# Association of cardiometabolic multimorbidity with mortality

The Emerging Risk Factors Collaboration

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**ABSTRACT**

**Importance:** The prevalence of cardiometabolic multimorbidity is increasing.

**Objective:** To estimate reductions in life expectancy associated with cardiometabolic multimorbidity.

**Design, Setting, and Participants:** We calculated age-and sex-adjusted mortality rates and hazard ratios (HRs) using individual-participant data from the Emerging Risk Factors Collaboration (ERFC; 689,300 participants; 91 cohorts; years of baseline surveys: 1960-2007; latest follow-up: 2013; 128,843 deaths). We compared HRs with those from UK Biobank (499,808 participants; years of baseline survey: 2006-2010; latest follow-up: 2013; 7995 deaths). We estimated cumulative survival by applying calculated age-specific HRs for mortality to contemporary US age-specific death rates.

**Exposure**: History of ≥2 of the following: diabetes mellitus, stroke, myocardial infarction (MI).

**Main Outcomes**: All-cause mortality and estimated reductions in life expectancy.

**Results:** In ERFC participants without diabetes, stroke, or MI at baseline ("reference group"), the all-cause mortality rate adjusted to age 60 years was 6.8 per 1000 person-years. Mortality rates were 15.6 with diabetes only, 16.1 with stroke only, 16.8 with MI only, 32.0 with both diabetes and MI, 32.5 with both diabetes and stroke, 32.8 with both stroke and MI, and 59.5 with diabetes, stroke, and MI. Compared to the reference group, HRs (95% CI) for all-cause mortality were 1.9 (1.8-2.0) with diabetes only; 2.1 (2.0-2.2) with stroke only; 2.0 (1.9-2.2) with MI only; 3.7 (3.3-4.1) with both diabetes and MI, 3.8 (3.5-4.2) with both diabetes and stroke, 3.5 (3.1-4.0) with both stroke and MI, and 6.9 (5.7-8.3) with diabetes, stroke and MI. HRs from the ERFC were similar to those from the more recently-recruited UK Biobank. HRs were little changed after further adjustment for markers of established intermediate pathways (e.g., lipids, blood pressure) and lifestyle factors (e.g., smoking, diet). At age 60 years, a history of a combination of any two conditions was associated with 12 years of reduced life expectancy; a history of three conditions was associated with 15 years of reduced life expectancy.

**Conclusions and Relevance:** Mortality associated with a history of diabetes, stroke, or MI was similar for each condition. As any combination of these conditions was associated with multiplicative mortality risk, life expectancy was substantially lower in people with multimorbidity.

## INTRODUCTION

The prevalence of cardiometabolic multimorbidity (defined here as a history of ≥2 of diabetes, stroke, myocardial infarction [MI]) is increasing rapidly.[1-3] Considerable evidence exists about the mortality risk of having any one of these conditions alone.[4-7] However, evidence is sparse about life expectancy among people who have two or three cardiometabolic conditions concomitantly. Valid estimation of the associations of cardiometabolic multimorbidity with mortality requires comparison of people with multimorbidity with participants within the same cohorts who did not have any of the conditions at baseline. However, few population cohorts have had sufficient power, detail, and longevity to enable such comparisons.[8-14]

We aimed to provide reliable estimates of the associations of cardiometabolic multimorbidity with mortality and reductions in life expectancy. We analyzed individual-participant data in the Emerging Risk Factors Collaboration (ERFC) on 689,300 participants recruited during 1960-2007 into 91 prospective cohorts that have recorded mortality during prolonged follow-up. We compared results with those from UK Biobank, a prospective cohort study of 499,808 participants recruited during 2006-2010.

## METHODS

### Overall design

Our analysis involved several inter-related components (**eFigure 1**). First, we quantified associations of cardiometabolic multimorbidity with all-cause mortality. To maximize power, we analyzed data from the ERFC in which a total of about 129,000 deaths have accrued. Second, we compared results from the ERFC with those from UK Biobank. UK Biobank recruited participants more recently than the ERFC, and had accrued about 8000 deaths at the time of this analysis. Third, we estimated reductions in life expectancy associated with cardiometabolic multimorbidity by applying results from the ERFC to contemporary US death rates. Fourth, we placed our findings in the context of previous relevant studies identified through a systematic review.

