ESC European Society of Cardiology

European Heart Journal Open (2022) **2**, 1–8
https://doi.org/10.1093/ehjopen/oeac050

ORIGINAL ARTICLE
Epidemiology and prevention

Anger frequency and risk of cardiovascular morbidity and mortality

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Received 16 May 2022; revised 22 July 2022; accepted 31 July 2022; online publish-ahead-of-print 6 August 2022

Handling Editor: Karolina Szummer

Aims Anger may increase the risk of cardiovascular diseases (CVDs) but previous findings are inconclusive and large prospective studies are needed. We investigated whether frequency of strong anger is associated with the incidence of specific CVDs and CVD mortality, and if sex, age, and cardiometabolic risk factors modify these associations.

Methods and results We used data from a population-based cohort of 47 077 Swedish adults (56–94 years of age) who completed questionnaires regarding their experience of anger, lifestyle habits, and health characteristics. Participants were followed for incident cardiovascular outcomes and death up to 9 years through linkage to the Swedish National Patient and Death Registers. Hazard ratios and confidence intervals adjusted for potential confounders were assessed.

In multivariable analyses, frequent episodes of strong anger were associated with an increased risk of heart failure, atrial fibrillation, and CVD mortality [hazard ratios (95% confidence intervals) = 1.19 (1.04–1.37), 1.16 (1.06–1.28), and 1.23 (1.09–1.40), respectively]. The link between anger frequency and heart failure was more pronounced in men and participants with a history of diabetes. No evidence of an independent association of anger frequency with risk of myocardial infarction, aortic valve stenosis, and abdominal aortic aneurysm was found.

Conclusion Our findings indicate that anger may contribute to the development of specific CVDs and CVD mortality, especially heart failure in men and in those with diabetes.

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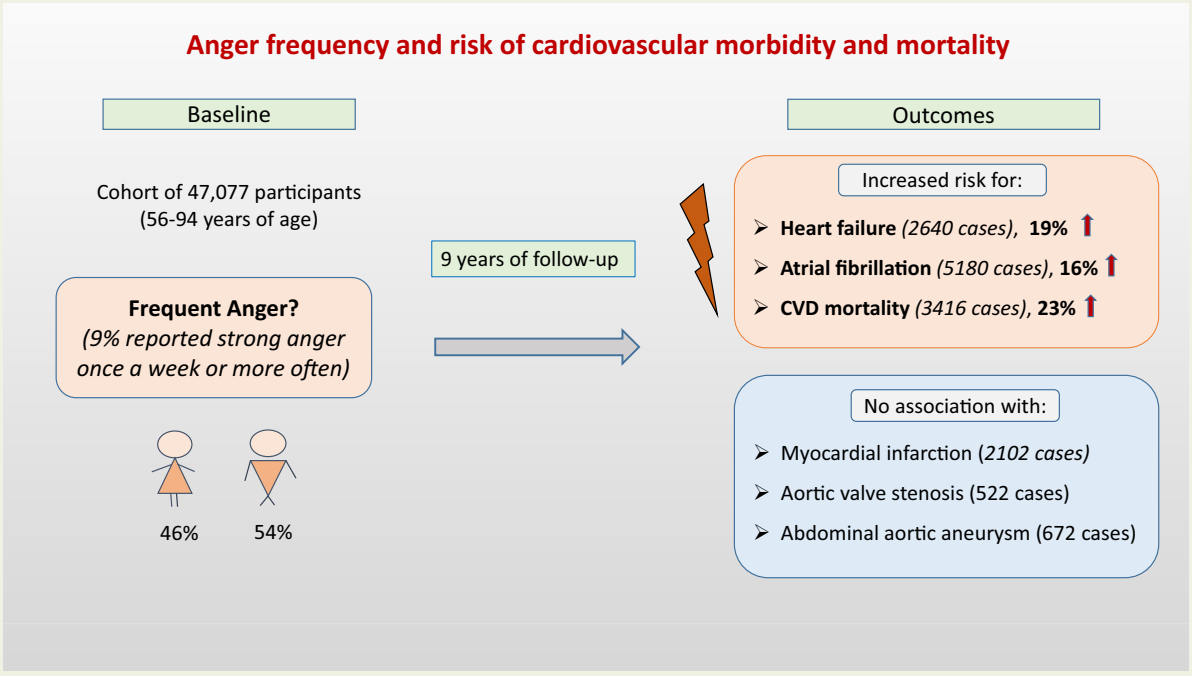
Graphical Abstract



