Association of Anxiety with Cardiovascular Disease in a Chinese Cohort of 0.5 Million Adults

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Abstract

Background: Anxiety might be a potentially modifiable risk factor of cardiovascular diseases (CVDs). Evidence relating anxiety symptoms and generalized anxiety disorder (GAD) to CVDs from prospective cohort study was still lacking in China.

Methods: Participants aged 30 to 79 years old from 10 areas across China were recruited during 2004-2008 and were followed up until 2017. 487,209 participants without CVDs at baseline remained for analyses. Anxiety symptoms (panic attacks and continuous anxiety) during the past 12 months were identified in a face-to-face interview. Participants with continuous anxiety were further assessed for GAD using Composite International Diagnostic Interview-Short Form. The primary outcomes were incident CVD, ischaemic heart disease (IHD), haemorrhagic stroke (HS), and ischaemic stroke (IS).

Results: During 4.7 million person-years of follow-up, we documented 140,365 incident cases of CVD. For panic attacks, the multivariable-adjusted HRs (95% CI) were 1.08 (1.04-1.13), 1.10 (1.02-1.19), 1.20 (1.05-1.38) and 1.20 (1.11-1.30) for CVD, IHD, HS and IS, respectively. Continuous anxiety was positively associated with incident CVD and IHD, and the corresponding HRs were 1.12 (1.04-1.20) and 1.21 (1.07-1.37).

Limitations: Anxiety symptoms were examined according to self-reported questionnaires, which could constitute key study limitations.

Conclusions: Among the Chinese adults, those with anxiety symptoms or GAD might be important at-risk population of CVD.

Key words: Anxiety; Panic; Cardiovascular diseases; Cohort study

Introduction

Anxiety disorders include a group of disorders that share figures of excessive fear, anxiety and related behavioural disturbances. Acute anxiety symptoms include panic attack, an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes. While a long-term anxiety symptom (continuous anxiety) could be diagnosed as generalized anxiety disorder (GAD), which means uncontrollable and irrational worry about various domains, occurring at least 6 months(American Psychiatric Association, 2013). Anxiety is one of the most common mental disorders with a global 1-year prevalence of 3.6% in 2015(World Health Organization, 2017). In China, a cross-sectional study of 32,552 participants across 31 provinces from 2013 to 2015 found out that, anxiety disorders were the most common class of mental disorders, with a lifetime prevalence of 7.6% (95%CI: 6.3%-8.8%)(Huang, et al., 2019). However, there's still a lack of emerging evidence of the health problems related to anxiety among Chinese people.

Anxiety is a potential risk factors for cardiovascular disease (CVD), the latter caused an estimated 4.5 million death in China in 2016, representing 43.1% of all death, including 2.0 million due to stroke followed by 1.9 due to ischaemic heart disease (IHD)(World Health Organization, 2018). Recently, A meta-analysis showed that anxiety was associated with a 52% increased risk of CVD, and the association appeared to be independent of traditional risk factors, such as smoking, physical inactivity, and unhealthy diet(Batelaan, et al., 2016). Subgroup analyses showed that the elevated CVD risk associated with panic and general anxiety were 55% and 52%, respectively. Previous studies have found a consistent association between anxiety and coronary heart disease (CHD)(Tully, et al., 2015, Roest, et al., 2010). However, the impact of different anxiety types on CHD has not been compared in a single study. Evidence on the association between two anxiety types and stroke is limited, with several studies reporting an increased risk(Lambiase, et al., 2014, Chou, et al., 2012), while others did not(Stewart, et al., 2016, Portegies, et al., 2016, Smoller, et al., 2007, Mathur, et al., 2016). Most of these studies failed to examine the impact of anxiety on specific stroke subtypes limited by few cases of stroke. Furthermore, there was little evidence based on China, where anxiety is a serious problem but has received less attention. Besides, anxiety could be reduced by exercise and increasing fitness(Lavie, et al., 2016). Thus, it's of great importance to estimate the association between anxiety and the risk of CVD among the Chinese.

