# Sex-based differences in risk factors for incident myocardial infarction and stroke in the UK Biobank

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**Acronyms**

| | |
|---|---|
| ApoA | Apolipoprotein A |
| BMI | Body mass index |
| CHD | Coronary heart disease |
| CI | Confidence interval |
| CVD | Cardiovascular disease |
| DBP | Diastolic blood pressure |
| HbA1c | Glycated haemoglobin |
| HDL-C | High-density lipoprotein cholesterol |
| HR | Hazard ratio |
| ICD | International classification of diseases |
| IQR | Interquartile range |
| LDL-C | Low-density lipoprotein cholesterol |
| MI | Myocardial infarction |
| NHS | National health service |
| RHR | Ratio of hazard ratios |
| RRR | Ratio of relative risks |
| SBP | Systolic blood pressure |
| T1DM | Type 1 diabetes |
| T2DM | Types 2 diabetes |
| UK | United Kingdom |
| VIF | Variance inflation factor |
| WHR | Waist-to-hip ratio |

## Abstract

**Aim:** This study examined sex-based differences in associations of vascular risk factors with incident cardiovascular events in the UK Biobank.

**Methods:** Baseline participant demographic, clinical, laboratory, anthropometric, and imaging characteristics were collected. Multivariable Cox regression was used to estimate independent associations of vascular risk factors with incident myocardial infarction (MI) and ischaemic stroke for men and women. Women-to-men ratios of hazard ratios (RHRs), and related 95% confidence intervals, represent the relative effect-size magnitude by sex.

**Results:** Among the 363,313 participants (53.5% women), 8,470 experienced MI (29.9% women) and 7,705 experienced stroke (40.1% women) over 12.66 [11.93, 13.38] years of prospective follow-up. Men had greater risk factor burden and higher arterial stiffness index at baseline. Women had greater age-related decline in aortic distensibility. Older age [RHR: 1.02 (1.01-1.03)], greater deprivation [RHR: 1.02 (1.00-1.03)], hypertension [RHR: 1.14 (1.02-1.27)], and current smoking [RHR: 1.45 (1.27-1.66)] were associated with a greater excess risk of MI in women than men. Low-density lipoprotein cholesterol was associated with excess MI risk in men [RHR: 0.90 (0.84-0.95)] and apolipoprotein A (ApoA) was less protective for MI in women [RHR: 1.65 (1.01–2.71)]. Older age was associated with excess risk of stroke [RHR: 1.01 (1.00-1.02)] and ApoA was less protective for stroke in women [RHR: 2.55 (1.58-4.14)].

**Conclusion:** Older age, hypertension and smoking appeared stronger drivers of cardiovascular disease in women, whereas lipid metrics appeared stronger risk determinants for men. These findings highlight the importance of sex-specific preventive strategies and suggest priority targets for intervention in men and women.

## Introduction

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide, claiming 18.6 million lives each year (1). Important differences in the incidence, patterns, and outcomes of CVD have been described between men and women but the reasons for these differences are not completely understood.

Traditionally, CVDs were considered to predominantly affect men (2), which in part was due to a higher prevalence of some traditional risk factors (e.g., smoking) in men, but also to a historical under-representation of in women in health research (3). Understanding differences in sex-specific markers such as obstetric history, and variation in traditional risk factors is essential to optimising CVD preventive strategies in men and women (4).

Despite the substantial improvement made in narrowing the gap between sexes in cardiovascular outcomes over the past decades, existing evidence remains limited by restricted cohort sizes, lack of granularity in assessment of exposures such as lipid profiles, and for some risk factors such as smoking, contradictory results have been identified across populations (5). Moreover, the sex-based differences of more recently identified cardiovascular risk markers, such as ApoA, remain poorly understood.

The present study characterises differences in distribution of cardiovascular risk factors between men and women in the UK Biobank cohort. These include traditional cardiovascular risk factors such as diabetes and hypertension, more novel risk factors such as ApoA, and emerging surrogate markers of cardiovascular risk such as aortic distensibility. Secondly, independent associations of a comprehensive host of risk factors with incident stroke and MI are examined with a focus on defining sex-based differences in magnitudes of these associations.

## Methods

### Study Population

The UK Biobank is a large population-based cohort that recruited over 500,000 people aged 40-69 years-old from across the UK between 2006 and 2010. Baseline assessment was performed according to a pre-defined protocol and included a touchscreen questionnaire, face-to-face interviews, a series of physical measures, and blood sampling (6). Incident health events are longitudinally tracked for all participants through electronic health record linkages with hospital admission and death registration data, with outcomes documented according to International Classification of Disease codes (7,8). Analysis was conducted on the set of participants for whom complete case data was available across the predefined set of exposures, outcomes, and covariates.

### Selection and ascertainment of covariates

Major risk factors were selected on basis of existing literature and biological knowledge of their role in risk of stroke and MI. The following factors were included: age, ethnicity, Townsend deprivation index (9), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference, hip circumference, waist-hip ratio (WHR), glycated haemoglobin (HbA1c), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, ApoA, apolipoprotein B (ApoB), smoking status, and diagnosed diabetes, hypertension and hypercholesterolaemia. All variables were extracted from baseline visit and were defined by UK Biobank field ID as identified in **Supplementary Tables 1 and 2**.

### Arterial phenotyping

Arterial compliance has previously been reported to be an important marker for cardiovascular risk prediction (10). To obtain a unifying reflection of the dynamic trend in

the cardiovascular risk profile across different ages and sexes, we evaluated two measures of arterial compliance: arterial stiffness index (ASI) and aortic distensibility (AoD). ASI provides an estimate of large artery stiffness and has been linked to incident cardiovascular events and mortality (11), whilst AoD provides an estimate of aortic compliance and is an indicator of local aortic bio-elastic function and has been demonstrated to predict ischaemic events (10).

Additional details regarding the extraction, outlier definition, and categorisation of variables are provided in **Supplementary Methods**.

**Ascertainment of outcomes**

The primary outcomes were incident MI and incident stroke. Outcomes were ascertained using linked hospital and mortality data, as outlined in **Supplementary Table 3**, over a mean of 12.66 [11.93, 13.38] years of prospective follow-up.

Individuals who had already experienced the outcome of interest prior to recruitment were excluded from analysis for that outcome. Individuals who suffered an endpoint during follow-up were left censored at the time of the event. In both analyses, individuals were right censored at date of death, or at the date of the last event reported in the UK Biobank (MI: 2021-11-12, stroke: 2021-10-25).

**Statistical analysis**

This study is reported following the STROBE Statement guidelines (12). Baseline characteristics are presented for the whole cohort and stratified by sex as number (percentage) for categorical variables, mean (standard deviation) for normally distributed continuous variables, and median [interquartile range] for non-normally distributed continuous variables. Normality of distribution was ascertained by visual inspection of histograms.