Keywords Cardiovascular disease • Cardiovascular mortality • Anger • Sex • Cohort • Diabetes

Introduction

As the major cause of severe long-term disability and pre-mature death, cardiovascular diseases (CVDs) impose a large burden on healthcare systems and society. In addition to traditional risk factors for CVDs (e.g. obesity, Type 2 diabetes, hypertension, and smoking), psychological factors, such as anxiety, depression, and stress, have been associated with an increased risk of some CVDs.[1–3] Negative emotions, including strong anger, may also influence the risk of CVDs. A meta-analysis of nine case-crossover studies found an increased risk of myocardial infarction (MI), acute coronary syndromes, stroke, and ventricular arrhythmia in the 2 h following outbursts of anger.[4] While there is evidence that strong anger may trigger acute cardiovascular events, the long-term influence of anger on CVD events has scarcely been investigated and the scarce available data are inconsistent. Several cohort studies have indicated that anger (higher anger expression, frequent episodes of anger, or trait anger) is linked to higher risk of total CVD,[5] atrial fibrillation (AF),[6] coronary heart disease (CHD),[7,8] heart failure (HF),[9] and CVD mortality,[10] but other cohort studies and meta-analyses showed no such associations[11,12] or demonstrated an inverse relationship with some CVDs such as MI and stroke.[13] There appear to be no cohort studies of anger and the incidence of aortic valve stenosis (AVS) or abdominal aortic aneurysm (AAA). Moreover, it remains unclear whether age, sex, and modifiable factors for CVDs (e.g. metabolic disorders) modify these associations.

Here we report the findings from a population-based cohort study of 47 077 middle-aged and elderly men and women in which we investigated whether the self-reported frequency of episodes of strong anger is associated with the later occurrence of specific CVDs, including MI, HF, AF, AVS, AAA, as well as with overall CVD mortality. In addition, we investigated whether age, sex, and a history of cardiometabolic CVD risk factors modify these associations.

Methods

Study population

We used data from the national research infrastructure SIMPLER (Swedish Infrastructure for Medical Population-based Life-course Environmental Research) that include the Cohort of Swedish Men (COSM) and the Swedish Mammography Cohort (SMC). COSM and SMC are population-based longitudinal cohorts which were designed to investigate the link between dietary exposures, lifestyle, and disease outcomes.[14] Details of the study cohorts have been reported elsewhere.[14] Briefly, the SMC was established between 1987 and 1990, when all women living in Västmanland and Uppsala counties and born between 1914 and 1948 received a questionnaire on dietary habits and other characteristics (90 303 women invited, 74% response rate). The COSM was established in 1997 and included men living in Västmanland and Örebro counties, born between 1918 and 1952 (100 303 men invited, 49% response rate).[14] In 1997, the 56 030 participants of SMC who were still alive and resided in the study area received an expanded diet and lifestyle questionnaire similar to one sent to COSM participants (70%

respond rate).[14] Questionnaire sent to the participants in 1997 did not include questions related to experience of anger. Therefore, information on lifestyle and health characteristics for the present study was obtained with structured questionnaires in 2008 and 2009 supplemented with national registry information. In the present analysis, we excluded individuals who died or had a specific CVD endpoint prior to 1 January 2009, as verified through linkage to the Swedish National Patient and Death Registers. In addition, we excluded those who had missing information on anger (see Supplementary material online, *Figure S1*). This left 47 077 eligible participants (21 442 women and 25 635 men) with a mean baseline age of 70 (56–94) years. In the statistical analysis of each CVD outcome, we excluded individuals with a diagnosis of the corresponding specific CVD before start of a follow up (e.g. those who received diagnosis of AF before baseline were excluded from the analysis of AF), as determined through linkage to the Swedish National Patient Register and based on the International Classification of Diseases (ICD) codes. The number of prevalent CVD cases excluded in each analysis is shown in Supplementary material online, *Figure S1*. The study was conducted following the Helsinki declaration, and has been approved by the Swedish Ethical Review Authority. Participants provided written informed consent.