### Data sources

Both the ERFC and UK Biobank have been described previously[15-17]. Prospective cohort studies contributing to the ERFC were included in this analysis if they met all the following criteria: 1) had recruited participants on the basis of informed consent, 2) had recorded information about the diagnosis of diabetes, stroke, and MI at the baseline survey, 3) did not select participants on the basis of having previous chronic disease (including cardiovascular disease and diabetes), 4) recorded cause-specific deaths, and 5) had accrued more than 1 year of follow-up. Details of contributing studies in the ERFC are presented in **eTable 1** and **eAppendix 2**. **eTable 2** provides information on methods used to characterize diagnosis of diabetes, stroke, and MI at the baseline survey. The contributing studies classified deaths according to the primary cause (or, in its absence, the underlying cause), on the basis of coding from the *International Classification of Diseases*, revisions 8 through 10, to at least three digits, or according to study-specific classification systems. Classification of deaths was based on death certificates, supplemented in 53 studies by medical records, findings on autopsy, and other sources. The date of latest mortality follow-up was April 2013.

In UK Biobank, information on a baseline history of diabetes, stroke, and MI was available for 499,808 participants recruited from 22 centres throughout the United Kingdom (**eAppendix 3**). After giving consent, participants provided biological samples and completed a touch-screen questionnaire, a computer-assisted interview, and a physical examination. Participants have been linked with death records of the UK Office for National Statistics through National Health Service identification numbers. Deaths were classified according to the primary cause (or, in its absence, the underlying cause), on the basis of coding from the *International Classification of Diseases* 10, to at least three digits. The date of latest mortality follow-up was November 2013.

**eAppendix 4** provides details of our systematic review of population-based prospective studies reported between January 1970 and April 2015. No language restrictions were applied to publications. Studies were not eligible for the review if they had contributed data to the ERFC.[8;13;18] Two investigators (PW and LOK) extracted and cross-checked information from publications according to a pre-specified protocol, with disagreements resolved by EDA.

Approval was provided by the Cambridgeshire ethics review committee.

**Statistical analysis**

For both the ERFC and UK Biobank, we categorized participants into eight mutually exclusive groups according to baseline disease, ie: 1) diabetes only; 2) stroke only; 3) MI only; 4) diabetes and MI only; 5) diabetes and stroke only; 6) stroke and MI only; 7) diabetes, stroke and MI; 8) none of these (reference group). We assessed associations of these baseline groups with risk of death from any cause.

Hazard ratios (HRs) were calculated using Cox proportional-hazards regression models. Because the principal objective of our study was to estimate reductions in life expectancy associated with having different combinations of cardiometabolic multimorbidity, our primary analysis calculated HRs stratified by sex and adjusted for age only. As a secondary objective was to explore the

extent to which markers of some established intermediate pathways (i.e., total and HDL cholesterol, blood pressure, body-mass index) and lifestyle factors (i.e., smoking, diet, socioeconomic status) could explain associations between cardiometabolic multimorbidity and mortality, subsidiary analyses calculated HRs adjusted for these additional factors. In the ERFC, HRs were calculated using a 2-stage approach, with estimates calculated separately within each study before pooling across studies by random-effects meta-analysis using an extension of the DerSimonian and Laird procedure.[16;19] Participants were included in analyses irrespective of previous non-fatal events. For each specific cause of death, outcomes were censored if a participant was lost to follow-up, died from other causes, or reached the end of the follow-up period. The proportional hazards assumptions was satisfied for all-cause mortality (**eFigure 2**). We used the $I^2$ statistic to quantify between-study heterogeneity and the Wald test to assess interactions.

Since age-specific mortality rates cannot be directly obtained from a 2-stage approach using Cox regression models (ie, these models estimate instantaneous probability of death), we used a 2-level mixed-effects Poisson regression model, with random study intercept, adjusted for baseline disease status, sex and age-at-risk (linear and quadratic terms) and interactions of age-at-risk with the preceding variables. This Poisson regression model was used to obtain mortality rates adjusted to age 60 years (i.e., marginal effects).

**eAppendix 5** provides detail of the methods used to estimate reductions in life expectancy. Briefly, estimates of cumulative survival from 40 years of age onwards among the eight baseline disease groups were calculated by applying cause-specific mortality HRs from the ERFC (specific to age-at-risk and sex) to the detailed mortality component of the CDC WONDER database of the US Centers for Disease Control and Prevention, which recorded almost 10 million deaths among over 305 million individuals during 2007-2010.[20;21] We modeled results throughout middle-age and old age, giving specific consideration to HRs with cardiometabolic multimorbidity recorded by

228 age 60, the period of life when multimorbidity becomes increasingly common[22]. Analyses involved
229 Stata (version 12.0), 2-sided P-values, and used a significance level of $P<0.05$.

## RESULTS

### Emerging Risk Factors Collaboration

The mean age of participants at baseline was 53 (SD 9) years; 51% were women (**Table 1**). The large majority were enrolled in Europe (69%) or North America (24%) (**eTable 1**). At enrollment, 24,677 (3.6%) participants had a history of diabetes only, 8583 (1.2%) stroke only, 21,591 (3.1%) MI only, 3233 (0.5%) both diabetes and MI, 1321 (0.2%) both diabetes and stroke, 1836 (0.3%) both stroke and MI, and 541 (0.1%) with diabetes, stroke, and MI. During 8.83 million person-years at risk (median follow-up 12.8 [$5^{th}$ and $95^{th}$ percentile: 4.0-29.5] years), there were 128,843 deaths (50,595 vascular, 39,266 cancer, 30,664 other causes, 8318 unknown or ill-defined; **eTable 1**).

