TITLE PAGE

Title: Incidence of 12 common cardiovascular diseases and subsequent mortality risk in the general population

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ABSTRACT

Background: Incident events of cardiovascular diseases (CVD) are heterogenous and may results in different mortality risks. Such evidence may help inform patient and physician decisions in CVD prevention and risk factor management.

Aim: To determine the extent to which incident events of common CVD show heterogeneous associations with subsequent mortality risk in the general population.

Methods: Based on England-wide linked electronic health records, we established a cohort of 1,310,518 people ≥30 years of age initially free of CVD and followed up for non-fatal events of 12 common CVD and cause-specific mortality. The 12 CVD were considered as time-varying exposures in Cox's proportional hazards models to estimate hazard rate ratios (HRR) with 95% confidence intervals (CI).

Results: Over the median follow-up of 4.2 years (2010-2016), 81,516 non-fatal CVD, 10,906 cardiovascular deaths, and 40,843 non-cardiovascular deaths occurred. All 12 CVD were associated with increased risk of cardiovascular mortality, with HRR (95% CI) ranging from 1.67 (1.47-1.89) for stable angina to 7.85 (6.62-9.31) for haemorrhagic stroke. All 12 CVD were also associated with increased non-cardiovascular and all-cause mortality risk but to a lesser extent: HRR (95% CI) ranged from 1.10 (1.00-1.22) to 4.55 (4.03-5.13) and from 1.24 (1.13-1.35) to 4.92 (4.44-5.46) for transient ischaemic attack and sudden cardiac arrest, respectively.

Conclusions: Incident events of 12 common CVD show significant adverse and markedly differential associations with subsequent cardiovascular, non-cardiovascular, and all-cause mortality risk in the general population.

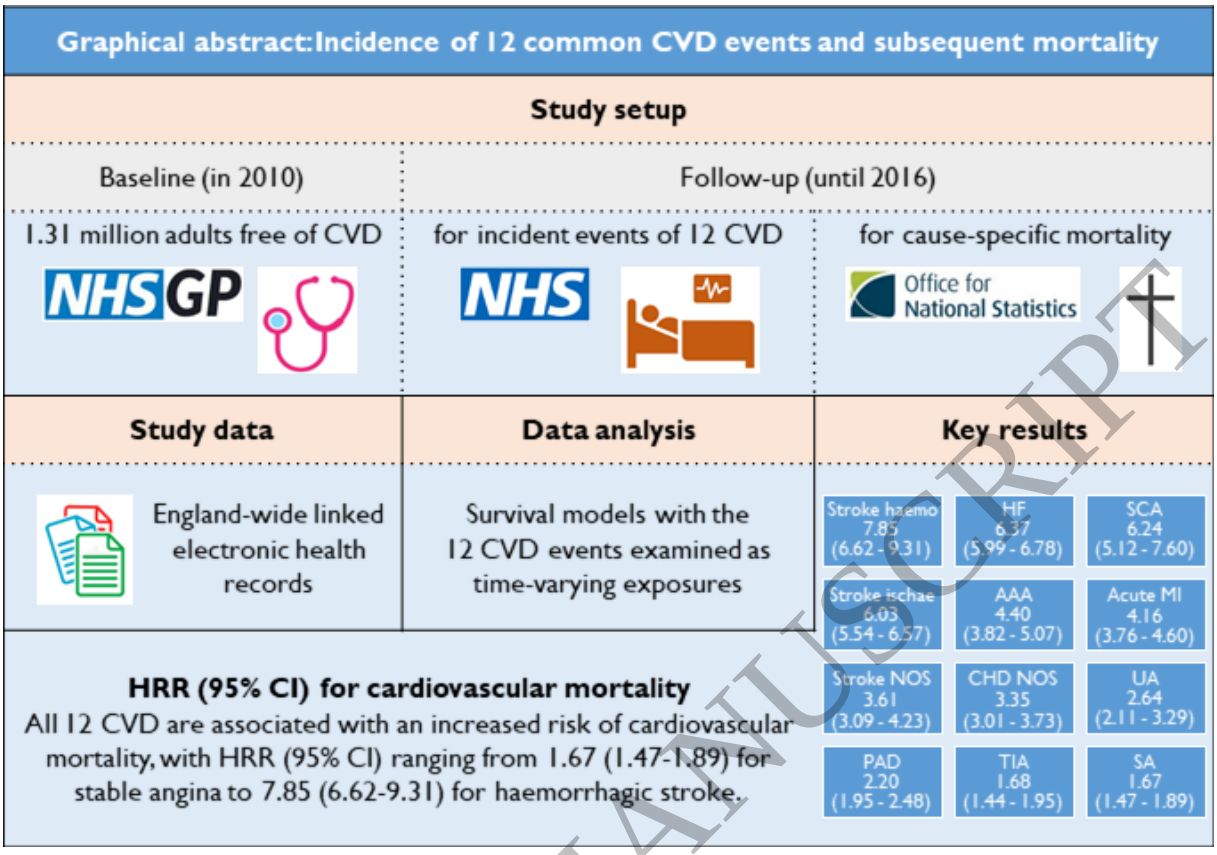
Abstract word count: 233 words

LAY ABSTRACT

We linked data available for 1.31 million people seen by English general practitioners in 2010 with data from hospital admissions and death certificates up to 2016 to investigate the risk of death in people who suffered from any of 12 common cardiovascular diseases (CVD) compared to those who did not.