In the China Kadoorie Biobank (CKB) cohort of 0.5 million adults, we prospectively examined the association of two types of anxiety symptoms (panic attack and continuous anxiety) with CVD and its various subtypes, including IHD, haemorrhagic stroke, and ischaemic stroke, and whether these associations were independent of traditional CVD risk factors. We further investigated the association between GAD status and CVD outcomes.

Methods

Study population

The CKB cohort is an ongoing prospective population-based study established in 10 geographically diverse localities (5 urban and 5 rural areas) across China. The study recruited

0.5million adults aged 30 to 79 years from 2004 to 2008. After registration, each participant completed an interviewer-administered electronic questionnaire, physical measurements, a collection of 10-ml non-fasting blood samples and written informed consent. Further details about the CKB study are available elsewhere(Chen, et al., 2011, Chen, et al., 2005). Our study obtained approval from the Ethics Review Committee of the Chinese Centre for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee at the University of Oxford (United Kingdom).

In the present study, we excluded 25,517 participants who had the previous diagnosis of cancer (n=2,578), heart disease (n=15,472) or stroke (n=8,884) at baseline and who had missing data on body mass index (BMI) (n=2) or were recorded with an implausible censoring date (n=1). 487,209 participants remained for the final analyses.

Assessment of anxiety symptoms

At baseline, participants were asked whether they had experienced the following two anxiety symptoms during the past 12 months: (1) Panic attack: having had a spell or an attack when all of sudden you felt frightened, anxious, or very uneasy accompanied by heart raced, blush or other symptoms (American Psychiatric Association, 2013); (2) Continuous anxiety: having a period lasting one month or longer when most of the time you felt worried, tense, or anxious and it interfered your life (Kessler, et al., 1998). If the answer was “yes” to continuous anxiety, participants were further assessed for generalized anxiety disorder (GAD) using the Chinese version of Composite International Diagnostic Interview-Short Form (CIDI-SF) by trained health workers in a face-to-face interview. The CIDI was a fully structured diagnostic instrument developed by the World Health Organization for assessing mental disorders. Participants were defined as having past year GAD if they had a period of feeling worried, tense, or anxious that lasted at least six months with the following three conditions: (1) the anxious period was stronger than in other people, lasted more days, and involved worrying about more than one thing; (2) had difficulty to control over the worries; (3) had at least three physiological symptoms(Gigantesco and Morosini, 2008). In our study, panic attacks, continuous anxiety, and GAD showed good reliability among 923 participants who completed a repeated questionnaire survey within one year after baseline, with all agreements >0.97, and Prevalence and Bias Adjusted Kappa (PABAK) >0.95.

Assessment of covariates

We collected sociodemographic characteristics, lifestyle factors, and medical history at the baseline interview. Sociodemographic characteristics included age, gender, level of education (no formal school, primary school, middle school, high school, college, university or higher) and marital status (married, widowed, divorced or separated, never married). Lifestyle factors included alcohol consumption (not weekly drinking, ex-regular drinking, not daily, daily <30, 30-59, or ≥60g/d), smoking status (never/occasional, former, current smoking 1-14, 15-24, or ≥25 cigarettes/day), intake frequencies of red meat, fruits, and vegetables (daily, 4-6 days/week, 1-3 days/week, monthly, rarely or never) and total physical activity (calculated as metabolic equivalent task hours per day [MET-h/day]). In addition, all participants were asked to report their family history of major chronic diseases and personal history of medical status. Trained staff measured body weight, height and blood pressure at baseline with calibrated instruments. BMI was calculated as weight in kilograms divided by height in meters squared. Prevalent hypertension was defined as measured systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, self-reported diagnosis of hypertension, or self-reported use of antihypertensive medication at baseline. Prevalent diabetes was defined as measured fasting blood glucose ≥7.0 mmol/L, measured random blood glucose ≥11.0 mmol/L, or self-reported diagnosis of diabetes.