Exposure and cardiometabolic risk factor assessment

In 2008–9, participants completed questionnaires that included information on how often they experienced strong anger. Frequency of feelings of strong anger was assessed by a single question without a specified period of time: 'How often do you feel strong anger?' A similar single question has been used in previous studies to evaluate anger frequency.[10,13] Participants indicated how many times per day or week they generally experience strong anger. 'Never' or 'seldom' was also possible responses. Individuals were divided into two groups: those who never or seldom felt strong anger and those who indicated generally having feelings of strong anger at least once a week. Educational attainment, employment status, smoking, alcohol consumption, weight, height, physical activity, and history of diabetes, depression, hypertension, and hypercholesterolaemia were assessed with structured questionnaires. A history of diabetes was defined based on the first available record of any type of diabetes mellitus (based on the ICD 8th, 9th, and 10th revision codes) before start of baseline, self-reported diabetes at baseline, glucose-lowering drug prescription (based on the Swedish Prescribed Drug Register), and information from the National Diabetes Register.

Identification of incident cardiovascular disease outcomes, cardiovascular disease–related mortality and follow up

Information regarding specific CVDs and death were obtained by linkage to the Swedish National Patient Register and the Cause of Death Register using the unique personal identification number assigned to all Swedish residents. The Patient Register contains information on all inpatient diagnosis since 1987 and outpatient specialist care since 2001.[15] Incident cases were classified according to the ICD 10th revision codes as follows: acute MI (I21), HF (I50 and I11.0), AF (I48), AVS (I35.0 and I35.2), AAA (I71.3 and I71.4), and CVD mortality (I00–I99, primary cause of death). Participants were followed up from 1 January 2009 to the date of diagnosis of CVD or CVD mortality, death from any cause, or 31 December 2017, whichever occurred first.

Statistical analysis

Descriptive data are presented as mean (standard deviation) or as percentages. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for specific CVDs. The main exposure variable, frequency of the experience of strong anger, was treated as a binary variable (at least once a week vs. never/seldom). A basic model incorporated age (as the time scale) and sex (as a stratification variable). In the first multivariable model, we added social and lifestyle factors as covariates including education (less than high school, high school, or university), employment status (working or not working), cigarette smoking (never, former, or current smokers), alcohol consumption (never drinkers; past or current drinkers of <1 drink/week; <7 drinks/week; 7 to <15 drinks/week; 15–21 drinks/week; or >21 drinks/week), walking/bicycling (never/seldom; <20 min/day; 20–40 min/day; or >40 min/day), and exercise (almost never; <1 h/week; 1 h/week; 2–3 h/week; 4–5 h/week; or ≥5 h/week). In the second multivariable model, we additionally adjusted for body mass index (weight divided by the square of height; <22.5, 22.5–24.9, 25.0–29.9, or ≥30 kg/m^2), and history of hypercholesterolaemia (no/yes), depression (no/yes), diabetes (no/yes), and hypertension (no/yes). Potential confounders were selected using directed acyclic graphs[16] based on our knowledge of the relationships among potential confounders, intermediate variables, exposure, and outcome variables, as well as on existing information regarding factors associated with CVD and anger.

Proportional hazard assumptions were assessed by Schoenfeld's test. We examined multiplicative interactions of the experience of strong anger with sex, age, and a history of metabolic risk factors for CVDs. The proportion of missing data on the potential confounders in the analysis was small (≤3%), and a separate category for variables containing missing values was created. With regard to CVD mortality, we performed a sensitivity analysis additionally excluding individuals who were diagnosed with any CVD before the start of a follow up ($n = 7625$). All statistical tests were two sided, and the analyses were performed using Stata version 15.1 (StataCorp, College Station, TX, USA).