The prevalence of prior MI and stroke at baseline visit, and subsequent incidence during follow-up were defined for the entire cohort and separately for each sex. Multivariable Cox proportional hazard regression models were used to obtain hazard ratios (HRs) and 95% confidence intervals (CIs) for each risk factor on the outcome. To calculate whether the HR differed between women and men, sex was added to the model as an interaction term to calculate RHRs, 95% CIs and p-values (13). These are presented as women-to-men RHRs in all cases, a RHR > 1 demonstrates a greater proportional hazard increase in women, whilst a RHR < 1 indicates a greater proportional hazard increase in men.

Unadjusted models including only sex and age were conducted **(Supplementary Table 4).** Multivariate models additionally included BMI, WHR, HbA1c, SBP, DBP, total cholesterol, HDL-C, LDL-C, triglycerides, ApoA, ApoB, and Townsend deprivation index as continuous variables. Abdominal obesity, smoking status, ethnicity, diabetes, high cholesterol and hypertension were also included as categorical variables.

Arterial stiffness measures were not included as covariates. This is because these measures act as 'proxy' measures capturing the downstream vascular consequence of a range of adverse cardiometabolic factors which, in this study, is described by the host of cardiometabolic covariates that are already included in the model. The additional inclusion of arterial stiffness measures in the main models is therefore likely to be problematic from a causal perspective as it is likely to attenuate significant (and biologically causal) associations due to adjustment for a mediator.

Each model was assessed for multi-collinearity to ensure variance inflation factors (VIF) for all covariates were less than 10. Each model was assessed for a violation of the proportional hazard assumption by visual assessment of scaled Schoenfeld residuals.

Poisson regression was used to obtain unadjusted incidence rates of stroke and MI per 1,000 person years by sex. All analyses were performed using R version 4.2.1 (14).

## Results

### Baseline characteristics

The baseline characteristics of the 363,605 participants (53.8% female) included in the study are reported in **Table 1**. Missingness and reasons for exclusion are shown in **Figure 1.** At baseline visit, 8,830 (19.6% female) participants reported a prior MI, and 6,377 reported a previous stroke (40.9% female). In both men and women, the median age at enrolment was 58 years, 94.9% were of white ethnicity, and median Townsend deprivation index was -2.18 in women and -2.17 in men (i.e., more affluent that the UK national average).

Men were more likely to be current or previous smokers compared to women (12.4% vs 8.8% current, and 38.7% vs 31.6% previous). Women had lower rates of diagnosed hypertension compared to men (25.7% vs 34.2%), as well as lower SBP (133 mmHg vs 139 mmHg) and DBP (81 mmHg vs 84 mmHg respectively). The prevalence of diabetes was higher in men than women (7.1% vs 3.8%) although levels of HbA1c were similar across the sexes. Compared to men, women had a lower BMI (26.08 kg/m$^2$ vs 27.29 kg/m$^2$), smaller WHR (0.82 vs 0.94), and lower prevalence of abdominal obesity (31.2% vs 71.4%).

Men had higher rates of diagnosed hypercholesterolaemia than women (25.6% vs 14.9%). Compared to men, women had higher total cholesterol (5.88 vs 5.49 mmol/L), HDL-C (1.56 vs 1.24 mmol/L), LDL-C (3.63 vs 3.49 mmol/L), ApoA (1.61 vs 1.41 g/L) and ApoB (1.02 s 1.01 g/L) but lower triglycerides (1.33 vs 1.69 mmol/L).

Women had lower ASI than men at baseline (8.20 m/s vs 9.77 m/s). At younger ages (≤ 53 year), women and men had similar AoD at the ascending (2.66 vs 2.63 $10^{-3}$ $mmHg^{-1}$) and descending (3.42 vs 3.37 $10^{-3}$ $mmHg^{-1}$) aorta. However, at older ages (≥ 70 years), women had lower AoD at both the ascending (0.60 vs 0.81 $10^{-3}$ $mmHg^{-1}$) and descending (1.40 vs 1.71 $10^{-3}$ $mmHg^{-1}$) aorta than men.

**Myocardial infarction**

During the study period, 8,470 incident cases of MI were recorded, of which 29% occurred in women **(Figure 2).** The crude unadjusted incidence rate of MI per 1,000 person years was 1.06 (95% CI 1.02 – 1.10) in women and 3.04 (95% CI 2.99 – 3.11) in men **(Supplementary Table 5).** Men had 2.8-times greater unadjusted hazard of incident MI than women (HR 2.81, 95% CI: 2.70 – 2.92, p<0.001).

Older age was associated with a higher hazard of MI in both sexes but conferred a greater hazard in women compared to men (RHR 1.02 95% CI 1.01 – 1.03, p<0.001). Similarly, greater deprivation was associated with a proportionally greater hazard of MI in women (RHR 1.02, 95% CI 1.00-1.03, p=0.045), as was current smoking when compared to never smoking (RHR 1.45, 95% CI 1.27-1.66, p<0.001).The presence of clinical hypertension was associated with a proportionally greater hazard in women (RHR 1.14, 95% CI 1.02-1.27, p=0.019), and so was higher SBP (RHR 1.00 95% CI 1.00-1.01, p=0.014). Conversely, the association between higher LDL-C and MI was more pronounced in men, with a 10% relative increase in the hazard of MI (RHR 0.90, 95% CI 0.84-0.95, p<0.001). Finally, the inverse association between ApoA and MI was stronger in men compared to women (RHR 1.65, 95% CI 1.01-2.71, p=0.047). There was no indication of differential impacts of other risk factors on MI. The results are reported in **Table 2 and Figure 4**.

**Stroke**

A total of 7,705 incident cases of stroke were recorded. Among these 40.1% occurred in women **(Figure 3).** The crude unadjusted incidence rate per 1,000 person years were 1.30 (95% CI 1.26 – 1.35) for women, and 2.30 (95% CI 2.24 – 2.37) in men **(Supplementary Table 5).** Overall, men had an unadjusted 1.7-times greater hazard of incident stroke than women (HR 1.73, 95% CI 1.67-1.80, p<0.001).

Older age was associated with proportionally greater hazard of stroke in women compared to men (RHR 1.01, 95% CI 1.00-1.02, p=0.002). Conversely, higher HDL-C was more strongly associated with hazard of stroke in men, with a 52% proportionally greater hazard per unit HDL-C (RHR 0.48, 95% CI 0.32 – 0.71, p<0.001). This was similar for LDL-C with a 6% proportionally greater hazard of stroke per unit LDL-C (RHR 0.94, 95% CI 0.88-1.00, p=0.036). Finally, there was a large sex difference in ApoA (RHR 2.55, 95% CI 1.58-4.14, p<0.001), suggesting a stronger protective effect in men compared to women. There was no indication of differential impacts of other risk factors on stroke. The results are reported in **Table 3 and Figure 5**.