In the reference group, the sex-adjusted mortality rate at age 60 years was 6.8 (95% CI 6.2-7.4) per 1000 person-years at risk. By contrast, age- and sex-adjusted mortality rates were 15.6 (14.1-17.0) with diabetes only, 16.1 (14.4-17.8) with stroke only, 16.8 (15.2-18.3) with MI only, 32.0 (28.1-35.9) with both diabetes and MI, 32.5 (27.0-37.9) with both diabetes and stroke, 32.8 (28.1-37.6) with both stroke and MI, and 59.5 (47.0-71.9) with diabetes, stroke, and MI. Compared with the reference group, HRs for mortality, adjusted for age and sex only, were 1.9 (1.8-2.0) with diabetes only, 2.1 (2.0-2.2) with stroke only, 2.0 (1.9-2.2) with MI only, 3.7 (3.3-4.1) with both diabetes and MI, 3.8 (3.5-4.2) with both diabetes and stroke, 3.5 (3.1-4.0) with both stroke and MI, and 6.9 (5.7-8.3) in people with diabetes, stroke, and MI (**Figure 1**). HRs with a history of ≥2 conditions were generally consistent with multiplicative effects ($P>0.05$ for deviation from multiplicative effects), with the exception of the HR with a history of stroke and MI ($P<0.001$). HRs were stronger among women than in men for patients with diabetes only, stroke only, or the combination of diabetes and MI ($P<0.001$; **eFigure 3**). HRs were little changed after additional adjustment for smoking (**Table 2**). HRs attenuated slightly after further adjustment for total and HDL cholesterol, systolic blood pressure, and body-mass index. In people with all three conditions at baseline, HRs, adjusted for age and sex only, were: 11.8 (9.6-14.6) for

cardiovascular mortality, 2.1 (1.5-2.9) for cancer mortality, and 7.9 (6.6-9.6) for the aggregate of nonvascular, noncancer deaths (**eFigure 4**).

Broadly similar HRs to those noted above were observed in analyses that: used alternative definitions of baseline disease (**eFigure 5**); were restricted to studies that supplemented death certificates with additional information (**eFigure 6**); excluded the initial 5 years of follow-up (**eFigure 7**); or used fixed-effect meta-analysis (**eFigure 8**). HRs for mortality appeared to decline somewhat with increasing calendar year of baseline study enrollment (**eFigure 9**).

**UK Biobank**

The mean age at baseline was 57 (SD 8) years; 55% were women (**Table 1**). At enrollment, 18,549 (3.7%) participants had a history of diabetes only, 6835 (1.4%) stroke only, 8770 (1.8%) MI only, 2036 (0.4%) both diabetes and MI, 966 (0.2%) both diabetes and stroke, 688 (0.1%) both stroke and MI, and 230 (0.05%) with diabetes, stroke, and MI. During 2.39 million person-years at risk (median follow-up 4.8 [IQR: 4.1-5.5] years), there were 7995 deaths. Compared with the reference group, HRs for mortality, adjusted for age and sex only, were: 1.6 (1.5-1.8) with diabetes only, 2.1 (1.9-2.4) with stroke only, 2.1 (1.9-2.3) with MI only, 4.3 (3.7-5.0) with both diabetes and MI, 3.9 (3.1-4.9) with both diabetes and stroke, 3.8 (2.9-4.9) with both stroke and MI, and 6.0 (4.2-8.7) in people with diabetes stroke, and MI (**Figure 2** & **eTable 3**). HRs were little changed after additional adjustment for smoking, systolic blood pressure, body-mass index, diet, and socioeconomic status (**Table 2**).

**Estimated reductions in life expectancy**

We estimated that at age 60 years men with any two of the cardiometabolic conditions we studied would, on average, have a reduced life expectancy of 12 years, and men with all three conditions would have a reduced life expectancy of 14 years (**Figure 3** & **eTable 4**). For women at age 60 years, the corresponding estimates were 13 and 16 years of life lost, respectively. When calculated for patients at younger ages, estimated reductions in life expectancy were greater than

for older patients (eg, 23 years of life were estimated to be lost for men at age 40 with three conditions, compared with 20 years of life lost for men at age 50 with three conditions). Estimated reductions in life expectancy in people with MI only were greater for men than women; estimated reductions in life expectancy in people with diabetes only were greater for women (**Figure 3** & **eTable 4**). On average, about 59% of the survival difference associated with cardiometabolic multimorbidity in men was attributed to excess cardiovascular deaths, and the remainder to excess nonvascular, noncancer deaths (36%), cancer deaths (4%), and unclassified deaths (1%). By contrast, for women, 45% of the estimated survival difference was attributed to excess cardiovascular deaths, and the remainder by nonvascular, noncancer deaths (49%), excess cancer deaths (5%), and unclassified deaths (2%) (**eFigure 10**). Broadly similar results were observed when modeling involved cause-specific death rates from the EU (**eFigure 11**).