Results

In total, 4266 participants (9%) reported experiencing strong anger once a week or more often. Baseline characteristics of study participants according to frequency of anger episodes are shown in *Table 1* and Supplementary material online, *Table S1*. Compared with participants who seldom or never experienced strong anger, those who indicated frequent episodes were more likely to report a history of depression, but there were only modest differences in age, sex, educational level, employment status, smoking status, alcohol intake, body stature, leisure time physical activity, prevalence of diabetes, and hypercholesterolaemia (*Table 1*).

The numbers of incident CVD events during up to 9 years of follow up can be found in *Figures 1* and *2* and see Supplementary material online, *Table S2*. For example, there were 2640 incident

Table 1 Baseline characteristics of the study participants according to reports of strong anger

Characteristics		Frequency of strong anger	
	All	Never/seldom	At least once a week
Number of participants	47 077	42 811	4266
Age at baseline, years, mean (SD)	70.0 (8.1)	70.2 (8.1)	67.9 (7.4)
Men, %	54.5	54.8	51.3
Education >12 years, %	21.3	20.8	26.1
Full-time or part-time employed, %	26.7	26.1	33.4
Cigarette smoking, %			
Former smokers	36.6	36.1	41.1
Current smokers	8.5	8.4	9.6
Alcohol intake ≥15 drinks/week, %	3.4	3.3	4.4
Walking/bicycling >40 min/day, %	33.3	33.5	31.6
Exercise ≥2 h/week, %	15.0	15.0	15.6
Body mass index, kg/m^2, %			
25.0–29.9	41.6	41.6	41.0
≥30.0	13.3	13.0	15.9
History of depression, %	8.4	7.5	17.3
History of hypertension, %	42.1	42.1	42.3
History of hypercholesterolaemia, %	25.4	25.2	27.0
History of diabetes, %	10.8	10.7	11.8

SD, standard deviation.

HF events identified in this cohort during 377 406 person-years of follow up. In the final multivariable model, frequent episodes of strong anger were associated with a 19% higher risk of HF (HR, 1.19; 95% CI, 1.04–1.37). In addition, a 16% higher risk of AF and 23% higher risk of CVD mortality were found in participants who reported frequent episodes of strong anger (HR, 1.16; 95% CI, 1.06–1.28; and HR, 1.23; 95% CI, 1.09–1.40, respectively; *Figure 1*, see Supplementary material online, *Table S2* and Graphical abstract). We found no link between frequency of self-reported anger and risk of MI, AVS, or AAA (*Figure 1*, see Supplementary material online, *Table S2* and Graphical abstract).

No interaction between frequent experience of strong anger and age was found for any CVD outcome (*P* for interaction >0.60, basic model; in this model, age was added as a covariate, not as the time scale). However, a statistically significant interaction with sex was observed in relation to incidence of HF only (*P* for interaction = 0.04, basic model; in this model, sex was added as a covariate). Subsequent multivariable analyses revealed a significant association of anger frequency and incidence of HF in men (HR, 1.30; 95% CI, 1.10–1.54) but not among women (HR, 1.02; 95% CI, 0.81–1.29; *Figure 2*). In addition, there was a significant interaction of anger with diabetes history in relation to HF (*P* for interaction = 0.048, basic model). The association was more pronounced in participants with a history of diabetes (multivariable HR, 1.39; 95% CI, 1.06–1.84) than in those without a diabetes history (*Figure 2*). No significant interaction of strong anger with BMI, history of hypertension, or hypercholesterolaemia in relation to any CVD outcome was observed (*P* > 0.10, basic model).

In a sensitivity analysis, the findings for CVD mortality were similar after additional exclusion of participants with any CVD before baseline (multivariable HR, 1.28; 95% CI, 1.08–1.53; *n* = 39 452, number of cases = 1811).

Discussion

In our large cohort study, we found positive associations of the frequency of the experience of strong anger with the incidence of HF, AF, and CVD mortality. There was some evidence that the link between frequent episodes of strong anger at baseline and risk of HF varied by sex and history of diabetes. Thus, our findings demonstrate that men as well as participants with a history of diabetes at baseline who experienced frequently strong anger are at particular risk of HF. No evidence of an association of anger frequency with risk of MI, AVS, and AAA was found.

