, Weiss A, Der G, Taylor MD, Deary IJ. Neuroticism, extraversion, and mortality in the UK health and lifestyle survey: a 21-year prospective cohort study. *Psychosom Med*. 2007;69:923–931. doi: 10.1097/PSY.0b013e31815abf83
15. Kubzansky LD, Kawachi I, Spiro A III, Weiss ST, Vokonas PS, Sparrow D. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. *Circulation*. 1997;95:818–824. doi: 10.1161/01.CIR.95.4.818
16. Vogt T, Pope C, Mullooly J, Hollis J. Mental health status as a predictor of morbidity and mortality: a 15-year follow-up of members of a health maintenance organization. *Am J Public Health*. 1994;84:227–231. doi: 10.2105/AJPH.84.2.227
17. Čukić I, Weiss A. Personality and diabetes mellitus incidence in a national sample. *J Psychosom Res*. 2014;77:163–168. doi: 10.1016/j.jpsychores.2014.07.004
18. Tang F, Wang G, Lian Y. Association between anxiety and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Psychoneuroendocrinology*. 2017;77:112–121. doi: 10.1016/j.psyneuen.2016.11.025
19. Sutin AR, Ferrucci L, Zonderman AB, Terracciano A. Personality and obesity across the adult life span. *J Pers Soc Psychol*. 2011;101:579–592. doi: 10.1037/a0024286
20. Terracciano A, Strait J, Scuteri A, Meirelles O, Sutin AR, Tarasov K, Ding J, Marongiu M, Orru M, Pilia MG, et al. Personality traits and circadian blood pressure patterns: a 7-year prospective study. *Psychosom Med*. 2014;76:237–243. doi: 10.1097/PSY.0000000000000035
21. Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS. Price of adaptation—allostatic load and its health consequences: MacArthur studies of successful aging. *Arch Intern Med*. 1997;157:2259–2268. doi: 10.1001/archinte.1997.00440400111013
22. Castagné R, Garès V, Karimi M, Chadeau-Hyam M, Vineis P, Delpierre C, Kelly-Irving M, Lifepath Consortium. Allostatic load and subsequent all-cause mortality: which biological markers drive the relationship? Findings from a UK birth cohort. *Eur J Epidemiol*. 2018;22:441–458. doi: 10.1007/s10654-018-0364-1

23. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. *J Am Coll Cardiol*. 2010;56:38–46. doi: 10.1016/j.jacc.2010.03.034
24. Bosse R, Eckerdt DJ, Silbert JE. The veterans administration normative aging study. In: Mednik SA, Harway M, Finello KM, eds. *Handbook of Longitudinal Research: Teenage and Adult Cohorts*. New York City, NY: Praeger; 1984:273–289.
25. Floderus B. Psychosocial factors in relation to coronary heart disease and associated risk factors. *Nord Hyg Tidskr*. 1974;6:7–148.
26. Eysenck HJ, Eysenck SB. *Manual for the Eysenck Personality Inventory*. San Diego, CA: Educational and Industrial Testing Service; 1968.
27. Levenson MR, Aldwin CM, Bosse R, Spiro A III. Emotionality and mental health: longitudinal findings from the Normative Aging Study. *J Abnorm Psychol*. 1988;97:94–96. doi: 10.1037/0021-843X.97.1.94
28. Franco OH, Massaro JM, Civil J, Cobain MR, O'Malley B, D'Agostino RB. Trajectories of entering the metabolic syndrome. *Circulation*. 2009;120:1943–1950. doi: 10.1161/CIRCULATIONAHA/109.855817
29. Shen B, Countryman AJ, Spiro A III, Niaura R. The prospective contribution of hostility characteristics to high fasting glucose levels. *Diabetes Care*. 2008;31:1293–1298. doi: 10.2337/dc07-1945
30. Sparrow D, Rowe JW, Silbert JE. Cross-sectional and longitudinal changes in the erythrocyte sedimentation rate in men. *J Gerontol*. 1981;36:180–184. doi: 10.1093/geronj/36.2.180
31. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung and Blood Institute scientific statement. *Circulation*. 2005;112:2735–2752. doi: 10.1161/CIRCULATIONAHA.105.169404
32. Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: a global public health problem and a new definition. *J Atheroscler Thromb*. 2005;12:295–300. doi: 10.5551/jat.12.295
33. Missing GJ. *Data: Analysis and Design*. New York City, NY: Springer; 2012: doi: 10.1007/978-1-4614-4018-5
34. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc Natl Acad Sci USA*. 2001;98:4770–4775. doi: 10.1073/pnas.081072698
35. Seplaki CL, Goldman N, Glei D, Weinstein M. A comparative analysis of measurement approaches for physiological dysregulation in an older population. *Exp Gerontol*. 2005;40:438–449. doi: 10.1016/j.exger.2005.03.002
36. Mitchell UA, Ailshire JA, Crimmins EM. Change in cardiometabolic risk among blacks, whites, and Hispanics: findings from the health and retirement study. *J Gerontol A Biol Sci Med Sci*. 2019;74:240–246. doi: 10.1093/gerona/gly026
37. Bozdogan H. Model selection and Akaike's Information Criterion (AIC): the general theory and its analytical extensions. *Psychometrika*. 1987;52:345–370. doi: 10.1007/BF02294361
38. Schwarz G. Estimating the dimension of a model. *Ann Stat*. 1978;6:461–464. doi: 10.1214/aos/1176344136
39. Hogan JW, Lancaster T. Instrument variables and inverse probability weighting for casual inference from longitudinal observational studies. *Stat Methods Med Res*. 2004;13:17–48. doi: 10.1191/0962280204sm351ra
40. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74:1376–1414. doi: 10.1161/CIR.0000000000000677
41. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
42. Kivimäki M, Vahtera J, Tabák AG, Halonen JI, Vineis P, Pentti J, Pahkala K, Rovio S, Viikari J, Kähönen M, et al. Neighbourhood socioeconomic disadvantage, risk factors, and diabetes from childhood to middle age in the Young Finns Study: a cohort study. *Lancet Public Health*. 2018;3:e365–e373. doi: 10.1016/S2468-2667(18)30111-7
43. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. *Psychol Bull*. 2011;137:959–997. doi: 10.1037/a0024768
44. Thurston RC, Rewak M, Kubzansky LD. An anxious heart: anxiety and the onset of cardiovascular diseases. *Prog Cardiovasc Dis*. 2013;55:534–537. doi: 10.1016/j.pcad.2013.03.007
45. Juster R, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev*. 2010;35:2–16. doi: 10.1016/j.neubiorev.2009.10.002
46. Lopez-Candales A, Burgos PMH, Hernandez-Suarez DF, Harris D. Linking chronic inflammation with cardiovascular disease: from normal aging to the metabolic syndrome. *J Nat Sci*. 2017;3:1–22.
47. Azevedo Da Silva M, Singh-Manoux A, Brunner EJ, Kaffashian S, Shipley MJ, Kivimäki M, Nabi H. Bidirectional association between physical activity and symptoms of anxiety and depression: the Whitehall II study. *Eur J Epidemiol*. 2012;27:537–546. doi: 10.1007/s10654-012-9692-8
48. Barbaresko J, Rienks J, Nöthlings U. Lifestyle indices and cardiovascular disease risk: a meta-analysis. *Am J Prev Med*. 2018;55:555–564. doi: 10.1016/j.amepre.2018.04.046
49. Vilsaint CL, NeMoyer A, Fillbrunn M, Sadikova E, Kessler RC, Sampson NA, Alvarez K, Green JG, McLaughlin KA, Chen R, et al. Racial/ethnic differences in 12-month prevalence and persistence of mood, anxiety, and substance use disorders: variation by nativity and socioeconomic status. *Compr Psychiatry*. 2019;89:52–60. doi: 10.1016/j.comppsych.2018.12.008
50. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596. doi: 10.1161/CIR.0000000000000757
51. Bray C, Bell LN, Liang H, Haykal R, Kaiksow F, Mazza JJ, Yale SH. Erythrocyte sedimentation rate and C-reactive protein measurements and their relevance in clinical medicine. *Wis Med J*. 2016;115:317–321.
52. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med*. 1999;340:448–454. doi: 10.1056/NEJM199902113400607

Supplemental Material

Data S1.

Supplemental Methods

Neuroticism and Worry Assessment

Missing data in neuroticism measure. To address item-level missing data in the 9-item EPI-Q, we computed a prorated total score for individuals who had completed ≥7 items. Fewer than 2% of the sample had missing EPI-Q total score due to incomplete data.

Missing data in worry measure. There were 2 sources of item-level missing data for the worry scale: (1) missing due to non-response by participants (≤0.7% across all items); (2) item coded as missing because it was rated as "does not apply" by the participant. On average, each item was rated as "does not apply" by 4.1% of the sample; this varied widely from <2% (for 13 of 18 items) to 29% (for the item "being laid off", which was irrelevant to retired men). The total worry score was calculated as the mean score on which participants provided a rating (from 0=never to 4=all the time).