Assessment of cardiovascular diseases

The vital status of each participant since enrolment was followed up through linkage with local disease and death registries as well as national health insurance system, and information of those who failed to be linked was supplemented by active follow-up through local research staff(Chen, et al., 2011). Fatal and non-fatal events were documented according to the International Classification of Diseases (10th Revision) by trained coders who were blinded to baseline information. The primary outcomes of interest were incident CVD [I00-I99], IHD [I20-I25], haemorrhagic stroke [I61] and ischaemic stroke [I63], as well as incident major coronary events (MCE, including fatal IHD [I20-I25] and non-fatal myocardial infarction [I21-I23]). The secondary outcomes were mortality from CVD, IHD, haemorrhagic stroke and ischaemic stroke.

Statistical analysis

Baseline characteristics of participants according to anxiety symptoms were described as means or proportions with adjustment for age, sex, and region as appropriate, by using multiple linear regression for continuous variables or logistic regression for categorical variables.

Person-years at risk were calculated from the baseline date to the diagnosis of outcomes, death, loss to follow-up, or 31 December 2017, whichever came first. We used Cox proportional hazards models to calculate the hazard ratio (HR) and 95% confidence interval (CI), with joint stratification by study regions and age at baseline in 5-year intervals, using age as the underlying timescale. We examined the proportional hazards assumption by visually checking the Kaplan-Meier curves or testing it by Schoenfeld residuals. Multivariable models were adjusted for age, sex, education level, marital status, alcohol consumption, smoking status, physical activity, intake frequencies of red meat, fruits, and vegetables, BMI, prevalent hypertension and diabetes at baseline, and family history of heart attack and stroke. We estimated HRs for two anxiety symptoms (panic attacks and continuous anxiety) and CVDs based on the models above. The same analyses were conducted to GAD status in three categories (no, continuous anxiety, or GAD) by detaching participants with diagnosed GAD from those with continuous anxiety.

We further performed sensitivity analyses based on multivariable-adjusted models to examine the robustness of our results by additionally adjusting for heart rate or major depression; or excluding participants whose outcomes occurred during the first two years of follow-up. We also conducted analyses for short and long duration of follow-up by splitting the follow-up time at 6 years.

All statistical analyses were performed using Stata (version 13.1). All *P* values were two-sided, and statistical significance was defined as $p<0.05$.

Results

Among the 487,209 participants, the mean age was 51.5±10.5 years, 40.9% were men, and 56.9% were from rural areas. Overall, 7268 participants (1.49%) had panic attacks, 2800 (0.57%) had continuous anxiety, and 624 (0.13%) had GAD during the past 12 months. Participants who had panic attacks or continuous anxiety were younger, more likely to be women, to live in rural areas and to be unmarried, had a lower level of education, and more likely to have prevalent diabetes at baseline. Those who had panic attacks were more likely to have prevalent hypertension, but the proportions of hypertension were similar between participants with and without continuous anxiety (Table 1).

During a median follow-up of 9.6 years (4.7 million person-years), we documented 140,365 incident cases of CVD (including 45,633 IHD, 10,075 haemorrhagic stroke and 43,329 ischaemic stroke), and 16,257 CVD deaths. Participants who ever had panic attacks during the past 12 months had significantly higher risks of incident CVDs, except MCE (Table 2). The multivariable-adjusted HRs (95% CI) were 1.08 (1.04-1.13) for CVD, 1.10 (1.02-1.19) for IHD, 1.20 (1.05-1.38) for haemorrhagic stroke, and 1.20 (1.11-1.30) for ischaemic stroke. Similar associations were observed for mortality from haemorrhagic stroke (HR 1.24, 95%CI 1.04-1.48) and ischaemic stroke (HR 1.47, 95%CI 1.05-2.05). Nevertheless, HR for IHD mortality was found to be insignificant (eTable 1). Continuous anxiety was positively associated with incident CVD (HR 1.12, 95%CI 1.04-1.20), which was driven mainly by IHD (HR 1.21, 95%CI 1.07-1.37) and MCE (HR 1.32, 95%CI 1.00-1.74) (Table 2). Similar associations were observed for CVD and IHD mortality with adjustment for sex. However, the HRs became insignificant after multivariate adjustment (eTable 1). The associations of continuous anxiety with the incidence of and mortality from haemorrhagic and ischaemic stroke were all found to be insignificant.