Our findings of a positive association between anger and incident HF agrees with the results from a cohort of 13 171 middle-aged men and women in the USA, which indicated a 26% increased risk of HF in men with high trait anger compared with low trait anger. No evidence of the association of anger-proneness and risk of HF was observed in women in this study.[9] In contrast, a multiethnic population-based study of 6782 initially healthy individuals (242 total incident HF cases) did not find an association of anger and other psychosocial factors with risk of incident HF.[11] The observed inconsistency of these findings with the others could be related to the smaller sample size and relatively small number of cases in the latter study.[11]

Prospective cohort studies evaluating the association of anger and risk of AF are limited and inconsistent. Our analysis indicates that frequent episodes of anger may increase the risk of AF. Another cohort study of 3873 men and women (age range 18–77 years) also

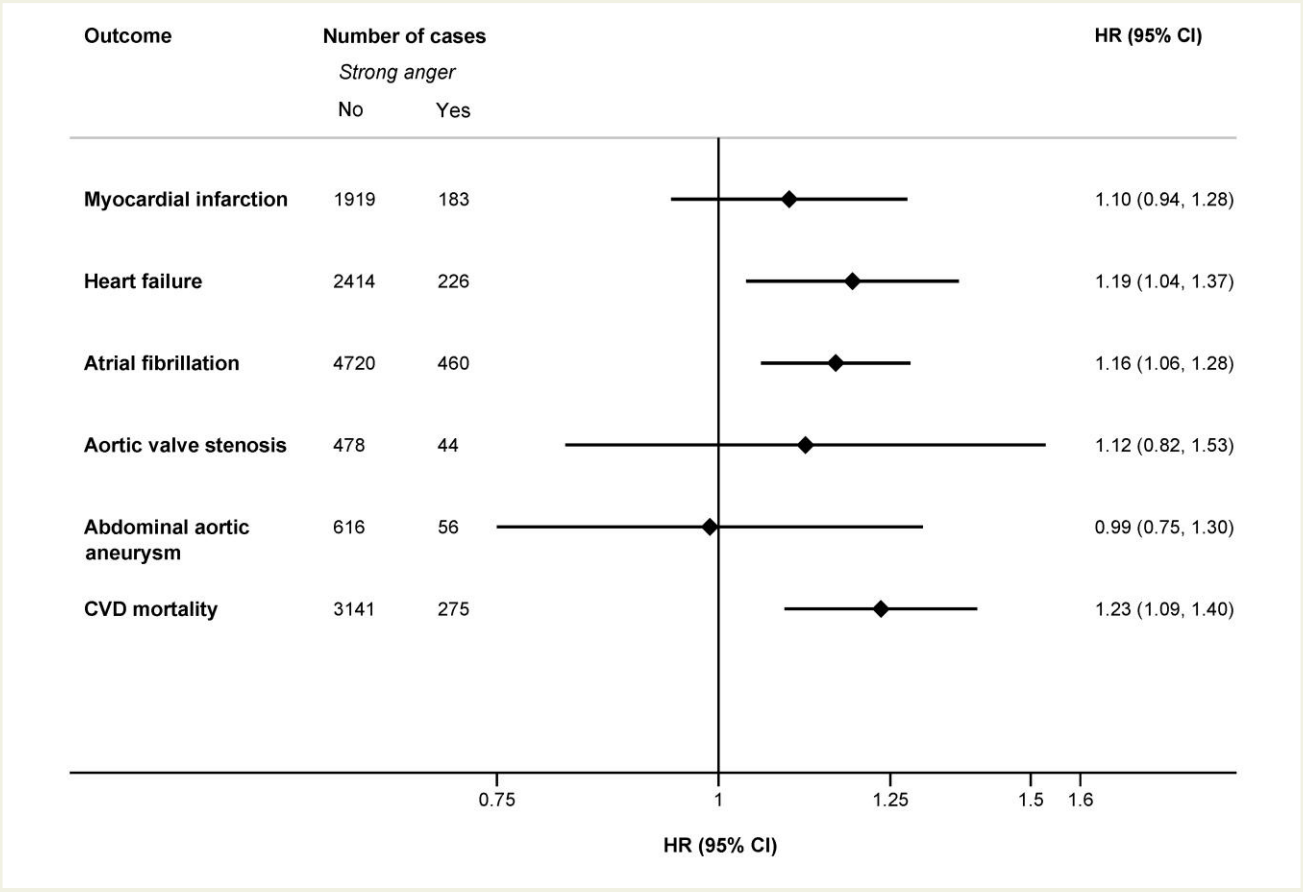


Figure 1 Multivariable hazard ratio (95% confidence interval) of cardiovascular diseases and cardiovascular disease mortality according to reports of frequency of strong anger. The Cox proportional hazards regression model was adjusted for age (underlying time scale), sex (as a stratification variable), education, employment status, cigarette smoking, alcohol intake, walking/bicycling, exercise, body mass index, and history of hypercholesterolaemia, hypertension, diabetes, and depression. CI, confidence interval; HR, hazard ratio.

demonstrated a relationship of measures of anger and hostility and increased risk of AF in men.[6] However, no association of anger and AF risk was observed in a multiethnic study of 6644 participants.[17] Several studies investigated the link of different anger-related measures, mainly hostility, and all-cause mortality risk, indicating a positive association [6,18,19] or null findings.[10,20] In addition, a recent cohort study of 17 352 men reported that frequent episodes of anger are associated with a 17% increased risk of CVD death over the 20-year follow-up period.[10] Our study, which included women as well as men, confirms these findings.