Operationalization of categorical variables. Categorical variables for neuroticism and worry were operationalized in terciles for neuroticism and quartiles for worry. We used more categories for worry than neuroticism because worry was based on 18 items on a Likert scale (vs. 9 dichotomous items for neuroticism) and yielded greater variability in the scores.

Cardiometabolic Risk (CMR) Assessment

Pre-processing of raw biomarker data. During the data processing stage, we visually inspected the raw data distribution of each biomarker. Erythrocyte sedimentation rate (ESR) values above 50 were considered outliers (found in <0.5% of observations) and set to missing. After adjustment for medications (described below), fasting triglycerides and fasting glucose were log-transformed due to skewness.

Medication adjustment. In computing CMR variables, we considered 4 classes of current medications that could affect biomarker values. These include:

- Antihypertensive agents: hypotensives, vasodilators, α-adrenergic blockers, β-adrenergic blockers, calcium-channel blockers, renin-angiotensin-aldosterone system inhibitors, and diuretics
- Statins
- Anti-inflammatory agents: corticosteroids, non-steroidal anti-inflammatory drugs
- Anti-diabetic agents

Medication adjustment in computation of CMR z-score. Values of SBP, DBP, total cholesterol, fasting triglycerides and glucose, and ESR at each visit were adjusted based on current use of the medications listed above. To do this, we first simulated age-specific distributions of each biomarker among medicated men (e.g., statin users for cholesterol) using the biomarker means and standard deviations in 5 age groups ((≤50, 51-60, 61-70, 71-80, >80). From the simulated distributions, we dropped values below the high-risk cut-points described in the main text. For men reporting use of medication affecting a biomarker, the observed biomarker value was substituted with a value randomly drawn from the truncated simulated distribution for medicated men in the corresponding age group. After medication adjustment, we computed a z-score for each biomarker at each time-point by standardizing against the sample's baseline values. Next, the overall CMR z-score was computed as the mean at each time-point across the 7 biomarker z-scores.

Revisit propensity score. The revisit propensity score was calculated by first performing a logistic regression modeling the probability of having a subsequent visit, given all relevant factors at a given visit including age, levels of cardiometabolic markers, medication use, baseline demographics, family CHD history, and occasion-specific health behaviors. We then took the inverse of the probability and used it as the revisit propensity score.

Data S2. Summary of sensitivity analyses to evaluate the role of study follow-up status and data outliers on findings

In this set of sensitivity analyses, we conducted influence diagnostics to identify the extent to which study follow-up status and data outliers might bias our findings. Specifically, we considered the influence of 3 subsets of participants: (1) Those who survived the entire follow-up; and those who were 3 standard deviations above or below the mean on (2) Cook's distance or (3) likelihood distance in the best-fitting CMR trajectory model. We re-ran analyses to estimate the best-fitting CMR trajectory model and evaluate the association of neuroticism and worry with CMR trajectories after eliminating each of the 3 subsets and comparing the results to those based on the entire sample.

Results from re-running the best-fitting age trajectory model of CMR are shown in Table I below. Compared to parameter estimates from the full sample (column A), excluding potentially influential cases based on these 3 methods had minimal influence on the intercept and age slopes of cardiometabolic risk. For example, comparing Columns A and B below shows that excluding 219 men who completed study follow-up resulted in a group with an average of 3.85 (vs. 3.78 in the full sample) cardiometabolic markers exceeding high-risk cut-points at the intercept of age 65. This reduced sample also had 0.02 (i.e., 0.82 minus 0.80) additional high-risk cardiometabolic marker per decade before the intercept of age 65, and 0.04 (i.e., 0.46 minus 0.50) fewer high-risk marker per decade after age 65.

Table I. Mean trajectory of cardiometabolic risk over age for the full sample and subsets of participants excluded based on follow-up status or influence diagnostics.