**Systematic review**

We could not identify any previous relevant reports of all-cause mortality that had investigated participants having the combination of diabetes, stroke, and MI, nor any previous relevant reports of participants having the combination of stroke and MI. We identified only one previous relevant report on the combination of diabetes and stroke, albeit of limited statistical power.[23] By contrast, we identified five previous reports on the combination of diabetes and MI, which generally yielded similar HRs as in the current analysis (**Figure 2** & **eTable 5**), although none estimated reductions in life expectancy associated with such multimorbidity.[9-12;14]

## DISCUSSION

Our analysis of over 135,000 deaths accrued during prolonged follow-up of almost 1.2 million participants in population cohorts has provided estimates of reductions in life expectancy associated with different combinations of cardiometabolic multimorbidity (i.e., a history of diabetes, stroke, and/or MI). Each of our three main findings has potential implications.

First, we observed HRs for mortality of about 2, 4, and 8, respectively, in people who had only one condition, or a combination of any two or three conditions that we studied. These results suggest that associations of cardiovascular disease and diabetes with mortality are multiplicative and essentially non-overlapping. This finding is consistent with previous observations that associations of diabetes with chronic disease outcomes are largely independent of major cardiovascular risk factors.[5;24] Consequently, our results emphasize the importance of measures to prevent cardiovascular disease in people who already have diabetes, and, conversely, to avert diabetes in people who already have cardiovascular disease.[25;26]

Second, our results suggest that estimated reductions in life expectancy associated with cardiometabolic multimorbidity are of similar magnitude to those previously noted for exposures of major concern to public health, such as lifelong smoking (10 years of reduced life expectancy[27]) and infection with human immunodeficiency virus (11 years of reduced life expectancy[28;29]). For example, cardiometabolic multimorbidity at age 60 years was associated with an average reduction in life expectancy of about 15 years. We estimated even greater reductions in life expectancy in patients with multimorbidity at younger ages, such as 23 years of life lost in patients with three conditions at age 40 years.

Third, we noted modification by sex of associations between cardiometabolic multimorbidity and mortality. For men, the association between baseline cardiovascular disease (i.e., a history of stroke or MI) and reduced survival was stronger than for women, whereas the association between baseline diabetes and reduced survival was stronger for women. Consequently, for men

about 60% of the years of life lost from cardiometabolic multimorbidity can be attributed to cardiovascular deaths, compared to only about 45% for women. Nevertheless, for both men and women, our findings indicate that associations of cardiometabolic multimorbidity extend beyond cardiovascular mortality. Future work will seek to elucidate explanations for these interactions by sex.

Our results highlight the need to balance "high-risk" approaches and population-wide strategies in order to optimize disease prevention. About 1% of the participants in the cohorts we studied had cardiometabolic multimorbidity, compared with an estimate of 3% from recent surveys in the US[30;31]. There are currently an estimated 10 million adults in the US and the European Union with cardiometabolic multimorbidity[1;3;20;21]. Nevertheless, an over-emphasis on the substantial reductions in life expectancy estimated for the subpopulation with multimorbidity could divert attention and resources away from population-wide strategies that aim to improve health for the large majority of the population.[32]

Our study had potential limitations. Our definition of cardiometabolic multimorbidity was both pragmatically motivated (we had information available on a history of diabetes, stroke, and MI) and biologically motivated (we purposefully focused on binary disease states). However, we did not include a history of hypertension in our definition of multimorbidity because categorizing elevated blood pressure as a binary variable would necessarily underestimate the true impact of blood pressure on chronic disease, since blood pressure has a continuous log-linear relationship with the risk of cardiovascular diseases throughout its range of values.[33] Furthermore, inclusion of hypertension in our definition would have created 16 possible disease combinations, too many for stable analyses even in the ERFC. We did not have access to time-varying exposure information to enable updating of multimorbidity status during follow-up. Only subsets of participants had information on some covariates, such as medication use, and dates of diagnosis of baseline conditions.

