Anger frequency and risk of cardiovascular morbidity and mortality

Brief title: Anger frequency and cardiovascular health

Olga E Titova, PhD a*, John A Baron, MD, professor a,b,c, Karl Michaëlsson, MD, professor a, Susanna C Larsson, associate professor a,d,*

a Unit of Medical Epidemiology, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
b Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, USA
c Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA
d Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

*Corresponding authors:
Olga E Titova
Email: olga.titova@surgsci.uu.se
ORCID ID: 0000-0003-2747-1606

Susanna C Larsson
Email: susanna.larsson@surgsci.uu.se
ORCID ID: 0000-0003-0118-0341

Unit of Medical Epidemiology,
Department of Surgical Sciences;
Uppsala University
Dag Hammarskjölds väg 14 B
75185 Uppsala

Twitter: @TitovaOE; @LarssonSC

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Abstract

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 modifies 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.

Conclusions. 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.

Keywords: cardiovascular disease; cardiovascular mortality; anger; sex; cohort; diabetes
Anger frequency and risk of cardiovascular morbidity and mortality

Baseline

Cohort of 47,077 participants (56-94 years of age)

Frequent Anger?
(9% reported strong anger once a week or more often)

46% 54%

Outcomes

Increased risk for:
- Heart failure (2640 cases, 19%)
- Atrial fibrillation (5180 cases, 16%)
- CVD mortality (3416 cases, 23%)

No association with:
- Myocardial infarction (2102 cases)
- Aortic valve stenosis (522 cases)
- Abdominal aortic aneurysm (672 cases)

9 years of follow-up
Introduction

As the major cause of severe long-term disability and premature death, cardiovascular diseases (CVDs) impose a large burden on health care 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.\(^4\) 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 two hours 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 includes 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 diseases outcomes. Details of the study cohorts have been reported elsewhere. 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). 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% response rate). 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 January 1, 2009, as verified through linkage to the Swedish National Patient and Death Registers. In addition, we excluded those who had missing information on anger (Supplementary figure 1). 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 figure 1**. 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 2008-2009, 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.\textsuperscript{10,13} Participants indicated how many times per day or week they generally experience strong anger. “Never” or “seldom” were 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 8\textsuperscript{th}, 9\textsuperscript{th}, and 10\textsuperscript{th} 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 CVD outcomes, CVD-related mortality and follow-up

Information regarding specific CVDs and death was 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. 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 January 1, 2009 to the date of diagnosis of CVD or CVD-mortality, death from any cause, or December 31, 2017, whichever occurred first.

Statistical analysis

Descriptive data are presented as means (standard deviation, SD) 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, current smokers), alcohol consumption (never drinkers; past or current drinkers of <1 drink/week; 1–<7 drinks/week; 7–<15 drinks/week; 15–21 drinks/week; >21 drinks/week), walking/bicycling (never/seldom; <20 min/day; 20-40 min/day; >40 min/day), and exercise (almost never; <1 h/week; 1 h/week; 2-3 h/week; 4-5 h/week; ≥5 hours/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 \(\geq 30\) kg/m\(^2\)), and history of hypercholesterolemia (no/yes), depression (no/yes), diabetes (no/yes), and hypertension (no/yes). Potential confounders were selected using directed acyclic graphs (DAGs) 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 (\(\leq 3\) %), 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, 4,266 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 table 1. 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, and prevalence of diabetes, and hypercholesterolemia (Table 1).
The numbers of incident CVD events during up to 9 years of follow-up can be found in Figure 1-2 and Supplementary table 2. For example, there were 2640 incident 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, Supplementary table 2 and Graphical Abstract). We found no link between frequency of self-reported anger and risk of MI, AVS or AAA (Figure 1, Supplementary table 2 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, 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 hypercholesterolemia 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 US, 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. 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. 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.