**Missing data and multi-collinearity assessment**

ASI measurement was added to the UK Biobank protocol towards the end of recruitment (available for 35%). AoD is an image-derived metric and was available for the random sub-set of participants included in the UK Biobank Imaging Study (available for 7%). Given that these variables were not included in the main models, the impact of their missingness was not further assessed. For the variables included in the main model, a sub-analysis comparing participants with complete data (72.37%) to those with missing data is reported in **Supplementary Table 6**. The results of the analysis suggest that retained cases did not systematically differ from those with missing data.

VIF scores for variables scoring over 10 in the initial model are reported in **Supplementary Table 7**. After removal of total cholesterol and ApoB from the model, all covariates had VIF score of less than 10.

## Discussion

This study demonstrates sex differences in major risk factors for MI and stroke. First, emerging risk markers, including LDL-C and ApoA, were more strongly associated with cardiovascular outcomes in men compared to women. Second, current smoking, socioeconomic deprivation, hypertension, and older age were associated with disproportionately greater increases in hazards of cardiovascular outcomes in women compared to men. Third, examination of arterial compliance measures, which have been previously found to predict cardiovascular events, validated a baseline higher risk in men but a steeper age-related trajectory of increasing risk in women.

### Lipid profiles

Previous studies have reported stronger associations between LDL-C and CVD in men. A prior Mendelian randomisation study reported a 32% increased odds of CVD per 1-SD increase in genetically predicted LDL-C in women, with a corresponding 52% increased odds in men (15). Similarly, the observational PURE registry reported higher magnitudes of association of non-HDL-C traits with CVD in men (5).

In this study, ApoA was associated with lower hazards of stroke and MI in men. Under causal assumptions, this suggests that ApoA might be less protective against CVD in women. This differential protective effect has been previously reported for MI (16), but not for stroke (17). This has important implications for the clinical investigation of interventions on ApoA aimed at reducing cardiovascular events and its use in risk prediction models.

Previous studies have highlighted inverse associations between HDL-C and CVD (18–20). This was replicated in this study for MI, but paradoxically for stroke we identified a direct association with a 52% relative higher hazard per unit increase in men. This result is likely due to the inclusion of ApoA in this model, which is a known component of the HDL-C particle. In a post-hoc analysis excluding ApoA, the previously reported inverse association between HDL-C and stroke in men was replicated (HR 0.83, 95% CI 0.74-0.93, p=0.001). In line with previous studies which did not demonstrate benefit of HDL-C augmentation on risk of cardiovascular events (21), this result suggests that previously described 'protective' signals of HDL-C on cardiovascular events may be conveyed predominantly by ApoA.

**Age**

Age was associated with an increased hazard of stroke and MI in women, compared with men. This is consistent with previous research that identified women experience their first stroke or MI event at older ages (22,23). This result was further validated by examining arterial compliance measures. Despite men having a higher baseline ASI, reflecting greater baseline cardiovascular risk, we observed a steeper age-related decline in AoD in women, which suggest a more rapid age-related increase in cardiovascular risk. Given the age demographic of this cohort, this increase in cardiovascular risk may occur after loss of the cardioprotective exposure to oestrogen. From a clinical perspective, this suggests that cardiovascular risk assessment and prevention strategies should be intensified with progressive age, particularly in women.

**Smoking status**

This study identified a proportionally greater association between current smoking status and MI in women, in line with previous findings (24,25). The mechanism behind the excess risk in women is likely multifactorial. It might relate to differences in smoking patterns, or it might be conferred by higher rates of smoking continuation: women are less likely to receive

counselling, to stop smoking, and on average quitters stop at an older age than men (26–28). Overall, the results highlight the key importance of smoking cessation in women and call for further research exploring whether the heterogeneity in hazards relates to biological or structural differences in healthcare systems.

**Hypertension**

In this study, we identified a disproportionately higher hazard of MI associated with hypertension in women compared to men. The INTERHEART (22) and PURE study (5) have both previously reported similar findings. In this study we did not identify any differences in hazards for stroke, though previous UK Biobank research found a higher risk in women only at higher stages of hypertension (29). There are multiple potential mechanisms behind this. Hypertension is known to be a major risk factor for hypertensive disorders of pregnancy (30) and the development of the acute, severe cardiac and endothelial dysfunction that ensues from these might act to heighten cardiovascular risk. Women with hypertension may also be treated differently to men, for example through avoidance of drug classes contraindicated in pregnancy (31). The results of this study provide evidence to support the growing view that sex-specific frameworks should be considered for screening, monitoring, and weighing of blood pressure as a component of global cardiovascular risk (32).

**Socioeconomic status**

The results of this study identified an association of larger magnitude between Townsend deprivation index and MI in women compared to men. Lower socioeconomic status (SES) is known to be associated with CVD (33), although in a previous study on the UK Biobank no sex difference was found (34). However, a large meta-analysis of more than 22 million participants, found that low SES was associated with 34% excess risk of developing coronary heart disease in women compared to men (35). The mechanism behind this is unclear. As the Townsend deprivation index is an area-based rather than individual-based measure, the

excess risk might reflect a greater relative deprivation among women compared to men within a single area. The findings might also reflect important inequities in access to healthcare with lower SES that might disproportionately impact women.

**Strengths and limitations**

The key strength of this investigation lies in the inclusion of a broad set of risk factors including a detailed lipid profile of LDL-C, HDL-C and ApoA, which highlighted the substantial differences in association across the sexes. Additionally, this study utilised a well-validated and intensely phenotyped population source, prospective outcome ascertainment with a substantial number of events ascertained through well-validated disease codes, and correlation of key findings with the novel cardiovascular risk marker of arterial compliance which further elucidate age-related cardiovascular risk trends.

Limitations of this study include the lack of diversity in ethnicity and SES in the UK Biobank, both of which may limit generalisability. The study population is also relatively healthy in comparison to the general public. The risk factor of smoking status was collected via self-report, which could lead to reporting bias. Finally, many of the lipid measures had more than 5% of data missing, though analysis of the characteristics of the individuals with missing data revealed no substantial systematic differences to the complete case cohort.

**Conclusions**

The results of this study identify that smoking, low SES and hypertension were more strongly associated with MI in women, whereas lipid traits were more strongly associated with both MI and stroke in men. Considering the historically male-predominance in health research providing the basis for decisions made in everyday clinical practice, these results encourage further elucidation of sex-specific treatment effects in order to better inform clinical decision-making and treatment prioritisation.

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**Conflict of interest**

SEP provides consultancy to Cardiovascular Imaging Inc, Calgary, Alberta, Canada. The remaining authors have nothing to declare.

**Data Availability Statement**

This research was conducted using the UK Biobank resource under access application 2964. UK Biobank will make the data available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any persons. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For more details on the access procedure, see the UK Biobank website: http://www.ukbiobank.ac.uk/register-apply.