	A. Full sample	B. Excluded men who completed study follow-up	C. Excluded outliers (3SD±M) per Cook's distance	D. Excluded outliers (3SD±M) per likelihood distance
	B (95%CI)	B (95%CI)	B (95%CI)	B (95%CI)

Intercept	**3.78 (3.71, 3.86)**	**3.85 (3.76, 3.93)**	**3.79 (3.71, 3.87)**	**3.80 (3.72, 3.88)**
Baseline age	**-0.06 (-0.06, -0.05)**	**-0.06 (-0.07, -0.05)**	**-0.06 (-0.07, -0.05)**	**-0.06 (-0.07, -0.05)**
CMR change per 10 years, age ≤ 65	**0.80 (0.74, 0.86)**	**0.82 (0.75, 0.89)**	**0.82 (0.76, 0.88)**	**0.82 (0.76, 0.87)**
CMR change per 10 years, age > 65	**0.50 (0.44, 0.56)**	**0.46 (0.39, 0.53)**	**0.53 (0.47, 0.59)**	**0.51 (0.45, 0.57)**
Sample size	N = 1561 Obs = 10331	N = 1342 Obs = 7930	N=1532 Obs = 10089	N = 1529 Obs=10009

Note: Bold: p < .05. obs = observations. CMR = cardiometabolic risk (count score of biomarkers exceeding high-risk cut-points). Results were weighted with inverse probability of revisits. Baseline age was centered at the sample mean of 53 years old.

We also considered the extent to which potentially influential cases identified using the three methods above may affect the association of neuroticism and worry with cardiometabolic risk trajectories. Therefore, we re-ran multilevel regression models with neuroticism and (in separate models) worry as predictors. Results are shown in Table II below; column A contains results from the full sample (displayed as Table 2, Model 2 in the manuscript). As before, the associations of neuroticism and worry with cardiometabolic risk were minimally affected by the removal of these cases.

Table II. Prospective association between continuous neuroticism and worry scores in 1975 and cardiometabolic risk trajectories between 1975 and 2015, full sample and subsets of participants excluded based on follow-up status or influence diagnostics.

	A. Full sample	B. Excluded men who completed study follow-up	C. Excluded outliers (3SD±M) per Cook's distance	D. Excluded outliers (3SD±M) per likelihood distance
	B (95%CI)	B (95%CI)	B (95%CI)	B (95%CI)
Neuroticism main effect (z-score)	**0.08 (0.02, 0.15)**	*0.07 (-0.005, 0.14)*	**0.08 (0.02, 0.15)**	**0.08 (0.02, 0.15)**
CMR change per 10 years, age≤65	**0.81 (0.75, 0.87)**	**0.83 (0.75, 0.90)**	**0.83 (0.77, 0.89)**	**0.82 (0.76, 0.88)**
CMR change per 10 years, age>65	**0.51 (0.44, 0.57)**	**0.46 (0.39, 0.54)**	**0.54 (0.47, 0.60)**	**0.52 (0.46, 0.58)**

Sample size	N = 1462 obs = 9818	N = 1255 obs = 7527	N=1434 obs = 9584	N=1430 obs=9496
	B (95%CI)	B (95%CI)	B (95%CI)	B (95%CI)
Worry main effect (z-score)	**0.07 (0.001, 0.13)**	*0.07 (-0.0003, 0.14)*	**0.08 (0.01, 0.14)**	**0.07 (0.01, 0.14)**
CMR change per 10 years, age≤65	**0.80 (0.74, 0.86)**	**0.81 (0.74, 0.88)**	**0.82 (0.76, 0.88)**	**0.81 (0.76, 0.87)**
CMR change per 10 years, age>65	**0.50 (0.44, 0.57)**	**0.47 (0.39, 0.54)**	**0.53 (0.47, 0.60)**	**0.52 (0.46, 0.57)**
Sample size	N = 1475 Obs = 9830	N = 1266 Obs = 7525	N = 1448 Obs = 9604	N = 1443 Obs = 9508

Note: Bold: p <.05; italics: .05 ≤ p <.10. CMR = cardiometabolic risk (count score of biomarkers exceeding high-risk cut-points). Results were weighted with inverse probability of revisits. All models were adjusted for baseline age and demographic factors, including race, father's occupation, education, family income, marital status, and family history of heart disease.

Table S1. Cardiometabolic risk count score and percentage of men exceeding the high-risk cut-point for each cardiometabolic marker at baseline, by neuroticism terciles (N=1462) and worry quartiles (N=1475).