The generalizability of our results was enhanced by involvement in the ERFC of individual-participant data from 91 cohorts in 18 different countries that recruited participants during 1960-2007. To what extent do the HRs from the ERFC reflect the contemporary situation? Our study addressed this concern in several ways. We analyzed data in the ERFC by calendar decade, and we did not find evidence of large differences in HRs by calendar period of recruitment. We noted broadly similar findings between the ERFC and UK Biobank, which recruited participants during 2006-2010. Our systematic review found that HRs reported in previous relevant publications were compatible to those in the ERFC, although previous data were sparse. Finally, in survival modeling, we applied HRs observed in the ERFC to death rates derived from the contemporary US (and, secondarily, European Union) population.

## CONCLUSIONS

Mortality associated with a history of diabetes, stroke, or MI was similar for each condition. As any combination of these conditions was associated with multiplicative mortality risk, life expectancy was substantially lower in people with multimorbidity.

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**Table 1.** Baseline characteristics of data from the Emerging Risk Factors Collaboration and UK Biobank contributing to the current analysis, according to participants' disease status at baseline

| *Disease status at baseline* | *None* | *Diabetes only* | *Stroke only* | *MI only* | *Diabetes & MI* | *Diabetes & Stroke* | *Stroke & MI* | *Diabetes, Stroke & MI* |
|---|---|---|---|---|---|---|---|---|
| **Emerging Risk Factors Collaboration** | | | | | | | | |
| (91 studies, 689,300 participants) | | | | | | | | |
| n | 627518 (91.0) | 24677 (3.6) | 8583 (1.2) | 21591 (3.1) | 3233 (0.5) | 1321 (0.2) | 1836 (0.3) | 541 (0.1) |
| Age at survey (yrs) | 52.1 (8.9) | 57.3 (8.1) | 50.9 (7.8) | 60.5 (7.0) | 69.4 (6.5) | 67.7 (6.8) | 69.8 (6.9) | 63.8 (6.9) |
| Sex, men | 305031 (49) | 12347 (50) | 4496 (52) | 14643 (68) | 2121 (66) | 738 (56) | 1232 (67) | 322 (60) |
| Current smokers | 197335 (31) | 5343 (22) | 2086 (24) | 5759 (27) | 515 (16) | 224 (17) | 412 (22) | 82 (15) |
| Systolic blood pressure (mmHg) | 132 (19) | 141 (21) | 142 (22) | 139 (22) | 142 (22) | 150 (22) | 144 (23) | 146 (22) |
| Body mass index (kg/m$^2$) | 25.6 (4.2) | 27.9 (5.3) | 26.3 (4.5) | 26.6 (4.3) | 30.5 (4.8) | 29.0 (5.2) | 27.3 (4.5) | 28.1 (5.1) |
| Total cholesterol (mmol/l) | 5.84 (1.12) | 5.67 (1.18) | 5.85 (1.12) | 5.87 (1.15) | 5.93 (1.14) | 5.70 (1.18) | 5.76 (1.14) | 5.30 (1.15) |
| HDL-C (mmol/l) | 1.37 (0.39) | 1.24 (0.37) | 1.33 (0.40) | 1.22 (0.36) | 1.10 (0.34) | 1.15 (0.34) | 1.12 (0.37) | 1.06 (0.33) |
| **UK Biobank** | | | | | | | | |
| (499,808 participants) | | | | | | | | |
| n | 461754 (92.4) | 18549 (3.7) | 6835 (1.4) | 8770 (1.8) | 2036 (0.4) | 966 (0.2) | 668 (0.1) | 230 (0.05) |
| Age at survey (yrs) | 56.7 (8.1) | 59.6 (7.2) | 60.8 (7.0) | 62.1 (6.3) | 62.7 (5.7) | 62.2 (6.2) | 62.5 (6.1) | 61.7 (6.5) |
| Sex, men | 202816 (44) | 11184 (60) | 3683 (54) | 6981 (80) | 1709 (84) | 627 (65) | 500 (75) | 178 (77) |
| Current smokers | 47771 (10) | 1983 (11) | 1057 (15) | 1249 (14) | 277 (14) | 131 (14) | 145 (22) | 55 (24) |
| Systolic blood pressure (mmHg) | 137 (19) | 141 (17) | 140 (19) | 136 (19) | 138 (19) | 141 (19) | 137 (20) | 137 (18) |
| Body mass index (kg/m$^2$) | 27.2 (4.7) | 31.2 (5.9) | 28.3 (4.9) | 28.8 (4.6) | 31.8 (5.4) | 31.8 (5.9) | 29.3 (5.1) | 31.9 (5.3) |
| Education (vocational/university) | 278419 (61) | 9813 (54) | 3344 (50) | 4127 (48) | 851 (43) | 409 (43) | 281 (43) | 89 (40) |
| Meat consumption (≥2/week) | 301797 (65) | 13006 (70) | 4555 (67) | 6154 (70) | 1479 (73) | 672 (70) | 474 (71) | 158 (69) |
| Fruit consumption (≥3/day) | 165676 (36) | 7915 (43) | 2393 (35) | 2966 (34) | 824 (41) | 433 (45) | 224 (34) | 99 (43) |