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 demonstrated a relationship of measures of anger and hostility and increased risk of AF in men. However, no association of anger and AF risk was observed in a multi-ethnic study of 6644 participants.
Several studies investigated the link of different anger-related measures, mainly hostility, and all-cause mortality risk, indicating a positive association or null findings. 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-years follow-up period. 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 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. Interestingly, a study of 23,522 male health professionals (aged 50 to 85 years) demonstrated a reduced risk of nonfatal MI during a 2-year follow-up in participants with moderate levels of anger-out expression (outwardly expressive behavior in response to feeling angry), whereas no association of high levels of anger expression and incidence of MI was observed. The conceptual difference between anger, cynical hostility and aggression used as exposure variables in different studies could explain discrepancies between studies’ findings 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. 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. Aggression is described as a verbal and physical behavior involving attacking and destructive actions. 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 or with a single question of
anger frequency\textsuperscript{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 \textsuperscript{25,26} or were performed on populations with preexisting CVDs,\textsuperscript{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.\textsuperscript{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 woman and men,\textsuperscript{30} biological (e.g., levels of sex hormones)\textsuperscript{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.\textsuperscript{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,\textsuperscript{34,35} and mood changes associated with fluctuations of blood glucose levels in participants with insulin-dependent diabetes mellitus have been previously reported.\textsuperscript{36} Mood changes such as anger and hostility often accompany depression including patients with diabetes.\textsuperscript{37} However, these relationships are likely bidirectional, and psychosocial factors may increase the risk of diabetes.\textsuperscript{38} In addition, diabetes is associated with a higher risk of CVDs and
CVD mortality.\textsuperscript{39} For example, epidemiological and clinical studies report a high prevalence of HF in patients with prediabetes or diabetes.\textsuperscript{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, unfavorable lifestyle, and behavior 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.\textsuperscript{41} For example, anger and hostility have been linked to elevated cortisol levels,\textsuperscript{42} which have been associated with cardiometabolic risk factors such as metabolic syndrome components\textsuperscript{43} as well as with AF,\textsuperscript{44} CVD morbidity\textsuperscript{45} and mortality.\textsuperscript{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) behaviors.\textsuperscript{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 preexisting 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.

Conclusions

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.

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decision to submit the manuscript for publication.

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**Authors’ 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.

**Conflicts of Interest:** The authors declare no conflict of interest.

**Patient and public involvement:** Patients and/or the public were not involved in the design, or
conduct, or reporting, or dissemination plans of this research.

**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 figure 1 and Supplementary Table 1 and 2.
References


29. Frasure-Smith N, Lesperance F. Depression and other psychological risks following myocardial infarction. *Arch Gen Psychiatry* 2003;60:627-636.


FIGURE LEGENDS

Figure 1. Multivariable HR (95% CI) of CVDs and CVD 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 hypercholesterolemia, hypertension, diabetes, and depression.

CI, confidence interval; HR, hazard ratio

Figure 2. Multivariable HR (95% CI) 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 hypercholesterolemia, hypertension, diabetes (analysis by sex) and depression.

CI, confidence interval; HR, hazard ratio; DM, diabetes mellitus.
Table 1. Baseline characteristics of the study participants according to reports of strong anger

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frequency of strong anger</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Number of participants</td>
<td>47,077</td>
</tr>
<tr>
<td>Age at baseline, years, mean (SD)</td>
<td>70.0 (8.1)</td>
</tr>
<tr>
<td>Men, %</td>
<td>54.5</td>
</tr>
<tr>
<td>Education &gt; 12 years, %</td>
<td>21.3</td>
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<tr>
<td>Full-time or part-time employed, %</td>
<td>26.7</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>36.6</td>
</tr>
<tr>
<td>Current smokers</td>
<td>8.5</td>
</tr>
<tr>
<td>Alcohol intake ≥ 15 drinks/week, %</td>
<td>3.4</td>
</tr>
<tr>
<td>Walking/bicycling &gt; 40 min/day, %</td>
<td>33.3</td>
</tr>
<tr>
<td>Exercise ≥ 2 hour/week, %</td>
<td>15.0</td>
</tr>
<tr>
<td>Body mass index, kg/m2, %</td>
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</tr>
<tr>
<td>25.0-29.9</td>
<td>41.6</td>
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<tr>
<td>≥ 30.0</td>
<td>13.3</td>
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<td>History of depression, %</td>
<td>8.4</td>
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<tr>
<td>History of hypertension, %</td>
<td>42.1</td>
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<tr>
<td>History of hypercholesterolemia, %</td>
<td>25.4</td>
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<tr>
<td>History of diabetes, %</td>
<td>10.8</td>
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Abbreviations: SD, standard deviation.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1919 / 183</td>
<td>1.10 (0.84, 1.46)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2414 / 226</td>
<td>1.19 (1.04, 1.37)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4720 / 460</td>
<td>1.16 (1.06, 1.27)</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>478 / 44</td>
<td>1.12 (0.82, 1.53)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>616 / 56</td>
<td>0.99 (0.75, 1.30)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>3141 / 275</td>
<td>1.23 (1.09, 1.40)</td>
</tr>
</tbody>
</table>

Figure 1
305x237 mm (x DPI)
<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
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<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Women</td>
<td>945</td>
<td>78</td>
</tr>
<tr>
<td>Men</td>
<td>1469</td>
<td>148</td>
</tr>
<tr>
<td>No history of DM</td>
<td>1973</td>
<td>167</td>
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<tr>
<td>History of DM</td>
<td>441</td>
<td>59</td>
</tr>
</tbody>
</table>

Figure 2

237x169 mm (x DPI)
Susanna Larsson is currently a Senior Lecturer at the Department of Surgical Sciences, Uppsala University, Sweden and affiliated with the Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. She has a PhD degree from 2006 from Karolinska Institutet, and she became an Associate Professor of epidemiology in 2011. Her research is focused on identifying the causes of cardiovascular diseases and other chronic diseases.