Our results on anger and MI support findings of other cohort studies that did not find a significant association of measures of anger and risk of MI[7,21] but our estimates cannot rule out modestly strong associations. Other cohort studies in men have reported that high levels of hostility or anger are associated with a considerably elevated risk of acute MI.[22,23] Interestingly, a study of 23 522 male health professionals (aged 50–85 years) demonstrated a reduced risk of non-fatal MI during a 2-year follow up in participants with moderate levels of anger-out expression (outwardly expressive behaviour in response to feeling angry), whereas no association of high levels of anger expression and incidence of MI was observed.[13] The conceptual difference between anger, cynical hostility, and aggression used as exposure variables in different studies could explain discrepancies between findings of the studies' in relation to MI. For example, hostility is considered as a cognitive characteristic, a negative aggressive attitude towards other people consisting of denigration, enmity, and ill will.[24] Anger, on the other hand, is a negative emotion of different intensity and as a personality trait, it refers to the tendency to experience frequent episodes of this emotion.[24] Aggression is described as a verbal and physical behaviour involving attacking and destructive actions.[24] We are unaware of any study of anger measures in relation to risk of AVS and AAA.

In the available literature, anger-related measures were evaluated with various instruments (e.g. the Spielberger Trait Anger Scale or Framingham scales[6,10,17] or with a single question of anger frequency[10,13]). The discrepancies in the results of different studies that investigated the relationship with the risk of specific CVDs or CVD mortality may be at least partially explained by differences in methodological tools or small number of cases. In addition, a number of studies had a case-crossover design[25,26] or were performed on populations with pre-existing CVDs,[27–29] and so were open to reporting bias or reverse causation. Another consideration is that the associations of anger with CVDs may vary by ethnicity.[9]

The sex-specific association of anger with HF observed in our study may be related to different ways of anger expression and coping style among women and men,[30] biological (e.g. levels of sex