**Ethical approval**

This study complies with the Declaration of Helsinki; the work was covered by the ethical approval for UK Biobank studies from the NHS National Research Ethics Service on 17th

June 2011 (Ref 11/NW/0382) and extended on 18th June 2021 (Ref 21/NW/0157) with written informed consent obtained from all participants.

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*Table 1 Characteristics of study cohort at baseline stratified by sex*

| | **Overall** | **Female** | **Male** |
|---|---|---|---|
| **No (%)** | 363,605 | 195,542 (53.8) | 168,063 (46.2) |
| **Age (years)** | 58.00 [50.00, 63.00] | 58.00 [50.00, 63.00] | 58.00 [50.00, 64.00] |
| **Ethnic group** | | | |
| All other ethnic groups combined | 18,574 (5.1) | 9,946 (5.1) | 8,628 (5.1) |
| White | 345,031 (94.9) | 185,596 (94.9) | 159,435 (94.9) |
| **Townsend Deprivation Index** | -2.18 [-3.66, 0.43] | -2.18 [-3.65, 0.37] | -2.17 [-3.67, 0.50] |
| **Smoking Status** | | | |
| Never | 198,656 (54.6) | 116,470 (59.6) | 82,186 (48.9) |
| Previous | 126,944 (34.9) | 61,832 (31.6) | 65,112 (38.7) |
| Current | 38,005 (10.5) | 17,240 (8.8) | 20,765 (12.4) |
| **Hypertension** | 107,814 (29.7) | 50,301 (25.7) | 57,513 (34.2) |
| **Blood pressure (mmHg)** | | | |
| Systolic blood pressure | 136.00 [124.50, 149.50] | 133.00 [121.00, 147.00] | 139.00 [128.50, 151.50] |
| Diastolic blood pressure | 82.23 (10.10) | 80.65 (9.93) | 84.07 (9.98) |
| **Diabetes** | 19,455 ( 5.4) | 7,472 (3.8) | 11,983 (7.1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **HbA1c (mmol/mol)** | 35.20 | [32.80, 37.90] | 35.20 | [32.70, 37.70] | 35.30 | [32.80, 38.10] |
| **BMI (kg/m$^2$)** | 26.72 | [24.13, 29.85] | 26.08 | [23.43, 29.64] | 27.29 | [24.98, 30.03] |
| **Waist-to-hip ratio** | 0.87 (0.09) | | 0.82 (0.07) | | 0.94 (0.06) | |
| **Abdominal obesity** | | | | | | |
| Normal | 182,633 (50.2) | | 134,536 (68.8) | | 48,097 (28.6) | |
| Abdominal obesity | 180,972 (49.8) | | 61,006 (31.2) | | 119,966 (71.4) | |
| **High cholesterol** | 72,296 (19.9) | | 29,209 (14.9) | | 43,087 (25.6) | |
| **Lipids** | | | | | | |
| Cholesterol (mmol/L) | 5.70 (1.13) | | 5.88 (1.11) | | 5.49 (1.12) | |
| HDL cholesterol (mmol/L) | 1.40 [1.17, 1.68] | | 1.56 [1.33, 1.82] | | 1.24 [1.06, 1.45] | |
| LDL direct (mmol/L) | 3.56 (0.86) | | 3.63 (0.86) | | 3.49 (0.86) | |
| Triglycerides (mmol/L) | 1.48 [1.05, 2.14] | | 1.33 [0.96, 1.89] | | 1.69 [1.18, 2.44] | |
| Apolipoprotein A (g/L) | 1.51 [1.35, 1.70] | | 1.61 [1.45, 1.79] | | 1.41 [1.27, 1.56] | |
| Apolipoprotein B (g/L) | 1.02 [0.86, 1.18] | | 1.02 [0.87, 1.18] | | 1.01 [0.86, 1.18] | |
| **Aortic distensibility** | | | | | | |

| | | | |
|---|---|---|---|
| **ascending** ($x10^{-3}$, $mmHg^{-1}$) (% missing = 92.93) | | | |
| ≤ 53 years | 2.64 [1.88, 3.55] | 2.66 [1.84, 3.66] | 2.63 [1.92, 3.39] |
| 54 to 69 years | 1.27 [0.79, 1.99] | 1.15 [0.69, 1.89] | 1.42 [0.92, 2.08] |
| ≥ 70 years | 0.71 [0.48, 1.06] | 0.60 [0.42, 0.88] | 0.81 [0.56, 1.18] |
| **Aortic distensibility descending** ($x10^{-3}$, $mmHg^{-1}$) (% missing = 92.67) | | | |
| ≤ 53 years | 3.40 [2.68, 4.28] | 3.42 [2.69, 4.31] | 3.37 [2.66, 4.24] |
| 54 to 69 years | 2.30 [1.70, 3.04] | 2.18 [1.58, 2.94] | 2.42 [1.84, 3.14] |
| ≥ 70 years | 1.56 [1.16, 2.05] | 1.40 [1.04, 1.83] | 1.71 [1.29, 2.19] |
| **Arterial stiffness index** (m/s) (% missing = 65.03) | 8.95 [6.86, 11.07] | 8.20 [6.30, 10.37] | 9.77 [7.72, 11.77] |
| **Myocardial infarction** | | | |
| Prevalent cases | 8,803 | 1,728 (19.6) | 7,075 (80.4) |
| Incident cases | 8,470 | 2,529 (29.9) | 5,941 (70.1) |
| **Stroke** | | | |
| Prevalent cases | 6,377 | 2,610 (40.9) | 3,767 (59.1) |
| Incident cases | 7,705 | 3,089 (40.1) | 4,616 (59.9) |

*N: number, mmHg: millimetres of mercury, HbA1c: glycated haemoglobin, mmol/mol: millimoles per mole, kg/m2: kilograms metres squared, mmol/L: millimoles per litre, HDL: high-density lipoprotein, LDL: low-density lipoprotein, g/L:*

*grams per litre, m/s: metres per second . Results are mean (standard deviation), number (percentage) or median [interquartile range].*