Neuroticism (T1 = lowest)	Criteria for high risk	T1	T2	T3		X^2 / F (*df*=2)	p
Cardiometabolic risk score (M (SD))	--	**2.64 (1.45)**	**2.96 (1.55)**	**2.89 (1.51)**		**5.48**	**.004**
N (%) with ≥6 markers exceeding high-risk cut-points at baseline	--	18 (1.2%)	30 (2.1%)	30 (2.1%)		2.82	.24
Systolic blood pressure (% high risk)	>130*	*33.3%*	*40.1%*	*38.8%*		*5.08*	*.08*
Diastolic blood pressure (% high risk)	>85*	17.2%	18.9%	21.6%		3.15	.21
Fasting triglycerides (mg/dL; % high risk)	≥150*	*29.8%*	*36.6%*	*32.0%*		*4.86*	*.09*
Fasting total cholesterol (mg/dL; % high risk)	≥240*	42.7%	45.7%	42.8%		1.10	.58
Fasting glucose (mg/dL; % high risk)	≥100*	61.5%	63.0%	61.6%		0.28	.87
Body-mass index (kg/m$^{2;}$ % high risk)	≥30	*9.2%*	*14.4%*	*12.2%*		*5.81*	*.05*
Erythrocyte sedimentation rate (mm/hr; % high risk)	≥14*	**70.9%**	**77.8%**	**79.8%**		**11.7**	**.003**
Worry (Q1 = lowest)	Criteria for high risk	Q1	Q2	Q3	Q4	X^2 / F (*df*=3)	p
Cardiometabolic risk score (M (SD))	--	**2.73 (1.43)**	**2.70 (1.50)**	**3.01 (1.56)**	**2.90 (1.47)**	**3.40**	**.02**
N (%) with ≥6 markers exceeding high-risk cut-points at baseline	--	13 (0.9%)	15 (1.0%)	27 (1.8%)	22 (1.5%)	6.25	.10
Systolic blood pressure (% high risk)	>130*	38.8%	35.2%	38.2%	37.2%	1.17	.76
Diastolic blood pressure (% high risk)	>85*	17.4%	18.0%	21.4%	20.6%	2.72	.44
Fasting triglycerides (mg/dL; % high risk)	≥150*	*32.5%*	*28.9%*	*38.2%*	*32.8%*	*7.28*	*.06*
Fasting total cholesterol (mg/dL; % high risk)	≥240*	41.3%	42.8%	46.2%	44.3%	1.88	.60
Fasting glucose (mg/dL; % high risk)	≥100*	59.8%	58.6%	66.8%	62.6%	6.08	.11

Body-mass index (kg/m$^{2;}$ % high risk)	≥30	10.3%	10.4%	12.9%	14.0%	3.73	.29
Erythrocyte sedimentation rate (mm/hr; % high risk)	≥14*	73.8%	76.6%	77.5%	78.6%	2.60	.46

Note: Bold: p <.05; italics: .05 ≤ *p* <.10. T = tercile; Q = quartile; M = mean; SD = standard deviation. Neuroticism and worry group differences in cardiometabolic risk score were evaluated using one-way analysis of variance, and group differences for all other variables were evaluated using chi-square tests. Asterisk (*) denotes biomarkers for which assignment to high-risk status was based on meeting the criteria shown here and/or current use of medications with known effect on the biomarker. These include use of anti-hypertensives (systolic and diastolic blood pressure), statins (fasting cholesterol and fasting triglycerides), and anti-inflammatory medications (erythrocyte sedimentation rate).

Table S2. Fit indices of multilevel models representing different cardiometabolic risk trajectories over age.

Model	Compared with:	Δ Parameters	Δ -2LL	Δ AIC	Δ BIC
Random intercept	--	Parameters = 4	-2LL = 36767.3	AIC = 36775.3	BIC = 36796.7
Random linear age	Random intercept	+3	-3143.2	-3137.2	-3121.1
Random quadratic age	Random linear age	+4	-161.3	-153.3	-131.9
Spline models:					
knot at age 65	Random quadratic age	0	n/a	-7.9	-7.9
knot at age 50	knot at age 65	0	n/a	+86.0	+86.0
knot at age 55	knot at age 65	0	n/a	+39.6	+39.6
Knot at age 60	knot at age 65	0	n/a	+0.6	+0.6
Knot at age 70	knot at age 65	0	n/a	+9.7	+9.7
Knot at age 75	knot at age 65	0	n/a	+53.5	+53.5
Knot at age 80	knot at age 65	0	n/a	+96	+96

Note: Δ = difference calculated as (current model – comparison model); LL = log-likelihood; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion. Δ-2LL is not shown for non-nested model comparisons.

Table S3. Hazard ratios for the association of neuroticism and worry with risk of having 6 or more cardiometabolic risk markers exceeding high-risk cut-points between 1975 and 2015 (Neuroticism, N=1288; Worry: N=1301).