- The results show heterogeneously increased risks of death in people who suffered from any of 12 common CVD when compared to people who remained CVD free
- The results support efforts of prevention for the entire spectrum of CVD including alleged minor types such as stable angina and transient ischaemic attack.

GRAPHICAL ABSTRACT



KEYWORDS

Coronary heart disease, stroke, epidemiology, incidence, prevention, survival analysis

INTRODUCTION

Incident cardiovascular disease (CVD) events are heterogenous and may therefore result in different mortality risks. Evaluating the mortality risk according to the initial CVD event may help inform patient and physician decisions in CVD prevention and risk factor management, identify best practices as well as missed opportunities in health care services, and orientate public health priorities and strategies. We previously investigated mortality risks after non-fatal coronary heart disease (CHD) and stroke in a cohort of middle-aged male Caucasians from France and Northern Ireland. The study showed a markedly increased all-cause mortality risk in the period after CHD and even more so after stroke - when compared to periods up to the occurrence of these CVD. [1] However, these preliminary findings need to be extended

considering the diversity of CVD and the possible influence of sex, age, ethnicity, and patient care. [2]

England-wide linked electronic health records, which combine primary care, hospital episodes, and death registry data, offer the opportunity to address these further questions. [3,4] We thus set up a study based on this data in which we dissociate periods up to and after 12 distinct incident CVD events. [5] This study compares for the first time mortality risks before and after various CVD events in the general population. The main study objective was to determine the extent to which non-fatal CVD events show heterogeneous associations with subsequent cardiovascular mortality (primary outcome) and non-cardiovascular as well as all-cause mortality (secondary outcomes). Further study objectives were to assess whether associations of non-fatal CVD events with cardiovascular mortality differed by sex, age, ethnicity, and referral for rehabilitation.

METHODS

Study design

This is a cohort study among English practitioner-registered patients initially free of CVD and followed up for the occurrence of 12 common CVD (exposures) and cardiovascular, non-cardiovascular, and all-cause mortality (outcomes). Each of the 12 CVD events was defined as the first recorded diagnosis in primary care, secondary care, or at death. In this study, we dissociate periods up to and after incident non-fatal CVD events. This approach enables to contrast the mortality risk after the incidence of CVD with a baseline mortality risk in the period up to its occurrence.

Linked data and study setup

We used linked electronic health records from the UK Clinical Practice Research Datalink (CPRD), the Hospital Episodes Statistics (HES), and the Office for National Statistics (ONS):

CPRD and HES data to define exposures, outcomes, and covariates, and ONS data to obtain information on date and cause of death in the deceased. People free of CVD entered the study when seen in primary care, i.e., when first recorded in the CPRD after the baseline date. Data on hospitalized CVD syndromes, both fatal and non-fatal, derived from hospital records of people as recorded in the HES Admitted Patient Care (APC) dataset. Cause-specific mortality from the ONS served to define the study endpoints, i.e., cardiovascular, non-cardiovascular, and all-cause death, and to identify fatal non-hospitalized CVD. The study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare Product Regulatory Agency (protocol 17_209).

Study period and population

The study period was from January 06, 2010 to June 27, 2016. We performed analyses in people who were eligible for all linkages and fulfilled the following criteria:

- People were registered at an English practice participating in the CPRD and consenting to data linkage, and they had not opted out or dissented from CPRD or the linkage scheme.
- Their practice was deemed to be contributing 'up-to-standard' data (with regard to recording continuity and deaths recorded) at least one year prior to the study start date.
- Their patient record was of acceptable data quality (based on registration status, recording of events, and validity of age and sex) as verified by the CPRD.

In terms of the population inclusion and exclusion criteria, patients fulfilled the following:

- 30 years or older at study start date or turned 30 years during the study period time
- No history of the CVD considered prior to entering the cohort

We followed people up until the earliest of the following dates:

- Date of death as defined by ONS
- Date a patient transferred out of a CPRD practice
- Practice last collection date

- Study end date

Incident CVD events

We used validated definitions of CVD based on CPRD and HES data.[6] Please see the Supplementary Materials for specifications. The 12 CVD considered comprise acute myocardial infarction, unstable angina, chronic stable angina, CHD not otherwise specified, ischaemic stroke, haemorrhagic stroke, stroke not otherwise specified, transient ischaemic attack, abdominal aortic aneurysm, peripheral artery disease, sudden cardiac arrest, and heart failure. The algorithms used to specify the CVD are available online. Link

Mortality outcomes

We specified cardiovascular mortality as the primary outcome and non-cardiovascular mortality as well as all-cause mortality as secondary outcome measures. We defined cardiovascular mortality as death from causes as recorded in the ONS data based on ICD-10 codes provided in the Supplementary Materials. We defined non-cardiovascular mortality as death from all other causes (= all-cause deaths – cardiovascular deaths) and all-cause mortality as death from any cause.