*Table 2 Hazard ratios for risk factors of MI by women and men, including women-to-men ratio of hazard ratio*

| | **Women** | **Men** | **Women-to-men RHR** |
|---|---|---|---|
| **Covariates** | **HR (95% CI, p value)** | **HR (95% CI, p value)** | **RHR (95% CI, p value)** |
| Age | 1.06 (1.06-1.07, p<0.001) | 1.04 (1.04-1.05, p<0.001) | 1.02 (1.01-1.03, p<0.001) |
| Ethnicity | | | |
| White | — | — | — |
| All other ethnic groups combined | 1.01 (0.83-1.23, p=0.924) | 1.00 (0.89-1.13, p=0.959) | 1.00 (0.80-1.26, p=0.988) |
| Townsend deprivation index | 1.03 (1.02-1.04, p<0.001) | 1.01 (1.00-1.02, p=0.005) | 1.02 (1.00-1.03, p=0.045) |
| Smoking status | | | |
| Never | — | — | — |
| Previous | 1.22 (1.11-1.33, p<0.001) | 1.11 (1.05-1.18, p<0.001) | 1.09 (0.98-1.22, p=0.096) |
| Current | 2.72 (2.43-3.04, p<0.001) | 1.86 (1.73-2.00, p<0.001) | 1.45 (1.27-1.66, p<0.001) |
| Hypertension | 1.48 (1.35-1.62, p<0.001) | 1.30 (1.22-1.38, p<0.001) | 1.14 (1.02-1.27, p=0.019) |
| Systolic blood pressure | 1.02 (1.01-1.02, p<0.001) | 1.01 (1.01-1.01, p<0.001) | 1.00 (1.00-1.01, p=0.014) |
| Diastolic blood pressure | 0.99 (0.99-1.00*, | 1.00 (0.99-1.00, | 1.00 (0.99-1.00, |

| | | | | | | |
|---|---|---|---|---|---|---|
| | p=0.001) | | p=0.008) | | p=0.240) | |
| Diabetes | 1.45 | (1.22-1.73, p<0.001) | 1.31 | (1.18-1.45, p<0.001) | 1.11 | (0.90-1.36, p=0.321) |
| HbA1c | 1.02 | (1.01-1.02, p<0.001) | 1.01 | (1.01-1.02, p<0.001) | 1.00 | (1.00-1.01, p=0.381) |
| BMI | 0.99 | (0.98-1.00, p=0.030) | 1.00 | (0.99-1.01, p=0.60 | 0.99 | (0.98-1.00, p=0.188) |
| Waist-to-hip ratio | 2.55 | (0.98-6.65, p=0.055) | 2.82 | (1.53-5.22, p=0.001) | 0.89 | (0.28-2.77, p=0.836) |
| Abdominal obesity | | | | | | |
| Normal | — | | — | | — | |
| Abdominal obesity | 1.04 | (0.92-1.19, p=0.508) | 1.00 | (0.92-1.09, p=0.959) | 1.04 | (0.89-1.22, p=0.595) |
| High cholesterol | 1.31 | (1.18-1.45, p<0.001) | 1.34 | (1.26-1.44, p<0.001) | 0.97 | (0.86-1.10, p=0.673) |
| HDL cholesterol | 0.64 | (0.46-0.88, p=0.006) | 0.72 | (0.56-0.93, p=0.013) | 0.88 | (0.58-1.32, p=0.529) |
| LDL cholesterol | 1.30 | (1.24-1.37, p<0.001) | 1.45 | (1.40-1.50, p<0.001) | 0.90 | (0.84-0.95, p<0.001) |
| Triglycerides | 1.01 | (0.96-1.07, p=0.566) | 1.00 | (0.98-1.03, p=0.769) | 1.01 | (0.96-1.07, p=0.704) |
| Apolipoprotein A | 0.77 | (0.52-1.14, p=0.191) | 0.47 | (0.35-0.64, p<0.001) | 1.65 | (1.01-2.71, p=0.047) |

*RHR: ratio of hazard ratios, HR: hazard ratio, CI: confidence intervals, BMI: body mass index, HbA1c: glycated haemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein.*

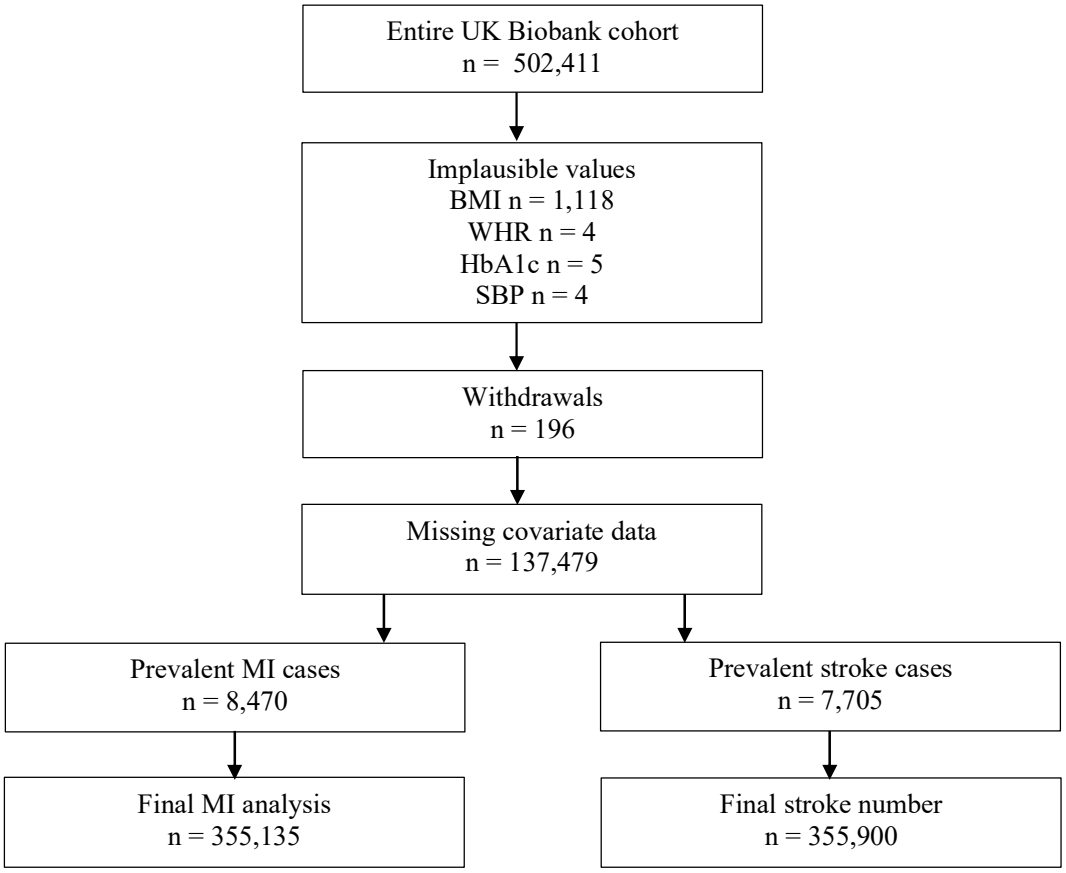
*Table 3 Hazard ratios for risk factors of stroke by women and men, including women-to-men ratio of hazard ratio*