After further adjusting for major depression, the associations for panic attacks changed little, and the association between continuous anxiety and IHD remained significant, although HRs for continuous anxiety slightly reduced. The associations of panic attacks and continuous anxiety with CVDs hardly changed after adjusting for heart rate, or after excluding participants whose outcomes occurred during the first two years of follow-up (eTable 2, 3). Analyses for the short and long duration of follow-up showed that there was no statistically significant heterogeneity (*P* for heterogeneity >0.05) (eTable 4).

We additionally examined the association between GAD status and CVDs. Compared to participants without continuous anxiety, those with GAD had an elevated but insignificant risk of IHD, MCE，haemorrhagic stroke and ischaemic stroke (Table 3). A similar trend was observed for mortality from CVDs (eTable 5). During follow-up time ≤ 6 years, GAD was associated with haemorrhagic stroke (HR 2.54, 95%CI 1.50-4.30), yet no significant association was observed for >6 years (*P* for heterogeneity=0.021). GAD was also significantly associated with IHD (HR 1.59, 95%CI 1.08-2.36) for ≤ 6 years of follow-up, although there was no evidence for heterogeneity (eTable 6).

Discussion

In this large prospective Chinese cohort study, we found that panic attacks were positively associated with the incidence and mortality of haemorrhagic and ischaemic stroke, also incident IHD. Continuous anxiety was positively associated with incident IHD and MCE, yet had no significant relationship with stroke. Diagnosed GAD had elevated risks of incident IHD and haemorrhagic stroke during follow-up time ≤6 years.

A most recent meta-analysis included 37 prospective studies, panic and general anxiety was associated with a 55% and a 52% increased risk of CVD, respectively, with a high degree of heterogeneity(Batelaan, et al., 2016). This meta-analysis pooled estimates of anxiety disorder and anxiety symptoms which were assessed by different scales, used atherosclerotic CVD as the outcome, and included only one study among Chinese people. In the present study, we observed significant but more moderate associations of panic attacks and continuous anxiety with total CVD. This discrepancy in the magnitude of effect size might result from difference in anxiety assessment, CVD assessment and sample characteristics. In another meta-analysis which included 20 prospective studies, anxiety was associated with a 26% increased risk of incident CHD(Roest, et al., 2010). Although previous meta-analyses with large sample sizes had great statistical efficacy, they failed to observe the effect of different anxiety types on each specific subtype of CVD. In our study, we observed a 9% increased risk of IHD for participants with panic attacks, and a 22% increased risk for those with continuous anxiety. Only one study about anxiety in relation to CHD was conducted in the Chinese population so far(Chen, et al., 2009). This study from Taiwan China included 33,696 participants and examined the association between panic disorder and acute myocardial infarction within only one year of follow-up (HR=1.75, 95%CI 1.55-1.97). The result may have a problem of reverse causality given the short duration of follow-up. Our results did not show a positive association between panic attacks and MCE during approximately 10 years of follow-up. Previous evidence on anxiety and stroke was limited. The latest meta-analysis included only eight studies and found a 24% increased risk of stroke for participants with anxiety(Pérez-Piñar, et al., 2017). The meta-analysis included one study focused on panic from in Taiwan China. The study investigated the effect of panic disorder on stroke among 390,309 adults and reported a 38% increased risk (HR=1.38, 95%CI 1.12-1.71)(Chou, et al., 2012). However, the study could not examine the association with specific stroke subtypes, as relatively few incident cases of stroke (n=88) were noted in patients with panic disorder. In our study, we documented 207 incident cases of haemorrhagic stroke and 570 of ischaemic stroke. Our results showed that panic attacks were associated with a 23% and a 19% increased risk of haemorrhagic stroke and ischaemic stroke. Several studies that examined the association between general anxiety symptoms and stroke found inconsistent results(Lambiase, et al., 2014, Stewart, et al., 2016, Portegies, et al., 2016).This discrepancy might partly be attributable to different tools used to assess general anxiety symptoms. In the present study, neither continuous anxiety nor GAD were associated with haemorrhagic stroke or ischaemic stroke during complete follow-up. However, GAD was significantly associated with haemorrhagic stroke during follow-up time ≤6 years. Two previous studies have reported an increased risk of stroke within the first 3 years of the detection of general anxiety, but found no significant risk for follow-up time more than 3 years(Stewart, et al., 2016, Portegies, et al., 2016), suggesting a possible short-term effect of general anxiety on stroke. However, we could not exclude the possibility of reverse causality, although we have excluded participants with stroke at baseline before analyses.