Covariates

We considered established risk and lifestyle factors as covariates in the analysis. Ethnic group was self-reported, categorized by 2001 Census categories, and recorded in the HES. Quintiles of socioeconomic deprivation followed the Index of Multiple Deprivation 2007 at the small area level. Smoking status distinguished never, ex-, and current smokers based on the closest recording in the period one year before to one year after study entry, if available and based on recordings older than one year before study entry otherwise. Blood pressure lowering and diabetes treatment reflect recordings of corresponding prescriptions at any time up to one year

after study entry. Lipid lowering treatment reflects a recording of statins prescribed from one year before to one year after study entry. We considered recordings of referral to rehabilitation within six months after incident CVD events.

Statistical analysis

We used descriptive statistics to present characteristics of the study population at baseline, overall and by sex, incident CVD, and referral to rehabilitation. We used Cox's proportional hazards models to estimated hazard rate ratios (HRR) with 95% confidence intervals (CI) for associations of CVD events with mortality. The models included non-fatal CVD during follow-up as time-dependent exposure variables. The unexposed and exposed groups thus changed during the follow-up.[7] People with incident CVD contributed person-time to the denominator of the unexposed up to the date of their event. People then contributed person-time to the exposed of the specific CVD, if they survived at least the first 28 days after the event. If they died within these 28 days, then they did not contribute person-time to the exposed (since we censored follow-up at event), in accordance with commonly used definitions for fatal CVD events.[8,9] Individuals without incident CVD contributed person-time to the unexposed until the end of follow-up or their date of death. For people suffering from CVD more than once, we only considered the first event in the models. The estimated HRR depict the total effect (composed of direct and indirect effects) of the first event on mortality and thus account for subsequent events as intermediates (i.e., indirect effects).

We conducted the following analysis steps to address our research aims:

a) In the main analysis, we ran separate models for each of the 12 CVD and cardiovascular-, non-cardiovascular, and all-cause mortality (36 models) adjusting for age (continuous), sex (women/men), ethnicity (white, non-white, and unknown), socioeconomic deprivation (quintiles), smoking status (never, ex, current), diabetes treatment (yes/no), and blood pressure as well as lipid lowering treatment (both yes/no).

b) For subgroup analyses, we ran separate models for each of the 12 CVD and cardiovascular mortality stratified by sex (24 models), age tertiles (36 models), and five ethnic groups (60 models) adjusting for the above variables except the stratification variable. We then added interaction terms of the time-dependent CVD exposure variable with sex and with age in 12 separate models.

c) For analysis by referral to rehabilitation, we ran separate models for each of the 12 CVD and cardiovascular mortality (12 models) adjusting for the above variables and including an interaction term of the time-dependent CVD exposure variable with rehabilitation.

We conducted complete case analyses since long processing time of our models hampered multiple imputations. In sensitivity analyses, we examined the robustness of estimates. First, we ran models for cardiovascular mortality after simple imputations inserting categories for missing values in smoking status (29.38%), ethnicity (26.95%), and socioeconomic deprivation (0.06%). Second, we subdivided acute myocardial infarction into ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and myocardial infarction not otherwise specified. Third, we updated the covariates diabetes treatment as well as blood pressure and lipid lowering treatment after incident CVD using them as time-varying variables. A p-value <0.05 was considered to be statistically significant. P-values from the analyses with interaction terms were adjusted by the Bonferroni method. We conducted the statistical analysis using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Reporting

Reporting follows the STROBE checklist for cohort studies (Supplementary Materials). A flow chart details the number of persons included and excluded from the eligible population (Supplemental Figure).

RESULTS

Overall, 1,310,518 people were eligible for analysis. Table 1 presents characteristics of the study population at baseline. Mean age was 51.02 (standard deviation (SD) 16.08) years and 58.13% were women. During follow up, 86,516 non-fatal CVD occurred, and 51,749 people died, 10,906 due to cardiovascular causes and 40,843 due non-cardiovascular causes. Median follow-up time for mortality was 4.16 (interquartile range 2.15-5.94) years. Referral to rehabilitation within six months was recorded in 3,018 (3.70%) CVD manifestations.

Differences between groups

When compared to people without CVD, people with CVD during follow-up were older and more frequently were men, ex- or current smokers, and using blood pressure and lipid lowering as well as diabetes treatment at baseline (Supplemental Table 1). Mean age at CVD events was 70.22 (SD 14.00) years and differed between women (72.82 (SD 14.23)) and men (68.02 (SD 13.41), $p<0.001$), non- (72.90 (SD 14.04)), ex- (73.31 (12.40)), and current smokers (63.59 (SD 13.26), $p<0.001$), and people with (73.59 (SD 12.75)) and without BP treatment (65.43 (14.29), $p<0.001$) at baseline.