| | **Women** | | **Men** | | **Women-to-men** | |
|---|---|---|---|---|---|---|
| **Covariates** | **HR (95% CI, p value)** | | **HR (95% CI, p value)** | | **RHR (95% CI, p value)** | |
| Age | 1.10 p<0.001) | (1.10-1.11, | 1.09 p<0.001) | (1.08-1.09, | 1.01 p=0.002) | (1.00-1.02, |
| Ethnicity | | | | | | |
| White | — | | — | | — | |
| All other ethnic groups combined | 0.82 p=0.047) | (0.68-1.00, | 0.95 p=0.463) | (0.82-1.09, | 0.87 p=0.259) | (0.68-1.11, |
| Townsend deprivation index | 1.04 p<0.001) | (1.02-1.05, | 1.03 p<0.001) | (1.02-1.04, | 1.01 p=0.199) | (0.99-1.03, |
| Smoking status | | | | | | |
| Never | — | | — | | — | |
| Previous | 1.07 p=0.088) | (0.99-1.16, | 1.09 p=0.013) | (1.02-1.16, | 0.99 p=0.786) | (0.89-1.09, |
| Current | 1.84 p<0.001) | (1.64-2.07, | 1.66 p<0.001) | (1.52-1.81, | 1.11 p=0.166) | (0.96-1.28, |
| Hypertension | 1.37 p<0.001) | (1.26-1.49, | 1.38 p<0.001) | (1.29-1.48, | 0.99 p=0.896) | (0.89-1.10, |
| Systolic blood pressure | 1.01 p<0.001) | (1.01-1.01, | 1.01 p<0.001) | (1.01-1.01, | 1.00 p=0.472) | (1.00-1.00, |
| Diastolic blood | 1.00 | (1.00-1.01, | 1.00 | (1.00-1.01, | 1.00 | (0.99-1.01, |

| | | | | | | |
|---|---|---|---|---|---|---|
| pressure | p=0.220) | | p=0.126) | | p=0.964) | |
| Diabetes | 1.16 | (0.98-1.37, | 1.30 | (1.16-1.46, | 0.89 | (0.72-1.08, |
| | p=0.088) | | p<0.001) | | p=0.241) | |
| HbA1c | 1.02 | (1.01-1.02, | 1.02 | (1.02-1.02, | 1.00 | (1.00-1.01, |
| | p<0.001) | | p<0.001) | | p=0.357) | |
| BMI | 1.00 | (0.99-1.01, | 0.99 | (0.98-1.00, | 1.01 | (1.00-1.02, |
| | p=0.650) | | p=0.141) | | p=0.165) | |
| Waist-to-hip ratio | 1.85 | (0.77-4.43, | 5.62 | (2.82-11.17, | 0.33 | (0.11-1.00, |
| | p=0.168) | | p<0.001) | | p=0.051) | |
| Abdominal obesity | | | | | | |
| Normal | — | | — | | — | |
| Abdominal obesity | 0.98 | (0.87-1.10, | 0.93 | (0.84-1.02, | 1.06 | (0.91-1.23, |
| | p=0.746) | | p=0.134) | | p=0.483) | |
| High cholesterol | 1.09 | (0.99-1.20, | 1.00 | (0.93-1.08, | 1.09 | (0.96-1.23, |
| | p=0.087) | | p=0.991) | | p=0.176) | |
| HDL cholesterol | 0.85 | (0.64-1.13, | 1.78 | (1.36-2.35, | 0.48 | (0.32-0.71, |
| | p=0.274) | | p<0.001) | | p<0.001) | |
| LDL direct | 0.96 | (0.91-1.00, | 1.02 | (0.98-1.07, | 0.94 | (0.88-1.00, |
| | p=0.065) | | p=0.280) | | p=0.036) | |
| Triglycerides | 1.00 | (0.95-1.05, | 0.97 | (0.94-1.00, | 1.03 | (0.97-1.09, |
| | p=0.970) | | p=0.068) | | p=0.346) | |
| Apolipoprotein A | 0.89 | (0.63-1.26, | 0.35 | (0.25-0.49, | 2.55 | (1.58-4.14, |
| | p=0.508) | | p<0.001) | | p<0.001) | |

*RHR: ratio of hazard ratios, HR: hazard ratio, CI: confidence intervals, BMI: body mass index, HbA1c: glycated haemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein.*

*Figure 1 Flowchart of exclusion and inclusion*




*BMI: body mass index, WHR: waist-to-hip ratio, HbA1c: glycated haemoglobin, SBP: systolic blood pressure, MI: myocardial infarction.*