Several potential mechanisms might help to explain the adverse association between anxiety and CVD. Anxiety can be directly associated with the evolution of atherosclerosis(Paterniti, et al., 2001). Anxiety may lead to excess activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, altered immune function(Wingo and Gibson, 2015), altered cardiovascular autonomic control such as reduced heart rate variability, and elevated cardiovascular reactivity to stress such as abnormality in ventricular repolarization, and thus may lower the threshold for ischemia(Thurston, et al., 2013). In addition, anxiety may indirectly affect CVD by driving other risk factors, such as depression, smoking, sedentary lifestyle, unhealthy diet, and metabolic abnormalities, which can contribute to the progression of CVD(Carroll, et al., 2009, Kachur, et al., 2016). However, the mechanism between GAD and haemorrhagic stroke is still unclear, since GAD was not associated with hypertension in our population.

To the best of our knowledge, this is the first study that detected the prospective association of anxiety with CVDs in mainland China. Various CVD outcomes and two types of anxiety were taken into account, and analyses have been carefully adjusted for multiple risk factors for CVD. However, some limitations still need to be acknowledged. First, our study has not assessed panic disorder at baseline and thus could not examine the effects of panic disorder on CVDs. However, we found panic attacks, which is a major symptom of panic disorders, had positive harmful effects on various CVD outcomes. We could assume that panic disorder, which is a more severe situation, may have a greater impact on CVDs. Given that sub-threshold anxiety may also be at elevated CVD risk, only focusing on anxiety disorders may lose a potentially at-risk population. Second, even though we used the same questions from standized questionnaires to evaluate anxiety symptoms, these questions hadn't been validated in our population, which might lead to the possibility of misclassification. However, measurement errors may be non-differential in prospective study design, and the associations were more likely to be biased toward the null. The single item could not measure the degree and severity of symptoms, but might be more simple and feasible for screening in large-scale epidemiological studies. Third, even though we have carefully adjusted the potential confounders, residual confounding by unknown and unmeasured factors may still exist. For example, some psychotropic medication related to higher cardiovascular risk might influence the association(Hamer, et al., 2011). Since the use of psychotropic drugs was rare in the present population, the effect might not change substantially(Patel, et al., 2016). Fourth, reverse causality could be possible as well. Participants may develop anxiety symptoms under diseases or subclinical condition, which could make them more susceptible to CVD. We excluded participants with previous major chronic diseases at baseline before analyses, and our results were robust after exclusion of CVD cases occurred in the first 2 years of follow-up. Finally, a small number of participants with GAD were recruited at baseline, thus we should be cautious when generalizing the results to other population.

Conclusions

Our study found panic attacks and continuous anxiety increased the risk of CVD independent of traditional risk factors among Chinese adults, and two anxiety types showed different patterns in relation to subtypes of CVD. The present study yields new information on Chinese adults that those with anxiety symptoms might be an important at-risk population of CVD. The mechanisms of the different associations of two anxiety types with stroke still need further exploration.

Supplementary

The eTable 1~5 and the members of the China Kadoorie Biobank collaborative group could be found online.

Ethics approval statement

The CKB cohort was approved by both the Ethical Review Committee of the Oxford Tropical Research Ethics Committee, University of Oxford (UK) and the Chinese Center for Disease Control and Prevention (Beijing, China) at the foundation of the project (2004-2008). At that time, the PI in China (professor Liming Li) was working at CDC China, but now he is a professor at Peking University. And the subsequent study of CKB also got approval from IRB at Peking University.

Patient consent approval

All participants provided informed consent.

Data availability statement

Requests for data should be submitted to the China Kadoorie Biobank (CKB) Data Access

Committee. As stated in the CKB data policy, the CKB Study Group (as data custodian) must maintain the integrity of the database for future use and regulate data access to comply with previous conditions agreed with the Chinese Government. Data security is an integral part of CKB Study protocols. Details of how to access China Kadoorie Biobank data and details of the data release schedule are available from www.ckbiobank.org/site/Data+Access.