Associations with mortality

Figure 1 presents HRR and 95% CI for associations of the CVD events with cardiovascular (1A), non-cardiovascular (1B), and all-cause mortality (1C). For exact figures, please refer to Supplemental Table 2. All 12 CVD were associated with an increased risk of cardiovascular mortality, with HRR ranging from 1.67 (95% CI 1.47-1.89) for stable angina to 7.85 (95% CI 6.62-9.31) for haemorrhagic stroke. The hazard rates for non-cardiovascular and all-cause mortality also increased with all 12 CVD, but at lower levels.

Subgroup-specific associations

Table 2 and Table 3 show associations of CVD with cardiovascular mortality by sex and age groups. HRR are higher in women than men for ischaemic stroke, and this sex interaction was statistically significant. HRR are higher in younger than older age with significant age interactions in heart failure, peripheral artery disease, myocardial infarction, stable angina, sudden cardiac arrest, and coronary heart disease not otherwise specified. Results by ethnic groups show wide 95% CI with a tendency towards higher HRR for most CVD in minorities compared to whites (Supplemental Table 3).

Referral for rehabilitation and associations with cardiovascular mortality

Women were less frequently referred for rehabilitation within six months after a CVD event than men. People referred less frequently had BP and lipid lowering as well as diabetes treatment at baseline (Supplemental Table 4). Associations of heart failure, myocardial infarction, and haemorrhagic stroke with cardiovascular mortality are attenuated among people who were referred to rehabilitation within six months compared to those who were not, indicated by statistically significant interactions (Supplemental Table 5).

Sensitivity analysis

In the sensitivity analysis, the results are largely consistent with those from the main analysis after simple imputations and when updating diabetic and blood pressure as well as lipid lowering treatment (Supplemental Table 6). We observed less pronounced associations for STEMI as compared to NSTEMI and myocardial infarction not otherwise specified (Supplemental Table 7).

DISCUSSION

In 1.31 million adult people from the general population in England, we compared the all-cause and cause specific mortality risk before and after incident events of 12 common CVD. All 12 CVD were associated with increased mortality risks, but the strengths of associations ranged widely. Associations between incident CVD and cardiovascular mortality differed between women and men, age categories, and ethnic groups. Referral to rehabilitation within six months was associated with lower cardiovascular mortality risk after several CVD.

Interpretation of results

The main analysis shows that even so-called 'soft' types of CVD, i.e., stable angina and transient ischaemic attack, increase the risk of cardiovascular mortality – by approximately 70%, the smallest but still relevant associations among all CVD studied. Less surprising were our findings showing an increased cardiovascular mortality risk after other CVD. However, our results offer insights into associations of a spectrum of CVD enabling to rank their importance for longevity. In terms of cardiovascular mortality risk, haemorrhagic stroke, heart failure, sudden cardiac arrest, and ischaemic stroke stand out; the remaining CVD exert a lower and gradually decreasing mortality risk, from acute abdominal aneurysm to peripheral artery disease. Although some of the CVD studied may belong to the same portion of the disease spectrum, our results showing heterogeneous associations for these CVD emphasize the importance of granularity.

Subgroup analyses indicate ischaemic stroke is more important for cardiovascular mortality in women than in men. A recent individual participant meta-analysis of observational studies supports this finding showing higher long-term mortality after stroke in females than males. [10] Further, our study shows six out of 12 CVD and thus half of investigated CVD have a stronger association with cardiovascular mortality when presented already in younger as compared to older age. This finding further supports the importance of starting early in life

the primary prevention of CVD in general and the primordial prevention of those CVD in particular (i.e., preventing the onset of risk factors in the first place). [11]

Our results further show lower strengths of associations with referral to rehabilitation in heart failure, acute myocardial infarction, and haemorrhagic stroke. This is consistent with evidence from meta-analyses of randomized controlled trials (RCTs) showing a beneficial effect of exercise-based rehabilitation on mortality in CHD and heart failure patients. [12,13] A recent meta-analysis of RCTs could not determine whether exercise training reduces mortality in stroke patients due to few fatal events observed. [14] Our current study based on large numbers of observations suggests that such an effect is present in haemorrhagic stroke.

Comparison with previous studies in the field

Using a similar approach in almost 10,000 Caucasian men 50 to 59 years of age from France and Northern Ireland in the PRIME study, we previously related incidence of CHD (HRR 1.58, 95% CI 1.18-2.12) and stroke (HRR 3.13, 95% CI 1.98-4.92) to an increased all-cause mortality risk over 10 years. [1] In that study, CHD and stroke were specified as broad phenotypes including myocardial infarction and stable as well as unstable angina and strokes of ischaemic, haemorrhagic, and unspecified origin. [15,16] In the current study, we could thus refine the results from this prior investigation, dissociating incident events of 12 common CVD and cardiovascular as well as non-cardiovascular mortality. Moreover, we extended the analysis to a >100 times larger sample, to both sexes, categories of age, and ethnic groups, and we considered rehabilitation in the analysis.

