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Original Investigation

Association of Cardiometabolic Multimorbidity With Mortality

The Emerging Risk Factors Collaboration

IMPORTANCE The prevalence of cardiometabolic multimorbidity is increasing.

OBJECTIVE To estimate reductions in life expectancy associated with cardiometabolic multimorbidity.

DESIGN, SETTING, AND PARTICIPANTS Age- and sex-adjusted mortality rates and hazard ratios (HRs) were calculated using individual participant data from the Emerging Risk Factors Collaboration (689 300 participants; 91 cohorts; years of baseline surveys: 1960-2007; latest mortality follow-up: April 2013; 128 843 deaths). The HRs from the Emerging Risk Factors Collaboration were compared with those from the UK Biobank (499 808 participants; years of baseline surveys: 2006-2010; latest mortality follow-up: November 2013; 7995 deaths). Cumulative survival was estimated by applying calculated age-specific HRs for mortality to contemporary US age-specific death rates.

EXPOSURES A history of 2 or more of the following: diabetes mellitus, stroke, myocardial infarction (MI).

MAIN OUTCOMES AND MEASURES All-cause mortality and estimated reductions in life expectancy.

RESULTS In participants in the Emerging Risk Factors Collaboration without a history of diabetes, stroke, or MI at baseline (reference group), the all-cause mortality rate adjusted to the age of 60 years was 6.8 per 1000 person-years. Mortality rates per 1000 person-years were 15.6 in participants with a history of diabetes, 16.1 in those with stroke, 16.8 in those with MI, 32.0 in those with both diabetes and MI, 32.5 in those with both diabetes and stroke, 32.8 in those with both stroke and MI, and 59.5 in those with diabetes, stroke, and MI. Compared with the reference group, the HRs for all-cause mortality were 1.9 (95% CI, 1.8-2.0) in participants with a history of diabetes, 2.1 (95% CI, 2.0-2.2) in those with stroke, 2.0 (95% CI, 1.9-2.2) in those with MI, 3.7 (95% CI, 3.3-4.1) in those with both diabetes and MI, 3.8 (95% CI, 3.5-4.2) in those with both diabetes and stroke, 3.5 (95% CI, 3.1-4.0) in those with both stroke and MI, and 6.9 (95% CI, 5.7-8.3) in those with diabetes, stroke, and MI. The HRs from the Emerging Risk Factors Collaboration were similar to those from the more recently recruited UK Biobank. The HRs were little changed after further adjustment for markers of established intermediate pathways (eg, levels of lipids and blood pressure) and lifestyle factors (eg, smoking, diet). At the age of 60 years, a history of any 2 of these conditions was associated with 12 years of reduced life expectancy and a history of all 3 of these 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. Because any combination of these conditions was associated with multiplicative mortality risk, life expectancy was substantially lower in people with multimorbidity.

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Group Information: The authors/members of the Emerging Risk Factors Collaboration appear at the end of this article. The investigators of the Emerging Risk Factors Collaboration appear in eAppendix 1 in the Supplement.

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The prevalence of cardiometabolic multimorbidity (defined herein as a history of ≥2 of the following: diabetes mellitus, stroke, myocardial infarction [MI]) is increasing rapidly.[1-3] Considerable evidence exists about the mortality risk of having any 1 of these conditions alone.[4-7] However, evidence is sparse about life expectancy among people who have 2 or 3 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) from 689 300 participants recruited during 1960 through 2007 into 91 prospective cohorts that have recorded mortality during prolonged follow-up. We compared the ERFC results with those from the UK Biobank, a prospective cohort study of 499 808 participants recruited during 2006 through 2010.

Methods

Overall Design

Our analysis involved several interrelated components (eFigure 1 in the Supplement). 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 the UK Biobank. The UK Biobank recruited participants more recently than the ERFC and it 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 age-specific 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 the UK Biobank have been described.[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) had recorded cause-specific deaths, and (5) had accrued more than 1 year of follow-up. Details of the contributing studies in the ERFC are presented in eTable 1 and eAppendix 2 in the Supplement. Information on the methods used to characterize diagnosis of diabetes, stroke, and MI at the baseline survey are presented in eTable 2. 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, Eighth-Tenth Revisions,* to at least 3 digits, or according to study-specific classification systems. Classification of deaths was based on death certificates, which was supplemented in 53 studies by medical records, findings on autopsy, and other sources. The date of the latest mortality follow-up was April 2013.

In the UK Biobank, information on a baseline history of diabetes, stroke, and MI was available for 499 808 participants recruited from 22 centers throughout the United Kingdom (eAppendix 3 in the Supplement). 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 the 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), or on the basis of coding from the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,* to at least 3 digits. The date of the latest mortality follow-up was November 2013.

Details of our systematic review of population-based prospective studies reported between January 1970 and April 2015 appear in eAppendix 4 in the Supplement. No language restrictions were applied to the publications. Studies were not eligible for the review if they had contributed data to the ERFC.[8,13,18] Two authors (P.W. and L.M.O.K.) extracted and cross-checked information from publications according to a prespecified protocol and disagreements were resolved by a third author (E.D.A.).