	Model 1 (Age-adjusted)		Model 2 (+ demographics, CHD family history)		Model 3 (+ health behaviors)	
	HR	95%CI	HR	95%CI	HR	95%CI
Neuroticism (z-score)	**1.13**	**(1.04, 1.24)**	**1.13**	**(1.03, 1.23)**	1.08	(0.98, 1.18)
Neuroticism: Lower tercile (reference)	--	--	--	--	--	--
Neuroticism: Middle tercile	**1.50**	**(1.19, 1.88)**	**1.49**	**(1.18, 1.87)**	**1.39**	**(1.10, 1.55)**
Neuroticism: High tercile	**1.37**	**(1.10, 1.71)**	**1.35**	**(1.08, 1.69)**	*1.23*	*(0.98, 1.55)*
Worry (z-score)	**1.10**	**(1.004, 1.20)**	**1.10**	**(1.01, 1.20)**	1.07	(0.98, 1.17)
Worry: Quartile 1 (lowest; reference)	--	--	--	--	--	--
Worry: Quartile 2	0.99	(0.76, 1.27)	1.00	(0.77, 1.30)	0.97	(0.75, 1.27)
Worry: Quartile 3	1.10	(0.85, 1.42)	1.13	(0.87, 1.46)	1.08	(0.84, 1.40)
Worry: Quartile 4	*1.25*	*(0.98, 1.61)*	*1.25*	*(0.97, 1.61)*	1.17	(0.91, 1.51)

Note: Bold: p <.05; italics: .05 ≤ *p* <.10. Model 1 adjusted for continuous baseline age. Model 2 additionally adjusted for baseline demographic factors, including race, father's occupation, education, family income, marital status, and family history of heart disease. Model 3 further adjusted for health behaviors, including time-varying smoking, alcohol consumption, and physical activity, and past-year physician visit at baseline. Sample sizes are smaller in Cox models relative to multilevel linear regression models because participants with only 1 visit were excluded.

Table S4. Prospective association between neuroticism terciles and worry quartiles in 1975, and cardiometabolic risk trajectories between 1975 and 2015 (Worry: N=1475, observations=9830; Neuroticism: N=1462, observations=9818).

	Model 1 (Age-adjusted)		Model 2 (+ demographics, CHD family history)		Model 3 (+ health behaviors)	
	B	95%CI	B	95%CI	B	95%CI
Neuroticism: Lower tercile (reference)	--	--	--	--	--	--
Neuroticism: Middle tercile	**0.31**	**(0.15, 0.48)**	**0.29**	**(0.12, 0.45)**	**0.26**	**(0.10, 0.43)**
Neuroticism: High tercile	**0.24**	**(0.09, 0.40)**	**0.21**	**(0.05, 0.37)**	**0.18**	**(0.02, 0.33)**
CMR change per 10 years, age≤65	**0.81**	**(0.75, 0.87)**	**0.81**	**(0.74, 0.87)**	**0.78**	**(0.72, 0.84)**
CMR change per 10 years, age>65	**0.50**	**(0.44, 0.57)**	**0.51**	**(0.44, 0.57)**	**0.49**	**(0.43, 0.56)**
Worry: Quartile 1 (lowest; reference)	--	--	--	--	--	--
Worry: Quartile 2	-0.02	(-0.21, 0.16)	-0.02	(-0.21, 0.16)	-0.06	(-0.24, 0.12)
Worry: Quartile 3	*0.18*	*(-0.003, 0.36)*	*0.18*	*(-0.003, 0.36)*	*0.16*	*(-0.03, 0.34)*
Worry: Quartile 4	*0.17*	*(-0.01, 0.35)*	*0.17*	*(-0.01, 0.35)*	0.14	(-0.04, 0.32)
CMR change per 10 years, age≤65	**0.80**	**(0.74, 0.86)**	**0.80**	**(0.74, 0.86)**	**0.77**	**(0.71, 0.83)**
CMR change per 10 years, age>65	**0.50**	**(0.44, 0.56)**	**0.50**	**(0.44, 0.57)**	**0.49**	**(0.43, 0.56)**

Note: Bold: p <.05; italics: .05 ≤ *p* <.10. CMR = cardiometabolic risk (count score). Results were weighted with inverse probability of revisits. Model 1 adjusted for baseline age. Model 2 additionally adjusted for baseline demographic factors, including race, father's occupation, education, family income, marital status, and family history of heart disease. Model 3 further adjusted for health behaviors, including time-varying smoking, alcohol consumption, and physical activity, and past-year physician visit at baseline.\