We are not aware of any other study, despite our previous investigation that assessed associations of incident CVD with mortality outcomes within the same study population.[1] Previous studies mostly investigated all-cause mortality of CVD patients using external reference populations (e.g., the general population) for comparison and focusing on selected CVD. For example, a hospital-based study in Nijmegen, the Netherlands with mean follow-up

duration of 11 years reported standardized mortality ratios (SMRs) of 2.6 (95% CI 1.8-3.7), 3.9 (95% CI 3.2-4.7), and 3.9 (95% CI 1.9-7.2) in 30-day survivors of transient ischaemic attack, ischaemic stroke, and haemorrhagic stroke, respectively (aged 18-50 years; admitted in 1980-2010). [17] A hospital-based study in Paris, France with a mean follow-up time of 28 months reported a SMR of 3.49 (95% CI 2.42-4.85) in intensive care unit survivors of out-of-hospital cardiac arrest (aged >75 years; admitted in 2000-2009). [18] A study in 71 primary care offices among Swiss outpatients with heart failure (mean age: 75 years; enrolled in 1999) reported a one-year SMR of 3.0 (95% CI 2.3-3.9). [19] A study based on the national Norwegian Prescription Database observed one-year SMRs in heart failure patients (aged ≥18 years) of 2.01 (95% CI 1.97-2.06) and 1.84 (95% CI 1.78-1.87) in 2013 and 2016, respectively. [20] A national study in New Zealand among patients with a discharge diagnosis of acute coronary syndrome (median age: 70 years; enrolled in 2002) followed up over 12.7 years on average observed a SMR of 1.3 (95% CI 1.2-1.5). [21]

Comparison with studies from other fields

A comparison with previous studies on other life events and mortality may help framing our results. [22,23] Associations of stable angina and transient ischaemic attack with cardiovascular mortality in our study are similar in size as the association of a first presentation of atrial fibrillation with all-cause mortality (HHR 1.7, 95% CI 1.5-2.2) in the Framingham Heart Study cohort 2001-2015. [24] The associations of more important CVD in our study are of similar size as the association of type-2 diabetes (T2D) with cardiovascular mortality in the first 2 years after T2D onset in elderly people (HRR 4.3, 95% CI 1.7-10.8) as shown by the Cardiovascular Health Study. [25] The strongest associations in our study are similar in size to the association of four or more comorbidities (including stroke, heart failure, myocardial infarction, and peripheral artery disease) – as compared to none – with cardiovascular

mortality in the first year after T2D diagnosis (HRR 6.91, 95% CI 6.08-7.84) another study based on the CPRD showed. [26]

Implications

Our main results support efforts of prevention for the entire spectrum of CVD including alleged minor CVD such as stable angina and transient ischaemic attack. They may provide physicians and their patients with convincing arguments for the management of risk factors and the preservation of cardiovascular health: controlling risk factors already in place (primary prevention) is crucial, preventing the onset of risk factors (primordial prevention) is even better. [27] Higher risk factor levels at baseline in people with as compared to people without CVD events during follow-up and higher mean age at the time of CVD events of people with as compared to those without baseline risk factors underline the importance of preventive efforts. Our study results further indicate referral to rehabilitation is both a best practice and missed opportunity, particularly after heart failure, myocardial infarction, and haemorrhagic stroke. These findings support efforts to increase the awareness among CVD patients and their treating physicians on the underutilization of rehabilitation and the potential impact of such programs on subsequent mortality risk. Of note, less than four percent of CVD events were referred to rehabilitation within six months. Not all CVD patients in our sample may have been eligible for referral, however, ineligibility cannot explain the observed low referral rate. The National Heart Failure Audit 2017/2018 based on hospital admissions in England and Wales showed about 15% of patients were referred for cardiac rehabilitation during hospitalization with enormous variations between settings indicating the need to investigate referral practice and barriers. [28]

Limitations

Data on physical activity and diet were not available for analysis because not captured systematically. We considered use of blood pressure and lipid lowering medication as proxies for high lipid and blood pressure levels, which were irregularly recorded with lag time mostly greater than one year. We lacked registry data of acute myocardial infarction, which can affect the positive predictive value of recordings.[29] However, this may have led to an underestimated strength of association for this CVD type, if any. Interpretation of results in the youngest age group needs caution due to the few CVD events observed. Despite stratified analysis by ethnicity, most patients belonged to the white group; further analyses should thus examine populations that are more diverse. People referred to rehabilitation may have been healthier than those who were not referred as indicated by drug treatment at baseline. Records on referral may have been less complete in primary care than in hospital, i.e., for late than early referral. Taken together, associations of CVD with referral should be interpreted with caution. The study is reflecting risk factor prevalence and general as well as clinical practice in England between 2010 and 2016. Future studies should evaluate the external validity both in terms of geography (i.e., outside the study region) and time (i.e., outside the study period).

Conclusion

Based on linked electronic health records from England, our study points out significant adverse and markedly heterogeneous associations of 12 common incident CVD events with subsequent cardiovascular, non-cardiovascular, and all-cause mortality in the general population.

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a research resource providing validated electronic health record phenotyping algorithms and tools for national structured data sources. This study is based on data from the Clinical Practice Research Datalink obtained under license from the Medicines and Healthcare Products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone.

FUNDING

No funding.