Values are mean (SD) or No. (%)

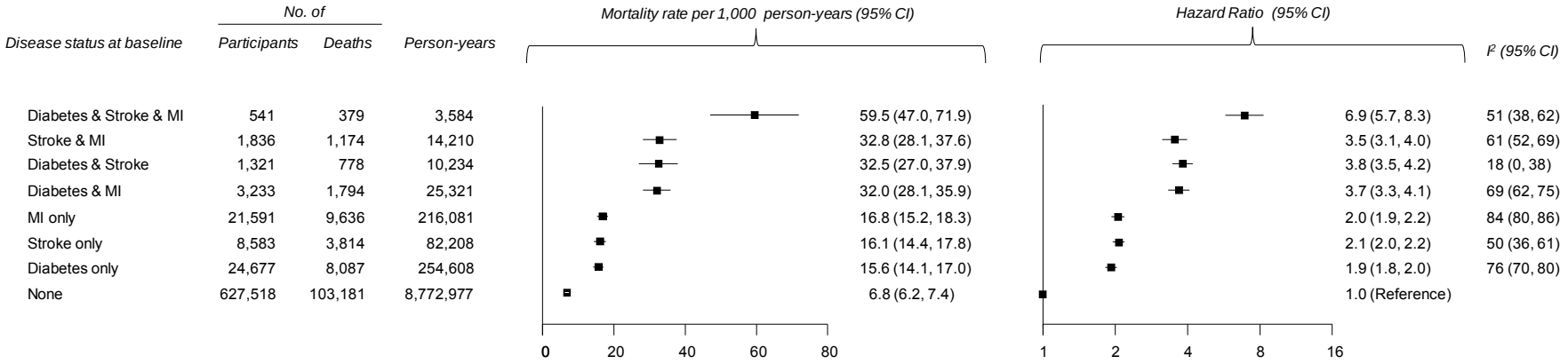
**Table 2.** Hazard ratios for all-cause mortality in subsets of participants with information on cardiovascular risk factors and other characteristics.

| *Disease status at baseline* | *No. of participants* | *No. of deaths* | *Hazard ratio (95% CI)* | | | |
|---|---|---|---|---|---|---|
| | | | *Age and sex* | *Age, sex, and smoking* | *Age, sex, smoking, and intermediate risk factors** | *Age, sex, smoking, intermediate risk factors, and other lifestyle factors†* |
| **ERFC** | | | | | | |
| (68 studies, 355,639 participants, 47,067 deaths) | | | | | | |
| Diabetes & Stroke & MI | 260 | 165 | 6.2 (5.1, 7.4) | 6.3 (5.2, 7.5) | 6.0 (5.0, 7.1) | - |
| Stroke & MI | 921 | 517 | 3.7 (3.1, 4.3) | 3.8 (3.2, 4.4) | 3.7 (3.2, 4.4) | - |
| Diabetes & Stroke | 654 | 334 | 3.7 (3.3, 4.2) | 3.9 (3.4, 4.4) | 3.6 (3.2, 4.1) | - |
| Diabetes & MI | 1,827 | 930 | 3.6 (3.1, 4.0) | 3.8 (3.3, 4.4) | 3.6 (3.2, 4.1) | - |
| MI only | 12,141 | 4,270 | 2.0 (1.9, 2.1) | 2.0 (1.9, 2.2) | 2.0 (1.9, 2.2) | - |
| Stroke only | 4,357 | 1,530 | 2.1 (1.9, 2.2) | 2.0 (1.9, 2.2) | 2.0 (1.8, 2.1) | - |
| Diabetes only | 12,887 | 3,629 | 1.9 (1.7, 2.0) | 1.9 (1.8, 2.0) | 1.8 (1.7, 1.9) | - |
| None | 322,592 | 35,692 | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) | - |
| **UK Biobank** | | | | | | |
| (491,424 participants, 7,688 deaths) | | | | | | |
| Diabetes & Stroke & MI | 218 | 26 | 5.8 (3.9, 8.5) | 5.2 (3.5, 7.7) | 4.9 (3.3, 7.2) | 4.9 (3.3, 7.2) |
| Stroke & MI | 638 | 51 | 3.6 (2.7, 4.7) | 3.2 (2.5, 4.3) | 3.1 (2.4, 4.1) | 3.1 (2.3, 4.0) |
| Diabetes & Stroke | 919 | 75 | 3.9 (3.1, 4.9) | 3.8 (3.0, 4.8) | 3.6 (2.9, 4.5) | 3.6 (2.8, 4.5) |
| Diabetes & MI | 1,943 | 190 | 4.3 (3.7, 5.0) | 4.2 (3.6, 4.8) | 4.0 (3.4, 4.6) | 3.9 (3.4, 4.5) |
| MI only | 8,572 | 407 | 2.1 (1.9, 2.3) | 2.0 (1.8, 2.3) | 2.0 (1.8, 2.2) | 2.0 (1.8, 2.2) |
| Stroke only | 6,632 | 259 | 2.1 (1.8, 2.4) | 2.0 (1.8, 2.3) | 2.0 (1.7, 2.2) | 1.9 (1.7, 2.2) |
| Diabetes only | 17,928 | 504 | 1.6 (1.5, 1.8) | 1.6 (1.5, 1.8) | 1.5 (1.4, 1.7) | 1.5 (1.4, 1.7) |
| None | 454,574 | 6,176 | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |

* Intermediate risk factors available in the ERFC were: body mass index, systolic blood pressure, total and HDL cholesterol. Intermediate risk factors available in the UK Biobank were: body mass index, and systolic blood pressure.

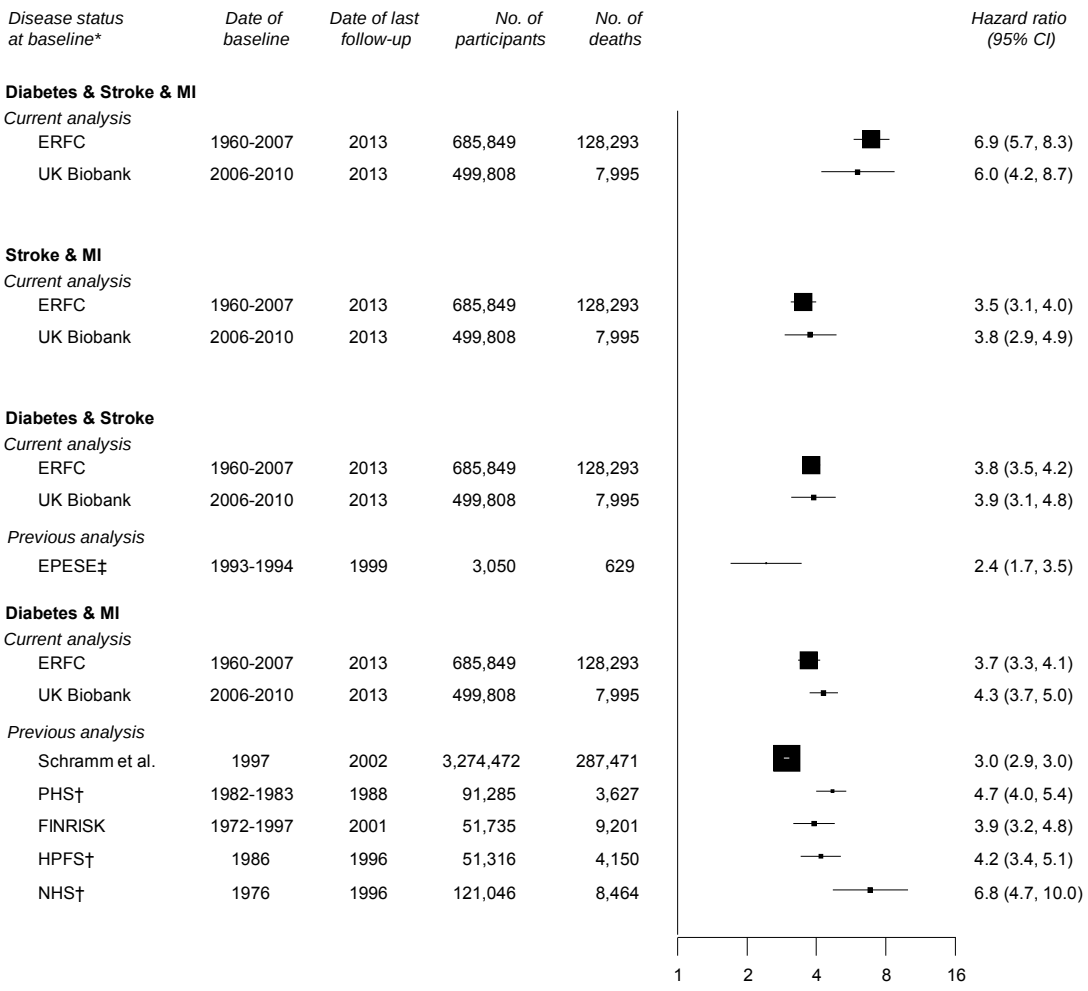
† Other lifestyle factors in the UK Biobank were: socioeconomic status (defined as education level) and diet (defined as self-reported meat and fruit consumption

**Figure 1.** Mortality rates and hazard ratios in the Emerging Risk Factors Collaboration for all-cause mortality, according to participants' disease status at baseline