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Declaration of competing interest

The authors declare no conflicts of interests.

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Authorship contribution statement

Man Wu prepared the manuscript, Man Wu and Yunqing Zhu performed data analysis and interpretation. Yu Guo, Ling Yang, Yiping Chen, Wei Tang, Shengping Xiang and Xiaohui Sun conducted the field investigation and data collection. Canqing Yu and Jun Lv developed the idea for the study and results interperation. Junshi Chen, Zhengming Chen and Liming Li conceived the CKB project. All authors critiqued and approved the final version of the manuscript for submission.

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Table 1. Baseline characteristics of 487,209 participants by symptoms of anxiety.

Characteristics	Panic attacks			Continuous anxiety		
	No	**Yes**	***P***	**No**	**Yes**	***P***
No. of participants	479,941	7,268		484,409	2,800	
Age (years)	51.6	50.4	<0.001	51.6	49.2	<0.001
Female (%)	58.9	72.8	<0.001	59.0	70.8	<0.001
Rural area (%)	56.6	74.8	<0.001	56.8	69.3	<0.001
Married (%)	90.9	88.9	<0.001	90.9	82.6	<0.001
Middle school and higher (%)	49.2	47.0	<0.001	49.2	45.5	<0.001
Current daily smoker (%)	29.4	29.6	0.536	29.3	30.5	0.079
Male	67.9	67.2	0.554	67.9	68.4	0.734
Female	2.7	3.4	<0.001	2.7	3.9	<0.001
Current daily drinker (%)	9.2	8.3	0.027	9.2	8.5	0.265
Male	21.1	18.4	0.007	21.1	18.7	0.085
Female	0.9	1.0	0.405	0.9	1.2	0.216
Physical activity (MET h/day)	21.6	21.2	0.005	21.6	21.7	0.398
Average weekly consumption (day)						
Red meat	3.7	3.7	0.123	3.7	3.4	<0.001
Fresh vegetables	6.8	6.2	<0.001	6.8	6.8	<0.001
Fresh fruits	2.6	2.3	<0.001	2.6	2.4	<0.001
Body mass index (kg/m^2)	23.6	23.6	0.478	23.6	23.4	<0.001
Diabetes (%)	5.4	6.3	0.002	5.4	7.5	<0.001
Hypertension (%)	33.7	38.5	<0.001	33.7	33.4	0.734
Family history of heart attack (%)	3.1	4.1	<0.001	3.1	5.5	<0.001
Family history of stroke (%)	17.6	20.8	<0.001	17.6	21.5	<0.001

* Values according to anxiety symptoms were either mean or proportion with adjustment for age, sex and region, except for these 3 variables.

Table 2. Association of anxiety symptoms with the risk of CVD among 487,209 participants.

Endpoints	Panic attacks		Continuous anxiety	
	No	Yes	No	Yes
CVD				
No. of cases	138,275	2,090	139,573	792
Cases/person-years (1/1000)	30.18	28.51	30.17	27.19
Model 1	1.00	1.13 (1.08-1.18)	1.00	1.14 (1.06-1.22)
Model 2	1.00	1.12 (1.07-1.17)	1.00	1.13 (1.05-1.21)
Model 3	1.00	1.08 (1.04-1.13)	1.00	1.12 (1.04-1.20)
IHD				
No. of cases	44,971	662	45,370	263
Cases/person-years (1/1000)	8.92	8.36	8.92	8.37
Model 1	1.00	1.14 (1.06-1.24)	1.00	1.23 (1.09-1.39)
Model 2	1.00	1.13 (1.04-1.22)	1.00	1.22 (1.08-1.38)
Model 3	1.00	1.10 (1.02-1.19)	1.00	1.21 (1.07-1.37)
MCE				
No. of cases	8,989	141	9,079	51
Cases/person-years (1/1000)	1.73	1.73	1.73	1.57
Model 1	1.00	1.20 (1.02-1.42)	1.00	1.42 (1.07-1.87)
Model 2	1.00	1.15 (0.97-1.36)	1.00	1.35 (1.03-1.78)
Model 3	1.00	1.09 (0.92-1.30)	1.00	1.32 (1.00-1.74)
Haemorrhagic stroke				
No. of cases	9,846	229	10,007	68
Cases/person-years (1/1000)	1.89	2.81	1.91	2.10
Model 1	1.00	1.32 (1.15-1.50)	1.00	1.28 (1.01-1.62)
Model 2	1.00	1.30 (1.13-1.49)	1.00	1.22 (0.96-1.54)
Model 3	1.00	1.20 (1.05-1.38)	1.00	1.20 (0.94-1.52)
Ischaemic stroke				
No. of cases	42,653	676	43,091	238
Cases/person-years (1/1000)	8.45	8.50	8.45	7.53
Model 1	1.00	1.24 (1.15-1.34)	1.00	1.12 (0.99-1.27)
Model 2	1.00	1.24 (1.15-1.34)	1.00	1.11 (0.97-1.26)
Model 3	1.00	1.20 (1.11-1.30)	1.00	1.09 (0.96-1.24)