*Figure 2 Unadjusted survival curve for myocardial infarction by sex*

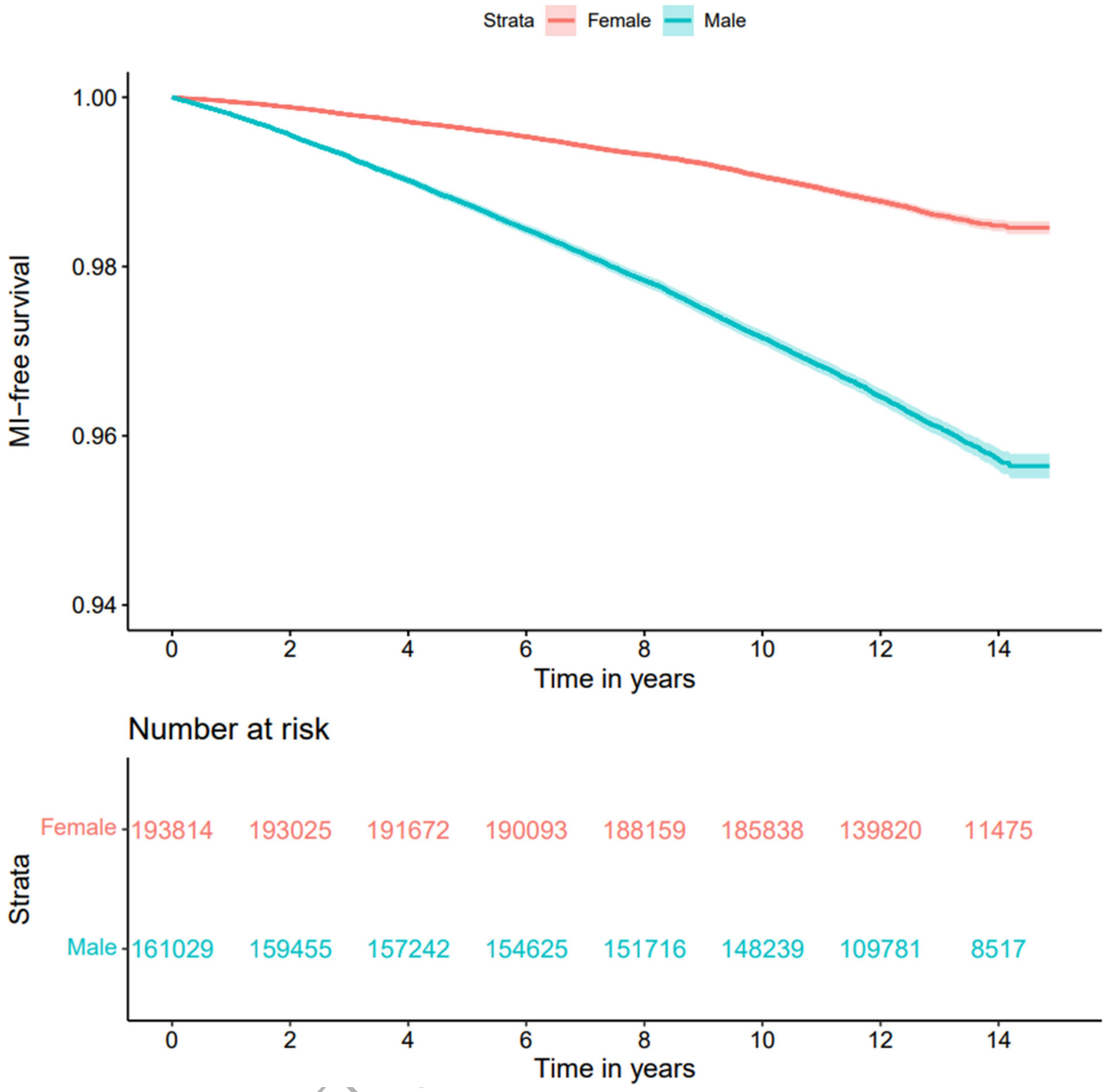


*Figure 3 Unadjusted survival curve for stroke by sex*

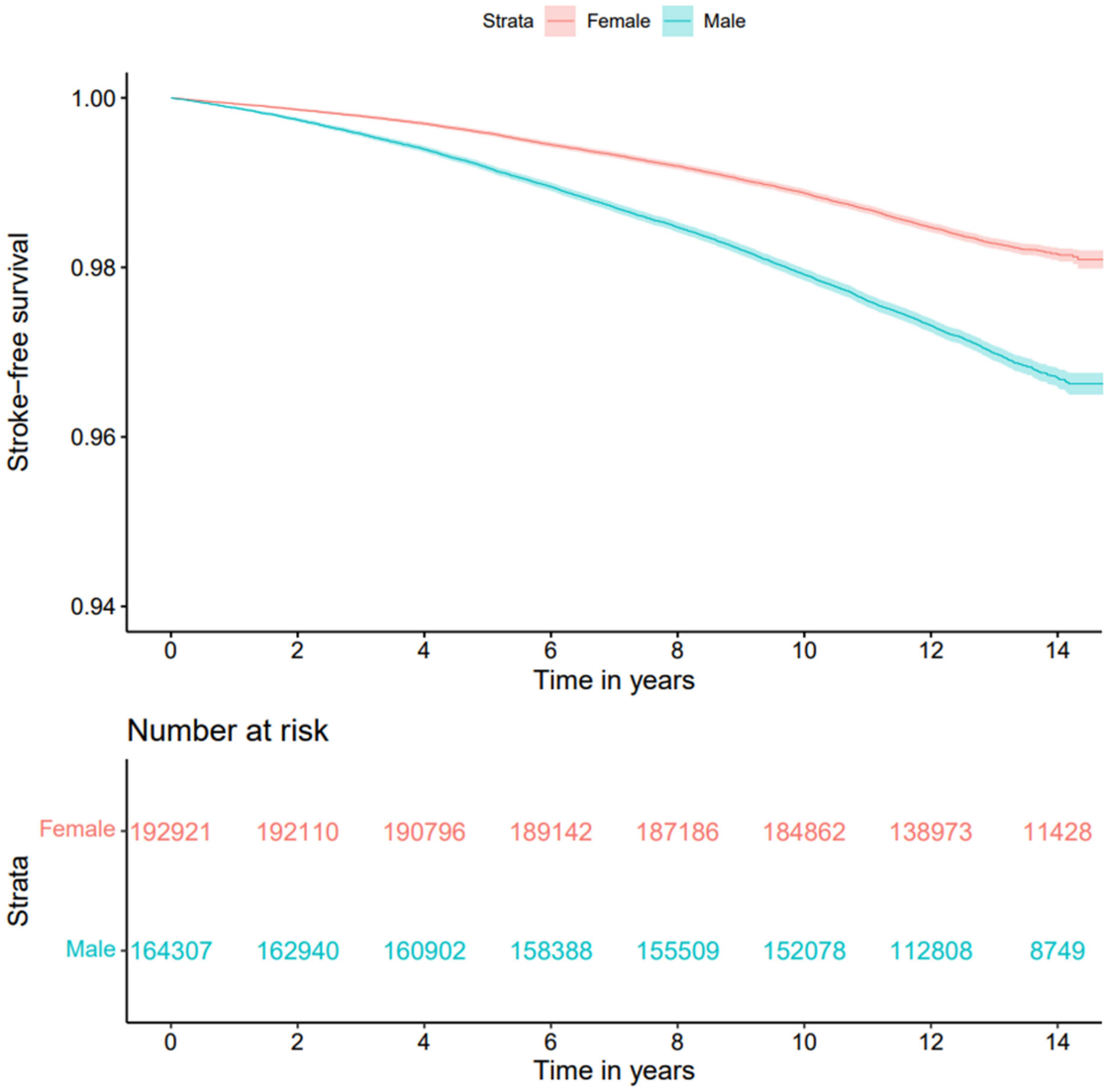
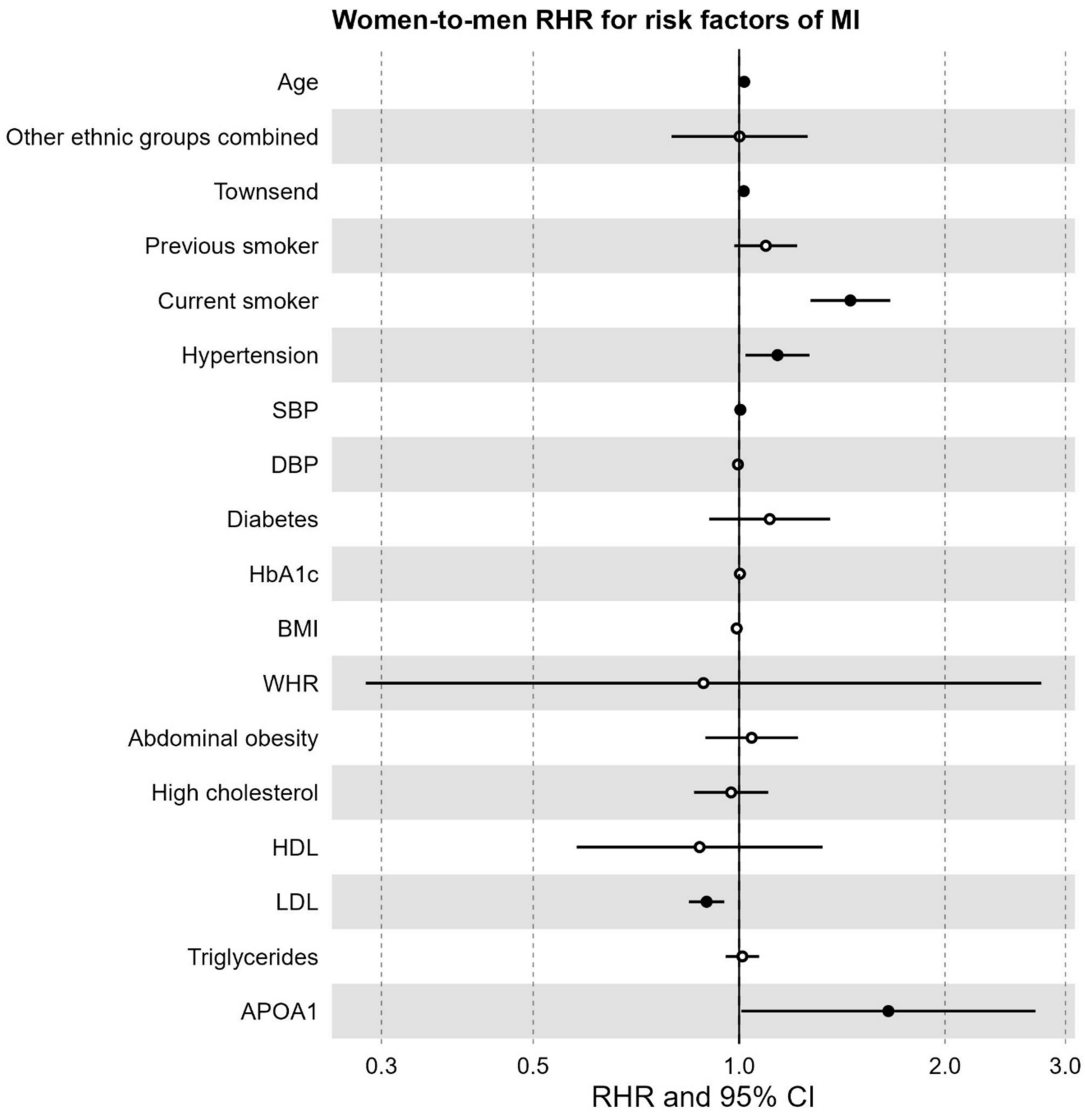
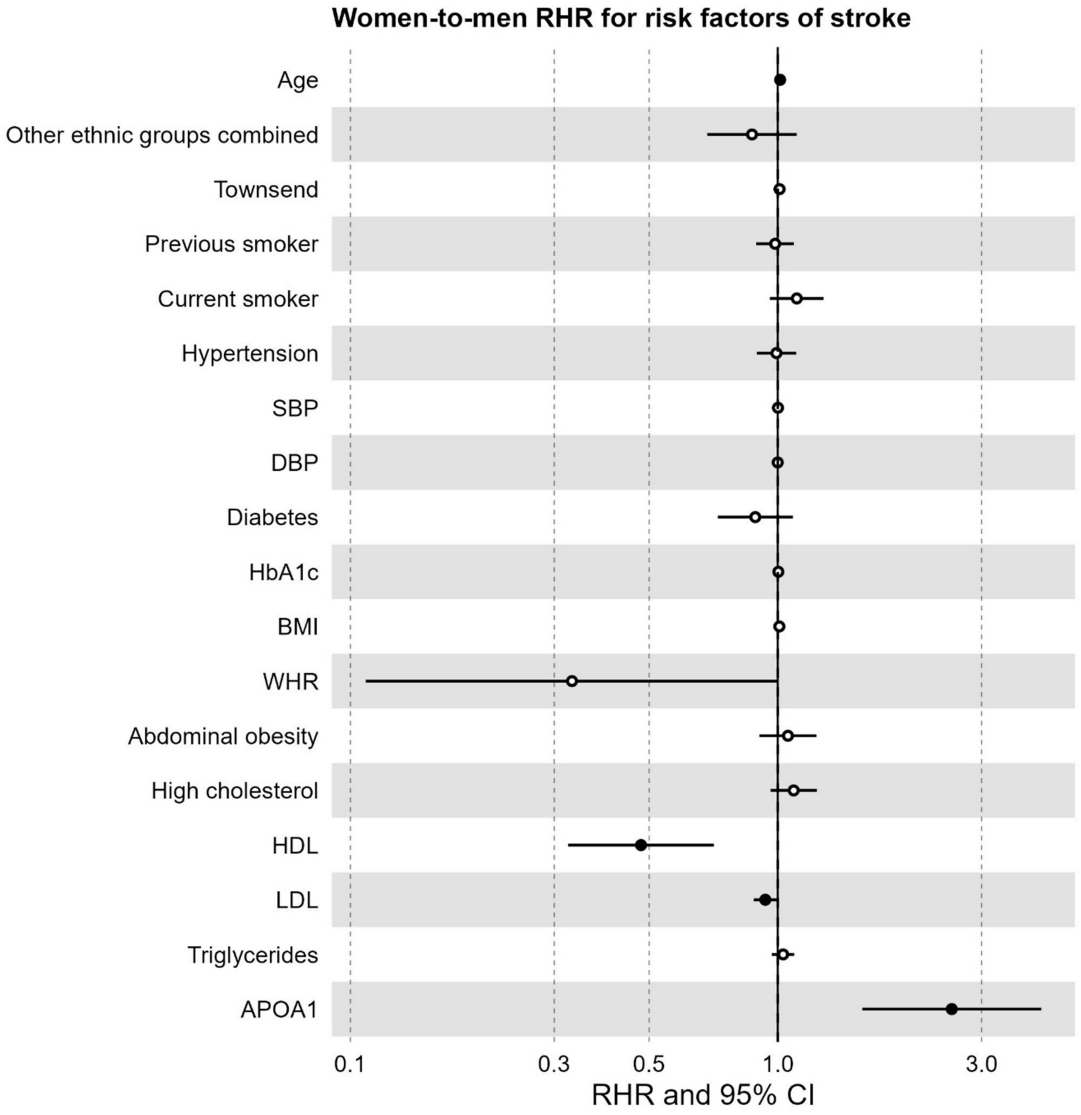


*Figure 4 Forest plot of women-to-men ratio of hazard ratios for risk factors of MI*




*RHR: ratio of hazard ratios, CI: confidence interval, SBP: systolic blood pressure, DBP: diastolic blood pressure, HbA1c: glycated haemoglobin, BMI: body mass index, WHR: waist-to-hip ratio, HDL: high-density lipoprotein, LDL: low-density lipoprotein, APOA1: Apolipoprotein A. Significant risk factors displayed as solid points (p-value < 0.05).*

*Figure 5 Forest plot of women-to-men ratio of hazard ratios for risk factors of stroke*




*RHR: ratio of hazard ratios, CI: confidence interval, SBP: systolic blood pressure, DBP: diastolic blood pressure, HbA1c: glycated haemoglobin, BMI: body mass index, WHR: waist-to-hip ratio, HDL: high-density lipoprotein, LDL: low-density lipoprotein, APOA1: Apolipoprotein A. Significant risk factors displayed as solid points (p-value < 0.05) .*