DECLARATION OF INTERESTS

All authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

CP had the original research idea. CP, MCP, and JPE designed the methodological approach. AGI prepare the data. MCP analysed the data. CP, MCP, and JPE interpreted the data. CP wrote the report. JPE commented on drafts of the report. MCP, AGI, HH, and JPE critically reviewed and commented the report. MCP and AGI assessed and verified the data. All authors gave final approval and agree to be accountable for all aspects of the work.

DATA AVAILABILITY

CALIBER has access to anonymised patient data solely for the purpose of research under the terms of a multi-study agreement with the Clinical Practice Research Datalink (CPRD). Due to privacy laws and the data user agreement between UCL and CPRD, researchers are not authorised to share individual patient data. No record-level data are exported outside the Data Safe Haven and no data are shared with any third-party organisation or user.

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FIGURE LEGENDS

Figure 1: A) Associations of 12 incident CVD events with cardiovascular mortality. B) Associations of 12 incident CVD events with non-cardiovascular mortality. C) Associations of 12 incident CVD events with all-cause mortality

Hazard rate ratios with 95% confidence intervals from separate Cox's proportional hazards models adjusted for baseline age, sex, ethnicity, social deprivation, smoking status, diabetes treatment, and blood pressure and lipid lowering treatment are presented. CVD is a time-dependent exposure variable.

95% CI: 95% confidence interval, AAA: abdominal aortic aneurysm, CHD NOS: coronary heart disease not otherwise specified, CVD: cardiovascular disease, HF: heart failure, MI: myocardial infarction, PAD: peripheral artery disease, SA: stable angina, SCA: sudden cardiac arrest, Stroke NOS: stroke not otherwise specified, TIA: transient ischaemic attack, UA: unstable angina

Graphical abstract: Incidence of 12 common CVD events and subsequent mortality

95% CI: 95% confidence interval, AAA: abdominal aortic aneurysm, CHD: coronary heart disease, CVD: cardiovascular disease, HF: heart failure, HRR: hazard rate ratio, MI: myocardial infarction, NOS: not otherwise specified, PAD: peripheral artery disease, SA: stable angina, SCA: sudden cardiac arrest, Stroke haemo: haemorrhagic stroke, Stroke ischae: ischaemic stroke, TIA: transient ischaemic attack, UA: unstable angina

1 **Table 1:** Baseline characteristics of the study population

Characteristic	All (N=1,310,518)	Men (N=548,720)	Women (N=761,798)
Age, years, mean (SD)	51.02 (16.08)	51.93 (15.34)	50.36 (16.57)
Index of multiple deprivation, n (%)			
Quintile 1	291,470 (22.24)	119,572 (21.79)	171,898 (22.56)
Quintile 2	287,776 (21.96)	119,488 (21.78)	168,288 (22.09)
Quintile 3	271,045 (20.68)	113,731 (20.73)	157,314 (20.65)
Quintile 4	247,560 (18.89)	104,382 (19.02)	143,178 (18.79)
Quintile 5	212,667 (16.23)	91,547 (16.68)	121,120 (15.90)
Ethnicity, n (%)			
Black	29,244 (2.23)	10,606 (1.93)	18,638 (2.45)
Mixed	35,017 (2.67)	13,247 (2.41)	21,770 (2.86)
South Asia	44,504 (3.40)	17,213 (3.14)	27,291 (3.58)
White	1,131,739 (86.36)	472,214 (86.06)	659,525 (86.57)
Unknown	70,014 (5.34)	35,440 (6.46)	34,574 (4.54)
BP lowering treatment, n (%)	375,590 (28.66)	156,290 (28.48)	219,300 (28.79)
Diabetes treatment, n (%)	106,599 (8.13)	53,042 (9.67)	53,557 (7.03)
Lipid lowering treatment, n (%)	188,946 (14.42)	97,991 (17.86)	90,955 (11.94)
Smoking status, n (%)			
Never smoker	581,367 (44.36)	194,965 (35.53)	386,402 (50.72)
Ex-smoker	320,367 (24.45)	149,691 (27.28)	170,676 (22.40)
Current smoker	408,784 (31.19)	204,064 (37.19)	204,720 (26.87)
Birth cohort, n (%)			
≤1947	332,171 (25.35)	143,908 (26.23)	188,263 (24.71)

>1947 – ≤1959	260,792 (19.90)	123,424 (22.49)	137,368 (18.03)
>1959 – ≤1968	247,791 (18.91)	109,396 (19.94)	138,395 (18.17)
>1968 – ≤1976	226,338 (17.27)	87,990 (16.04)	138,348 (18.16)
>1976	243,426 (18.57)	84,002 (15.31)	159,424 (20.93)

1

2 BP: blood pressure, SD: standard deviation

Table 2: Associations of 12 incident CVD events with cardiovascular mortality by sex