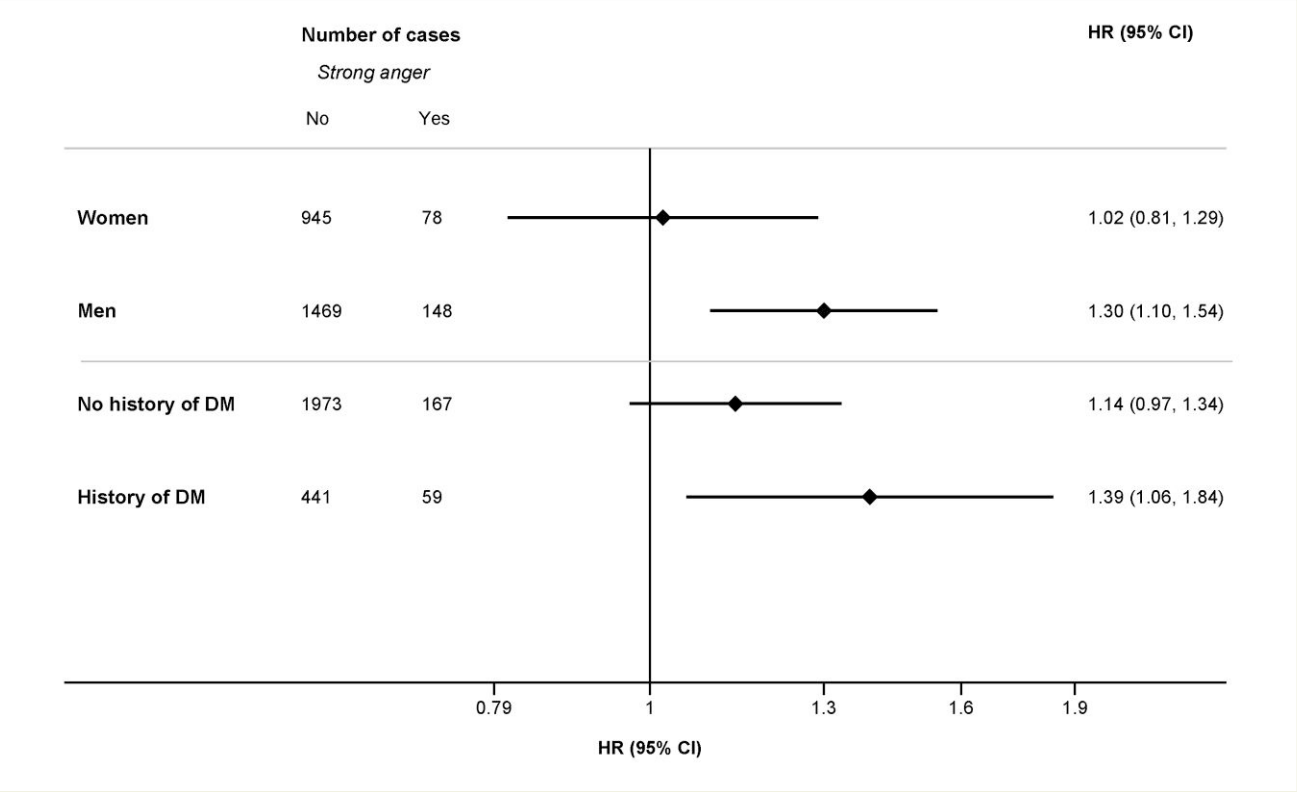


Figure 2 Multivariable hazard ratio (95% confidence interval) of heart failure according to anger frequency stratified by sex and history of diabetes. The Cox proportional hazards regression model was adjusted for age (underlying time scale), sex (as a stratification variable, analysis by diabetes history), education, employment status, cigarette smoking, alcohol intake, walking/bicycling, exercise, body mass index, and history of hypercholesterolaemia, hypertension, diabetes (analysis by sex), and depression. CI, confidence interval; HR, hazard ratio; DM, diabetes mellitus.

hormones)[31] and lifestyle differences, and comorbidities. Several previous studies and meta-analyses have also reported sex-specific relationship of anger measures with CVD events and cardiometabolic risk factors, and demonstrated a stronger association in men than in women.[32,33]

There is still uncertainty in the findings of anger and specific CVDs risk, and factors other than sex and age may influence these associations. Besides sex differences, we have found that the association of anger frequency and risk of HF is stronger in participants with a history of diabetes, suggesting that diabetes may modify this association. Evidence suggests that the prevalence of anxiety and depression is higher in individuals with diabetes mellitus than in healthy controls,[34,35] and mood changes associated with fluctuations of blood glucose levels in participants with insulin-dependent diabetes mellitus have been previously reported.[36] Mood changes such as anger and hostility often accompany depression including patients with diabetes.[37] However, these relationships are likely bidirectional, and psychosocial factors may increase the risk of diabetes.[38] In addition, diabetes is associated with a higher risk of CVDs and CVD mortality.[39] For example, epidemiological and clinical studies report a high prevalence of HF in patients with prediabetes or diabetes.[40]