* Cox proportional hazards models were stratified by study regions and age at baseline in 5-year intervals. Multivariate models were adjusted for: model 1: sex; model 2: additionally included level of education, marital status, alcohol consumption, smoking status, intake frequencies of red meat, fruits, and vegetables and physical activity; model 3: additionally included BMI, prevalent hypertension at baseline, prevalent diabetes at baseline, family history of heart attack, family history of stroke.

Table 3. Association of GAD with the risk of CVD among 487,209 participants.

Endpoints	No	Continuous anxiety	GAD
CVD			
No. of cases	139,573	611	181
Cases/person-years (1/1000)	30.17	26.92	28.12
Model 1	1.00	1.14 (1.05-1.23)	1.15 (1.00-1.33)
Model 2	1.00	1.13 (1.04-1.22)	1.14 (0.99-1.32)
Model 3	1.00	1.11 (1.03-1.20)	1.14 (0.99-1.32)
IHD			
No. of cases	45,370	207	56
Cases/person-years (1/1000)	8.92	8.45	8.10
Model 1	1.00	1.25 (1.09-1.43)	1.16 (0.89-1.50)
Model 2	1.00	1.24 (1.08-1.42)	1.15 (0.89-1.50)
Model 3	1.00	1.23 (1.07-1.41)	1.15 (0.89-1.50)
MCE			
No. of cases	9,079	39	12
Cases/person-years (1/1000)	1.73	1.54	1.67
Model 1	1.00	1.41 (1.03-1.94)	1.43 (0.81-2.51)
Model 2	1.00	1.36 (0.99-1.87)	1.32 (0.75-2.32)
Model 3	1.00	1.32 (0.97-1.81)	1.32 (0.75-2.32)
Haemorrhagic stroke			
No. of cases	10,007	48	20
Cases/person-years (1/1000)	1.91	1.90	2.81
Model 1	1.00	1.18 (0.89-1.57)	1.61 (1.04-2.49)
Model 2	1.00	1.13 (0.85-1.50)	1.49 (0.96-2.32)
Model 3	1.00	1.10 (0.83-1.46)	1.53 (0.98-2.37)
Ischaemic stroke			
No. of cases	43,091	184	54
Cases/person-years (1/1000)	8.45	7.47	7.73
Model 1	1.00	1.11 (0.96-1.29)	1.15 (0.88-1.50)
Model 2	1.00	1.10 (0.95-1.28)	1.12 (0.86-1.47)
Model 3	1.00	1.08 (0.93-1.25)	1.14 (0.87-1.49)

* Continuous anxiety in this table referred to participants who had continuous anxiety but did not meet the criteria for GAD. Cox proportional hazards models were stratified by study regions and age at baseline in 5-year intervals. Multivariate models were adjusted for: model 1: sex; model 2: additionally included level of education, marital status, alcohol consumption, smoking status, intake frequencies of red meat, fruits, and vegetables and physical activity; model 3: additionally included BMI, prevalent hypertension at baseline, prevalent diabetes at baseline, family history of heart attack, family history of stroke.