	Men (N=548,720)		Women (N=761,798)		p-value* for sex
CVD event	exposed, n	HRR (95% CI)	exposed, n	HRR (95% CI)	interaction
AAA	2,286	4.31 (3.64 ; 5.10)	773	5.02 (3.87 ; 6.52)	1.00
HF	7,363	6.73 (6.15 ; 7.38)	8,021	6.07 (5.58 ; 6.61)	1.00
PAD	4,443	2.32 (1.98 ; 2.73)	3,427	2.08 (1.73 ; 2.49)	1.00
Acute MI	6,948	3.83 (3.33 ; 4.41)	3,949	4.53 (3.91 ; 5.23)	0.54
SA	6,993	1.80 (1.52 ; 2.13)	6,056	1.51 (1.24 ; 1.84)	1.00
UA	1,510	3.16 (2.38 ; 4.20)	1,217	2.10 (1.48 ; 2.99)	1.00
SCA	2,123	6.80 (5.30 ; 8.73)	1,671	5.42 (3.92 ; 7.50)	1.00
CHD NOS	6,416	3.47 (3.00 ; 4.02)	4,488	3.21 (2.73 ; 3.77)	1.00
Stroke ischae	3,718	4.76 (4.16 ; 5.45)	3,737	7.29 (6.53 ; 8.14)	<0.001
Stroke NOS	1,437	2.98 (2.31 ; 3.85)	1,809	4.16 (3.40 ; 5.08)	0.11
Stroke haemo	1,204	6.43 (4.91 ; 8.41)	1,408	9.24 (7.41 ; 11.51)	0.22
TIA	2,643	1.54 (1.22 ; 1.94)	2,876	1.80 (1.47 ; 2.20)	1.00

Hazard rate ratios with 95% confidence intervals from separate Cox's proportional hazards models adjusted for baseline age, ethnicity, social deprivation, smoking status, diabetes treatment, and blood pressure and lipid lowering treatment are presented. CVD is a time-dependent exposure variable. * Bonferroni-adjusted p-values.

HRR: hazard rate ratio, 95% CI: 95% confidence interval, AAA: abdominal aortic aneurysm, CHD NOS: coronary heart disease not otherwise specified, CVD: cardiovascular disease, HF: heart failure, MI: myocardial infarction, PAD: peripheral artery disease, SA: stable angina, SCA: sudden cardiac arrest, Stroke haemo: haemorrhagic stroke, Stroke ischae: ischaemic stroke, Stroke NOS: stroke not otherwise specified, TIA: transient ischaemic attack, UA: unstable angina

Table 3: Associations of 12 incident CVD events with cardiovascular mortality by age groups

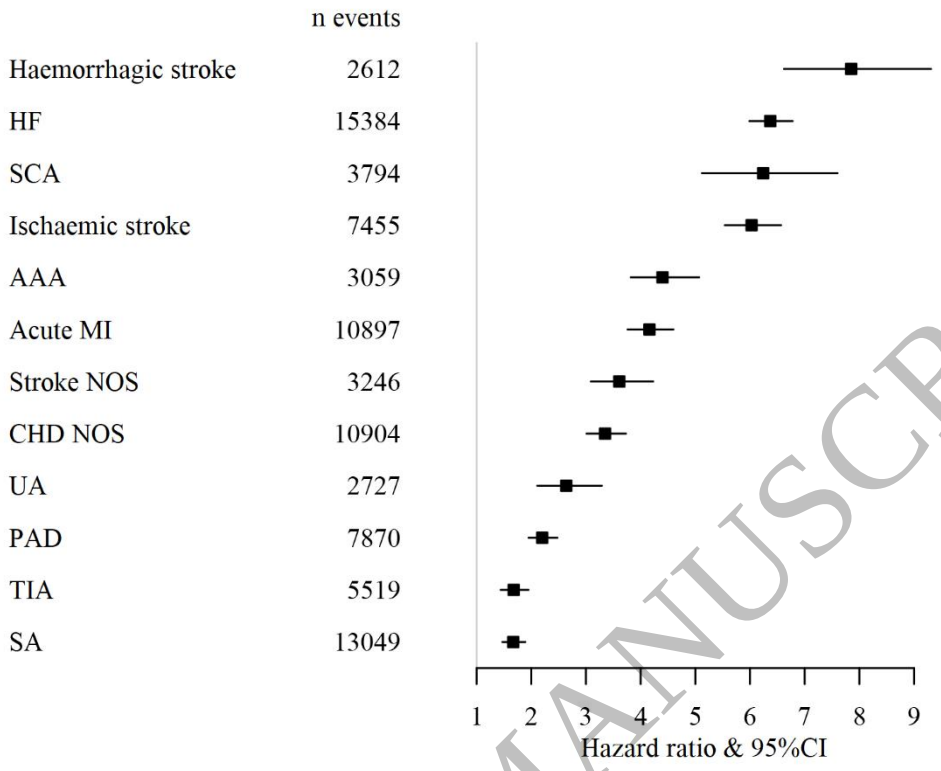
CVD event	≤41 years (N=428,669)		>41 years - ≤58 years (N=437,064)		>58 years (N=444,785)		p-value* for age interaction
	exposed, n	HRR (95% CI)	exposed, n	HRR (95% CI)	exposed, n	HRR (95% CI)	
AAA	27	NA	171	6.63 (2.13 ; 20.64)	2,861	5.39 (4.68 ; 6.22)	1.00
HF	267	32.68 (13.08 ; 81.68)	1,738	18.25 (14.04 ; 23.74)	13,379	10.06 (9.44 ; 10.71)	<0.001
PAD	252	5.23 (0.72 ; 38.05)	1,693	5.51 (3.86 ; 7.84)	5,925	2.54 (2.23 ; 2.89)	<0.001
Acute MI	384	22.25 (8.91 ; 55.54)	3,108	6.67 (4.83 ; 9.22)	7,405	4.99 (4.48 ; 5.55)	<0.001
SA	516	6.68 (2.08 ; 21.48)	4,041	1.57 (0.97 ; 2.54)	8,492	1.62 (1.42 ; 1.85)	0.030
UA	160	NA	878	3.19 (1.52 ; 6.70)	1,689	3.22 (2.55 ; 4.05)	1.00
SCA	262	24.06 (5.90 ; 98.13)	940	16.22 (9.71 ; 27.08)	2,592	6.17 (4.97 ; 7.66)	0.001
CHD NOS	240	11.86 (2.85 ; 49.40)	2,234	7.56 (5.28 ; 10.84)	8,430	3.57 (3.19 ; 4.00)	<0.001
Stroke ischae	213	23.03 (7.17 ; 74.04)	1,217	5.53 (3.25 ; 9.39)	6,025	8.71 (7.98 ; 9.49)	0.47
Stroke NOS	65	NA	496	0.80 (0.11 ; 5.66)	2,685	5.07 (4.33 ; 5.94)	1.00
Stroke haemo	214	19.09 (4.68 ; 77.89)	664	14.59 (8.24 ; 25.83)	1,734	9.10 (7.61 ; 10.90)	1.00
TIA	127	NA	992	2.36 (1.05 ; 5.26)	4,400	2.31 (1.98 ; 2.70)	1.00