Although the exact biological mechanism by which anger may increase the risk of specific CVDs remains unknown, several potential pathways may explain the role of anger in the development of CVDs such as exposure to stress and physiological response to stress (e.g. increased heart rate and blood pressure), inflammation, unfavourable lifestyle, and behaviour choices. Irritability and anger can appear as a consequence of acute or chronic stress. Psychosocial stress activates neuroendocrine stress–response systems, the sympathetic–adrenal–medullary system, and hypothalamus–pituitary–adrenal–cortical axis system, which results in release of adrenaline, noradrenaline, and cortisol as well as increased heart rate and blood pressure.[41] For example, anger and hostility have been linked to elevated cortisol levels,[42] which have been associated with cardiometabolic risk factors such as metabolic syndrome components[43] as well as with AF,[44] CVD morbidity[45] and mortality.[46]

Strength and limitations

There are several strengths of our study, including a large sample size providing a large number of cases of a broad range of CVD outcomes, complete case identification with no loss to follow up, adjustment for potential confounders, and inclusion of both women and men. We cannot exclude that pharmacological agents used to treat metabolic conditions and not considered in the present analysis, could affect the expression of anger and risk of CVDs. In addition, as anger was measured with a single question, we cannot distinguish between 'anger-in' (anger suppression and direction it towards themselves) and 'anger-out' (anger expression directed towards

others) behaviours.[47] Furthermore, although we excluded individuals with prevalent specific CVDs based on the ICD codes, participants did not undergo clinical diagnostic investigations at baseline, and therefore we cannot rule out any pre-existing but undiagnosed forms of CVD. We conducted several interaction analyses for several outcomes, and we cannot rule out that the observed interactions are chance findings. Since our study included women and men of mainly northern European origin, our findings might be not generalizable to other ethnic groups. Finally, due to the observational nature of this study, we cannot exclude residual and unmeasured confounding.

Conclusion

In the present study, frequent experience of strong anger was associated with increased risk of HF, AF, and CVD mortality in the initially healthy middle-aged and older individuals. A stronger association of anger frequency with risk of HF was found in men and participants with a history of diabetes. Our findings extend the recent biological and epidemiological findings that anger may contribute to the development of specific CVDs and CVD mortality.

Lead author biography

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Author contributions

O.E.T. and S.C.L. contributed to the conception and design of the study; O.E.T. acquired the data, performed the statistical analysis, and drafted the manuscript. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript.

Data availability

The data that support findings of this prospective cohort study are available upon application to the Swedish Infrastructure for Medical Population-based Life-course Environmental Research (SIMPLER; https://www.simpler4health.se).

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Acknowledgements

The authors thank the national research infrastructure SIMPLER for provisioning of facilities and experimental support. The computations were performed on resources provided by the Swedish National Infrastructure for Computing (www.snic.se) support for sensitive data SNIC-SENS through the Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project SIMP2019004.

Funding

Work of the authors is supported by grants from the Börjeson, Emil and Ragna Foundation (to O.E.T.), PO Zetterlings stiftelse (to O.E.T.); the Swedish Research Council for Health, Working Life and Welfare (Forte; grant number 2018-00123) (to S.C.L.), the Swedish Research Council (Vetenskapsrådet; grant number 2016-01042 and 2019-00977) (to S.C.L.), and the Swedish Heart-Lung Foundation (Hjärt-Lungfonden; grant number 20210351) (to S.C.L.). The study was also supported by additional grants from the Swedish Research Council (https://www.vr.se; grant numbers 2015-03257, 2017-00644, and 2017-06100 to K.M.). SIMPLER receives funding through the Swedish Research Council under the grant number 2017-00644 (to Uppsala University and K.M.). SNIC is financially supported by the Swedish Research Council. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of interest: None declared.

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