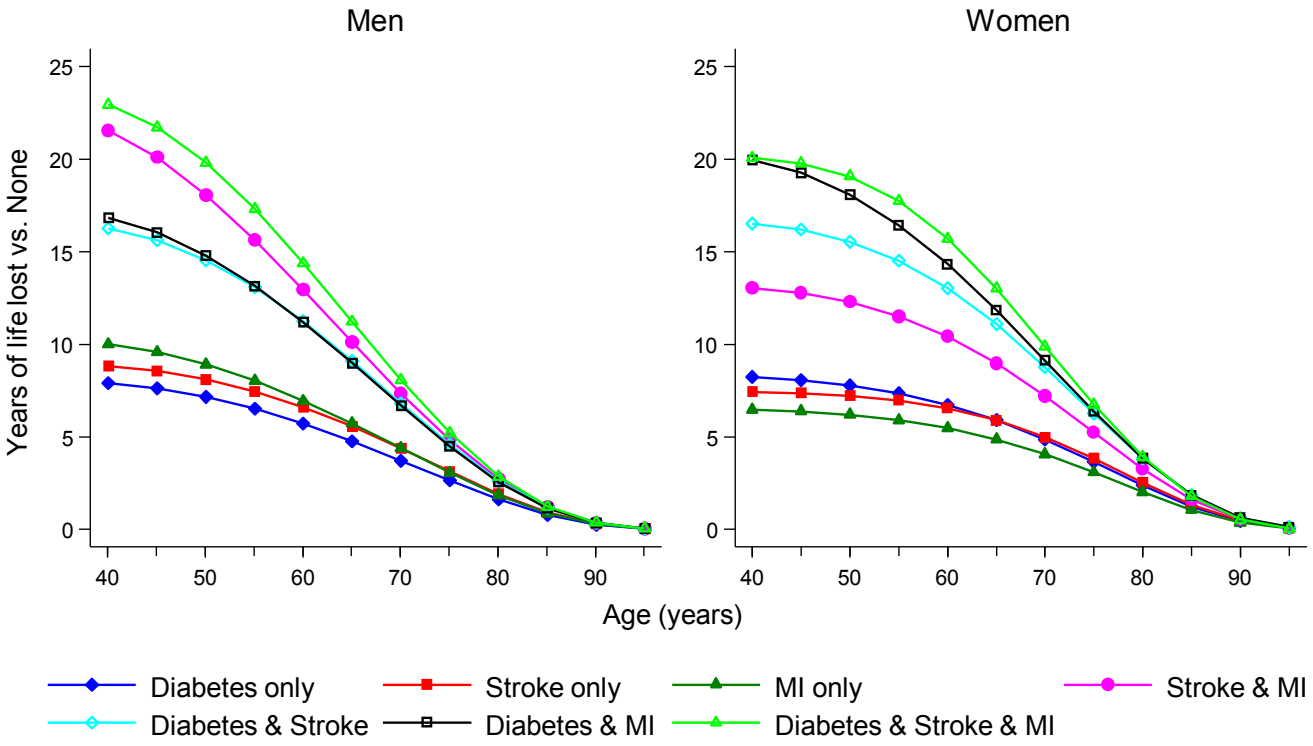

Mortality rates were calculated using a Poisson regression model and are sex-adjusted rates at age 60 years. Hazard ratios were calculated using a Cox proportional-hazards regression model and are stratified by sex and adjusted by age at baseline. Analyses were based on participants from 91 studies.

**Figure 2.** Comparison of hazard ratios for all-cause mortality from the Emerging Risk Factors Collaboration with those from UK Biobank and previous reports.




Abbreviations: CI, confidence interval; EPESE, Hispanic Established Population for the Epidemiological Study of the Elderly; ERFC, Emerging Risk Factors Collaboration; HPFS, Health Professionals Follow-up Study; MI, myocardial infarction; NHS, Nurses' Health Study; PHS, Physicians' Health Study. *For participant-level analyses in the ERFC and UK Biobank, participants with the disease status indicated at baseline have been compared with participants within the same cohorts without diabetes, stroke, or myocardial infarction at baseline. For previously published studies, participants with cardiometabolic multimorbidity at baseline were compared with participants without any such conditions. †Used history of CHD instead of history of MI. Hazard ratios are adjusted for sex (when appropriate) and age, except those for EPESE and Renfrew Paisley which are adjusted for additional variables.

**Figure 3.** Modeling of years of life lost according to participants' disease status at baseline compared to participants free of diabetes, stroke and myocardial infarction




Estimates of cumulative survival from 40 years of age onwards among the eight baseline disease groups were calculated by applying hazard ratios (specific to age-at-risk and sex) for cause-specific mortality associated with baseline disease status to US cause-specific death rates at 40 years of age and older.