Hazard rate ratios with 95% confidence intervals from separate Cox's proportional hazards models adjusted for baseline sex, ethnicity, social deprivation, smoking status, diabetes treatment, and blood pressure and lipid lowering treatment are presented. CVD is a time-dependent exposure variable. Age groups correspond to tertiles calculated in the whole population. * Bonferroni-adjusted p-values.

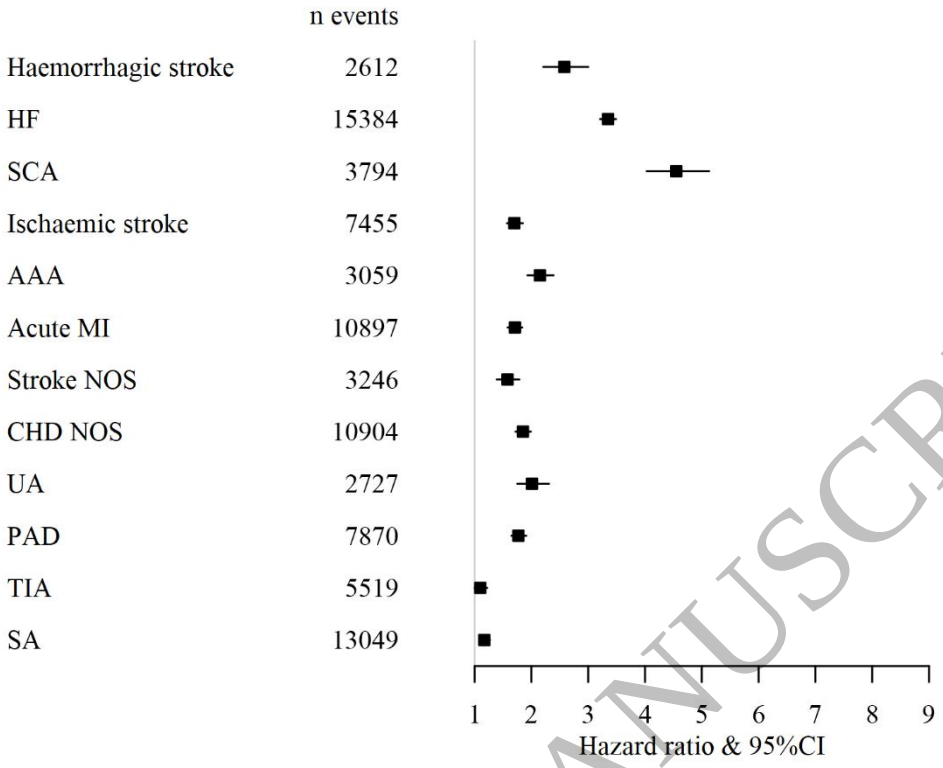
HRR: hazard rate ratio, 95% CI: 95% confidence interval, AAA: abdominal aortic aneurysm, CHD NOS: coronary heart disease not otherwise specified, CVD: cardiovascular disease, HF: heart failure, MI: myocardial infarction, PAD: peripheral artery disease, SA: stable angina, SCA: sudden cardiac arrest, Stroke haemo: haemorrhagic stroke, Stroke ischae: ischaemic stroke, Stroke NOS: stroke not otherwise specified, TIA: transient ischaemic attack, UA: unstable angina

Figure 1

A



B



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