Approval was provided by the Cambridgeshire Ethics Review Committee.

Statistical Analysis

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

Hazard ratios (HRs) were calculated using Cox proportional hazards regression models. The principal objective of our study was to estimate reductions in life expectancy associated with having different combinations of cardiometabolic multimorbidity. To this end, our primary analysis calculated HRs stratified by sex and adjusted for age only. A secondary objective was to explore the extent to which markers of some established intermediate pathways (ie, total and high-density lipoprotein cholesterol, blood pressure, body mass index) and lifestyle factors (ie, smoking, diet, socioeconomic status) could explain associations between cardiometabolic multimorbidity and mortality. To this end, subsidiary analyses calculated HRs adjusted for these additional fac-

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Table 1. Baseline Characteristics of Participants by Disease Status at Baseline

	Disease Status at Baseline							
	None	Diabetes	Stroke	MI	Diabetes and MI	Diabetes and Stroke	Stroke and MI	Diabetes, Stroke, and MI
Emerging Risk Factors Collaboration (91 Studies; 689 300 Participants)								
No. (%) of participants	627 518 (91.0)	24 677 (3.6)	8583 (1.2)	21 591 (3.1)	3233 (0.5)	1321 (0.2)	1836 (0.3)	541 (0.1)
Age at survey, mean (SD), y	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)
Male sex, No. (%)[a]	305 031 (49)	12 347 (50)	4496 (52)	14 643 (68)	2121 (66)	738 (56)	1232 (67)	322 (60)
Current smoker, No. (%)[a]	197 335 (31)	5343 (22)	2086 (24)	5759 (27)	515 (16)	224 (17)	412 (22)	82 (15)
Systolic blood pressure, mean (SD), mm Hg	132 (19)	141 (21)	142 (22)	139 (22)	142 (22)	150 (22)	144 (23)	146 (22)
Body mass index, mean (SD)[b]	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)
Cholesterol, mean (SD), mmol/L								
Total	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)
High-density lipoprotein	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)								
No. (%) of participants	461 754 (92.4)	18 549 (3.7)	6835 (1.4)	8770 (1.8)	2036 (0.4)	966 (0.2)	668 (0.1)	230 (0.05)
Age at survey, mean (SD), y	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)
Male sex, No. (%)[c]	202 816 (44)	11 184 (60)	3683 (54)	6981 (80)	1709 (84)	627 (65)	500 (75)	178 (77)
Current smoker, No. (%)[c]	47 771 (10)	1983 (11)	1057 (15)	1249 (14)	277 (14)	131 (14)	145 (22)	55 (24)
Systolic blood pressure, mean (SD), mm Hg	137 (19)	141 (17)	140 (19)	136 (19)	138 (19)	141 (19)	137 (20)	137 (18)
Body mass index, mean (SD)[b]	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 or university), No./Total (%)	278 419/ 457 263 (61)	9813/ 18 162 (54)	3344/ 6746 (50)	4127/ 8636 (48)	851/ 1989 (43)	409/ 945 (43)	281/ 657 (43)	89/ 224 (40)
Food consumption								
Meat (≥2/wk), No. (%)[c]	301 797 (65)	13 006 (70)	4555 (67)	6154 (70)	1479 (73)	672 (70)	474 (71)	158 (69)
Fruit (≥3/d)[c]	165 676 (36)	7915 (43)	2393 (35)	2966 (34)	824 (41)	433 (45)	224 (34)	99 (43)

Abbreviation: MI, myocardial infarction.

SI conversion factors: To convert high-density lipoprotein and total cholesterol to mg/dL, divide by 0.0259.

[a] The denominators used to calculate the percentages are in row 2 of this Table.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] The denominators used to calculate the percentages are in row 12 of this Table.

tors. The HRs in the ERFC 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 the analyses irrespective of previous nonfatal events. For each specific cause of death, outcomes were censored if a participant was lost to follow-up, died of other causes, or reached the end of the follow-up period. The proportional hazards assumption was satisfied for all-cause mortality (eFigure 2 in the Supplement). We used the I^2 statistic to quantify between-study heterogeneity and the Wald test to assess interactions.

Because 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 the age of 60 years (ie, marginal effects).

Detail of the methods used to estimate reductions in life expectancy is in eAppendix 5 in the Supplement. Briefly, estimates of cumulative survival from 40 years of age onward among the 8 baseline disease groups were calculated by applying the HRs for cause-specific mortality from the ERFC (specific to age at risk and sex) to the detailed mortality component of the US Centers for Disease Control and Prevention's CDC WONDER database, which recorded almost 10 million deaths among more than 305 million individuals during 2007 through 2010.[20,21] We modeled results throughout middle age and old age, giving specific consideration to the HRs with cardiometabolic multimorbidity recorded by the age of 60 years, the period of life when multimorbidity becomes increasingly common.[22] Analyses involved Stata version 12.0 (StataCorp), 2-sided P values, and used a significance level of $P < .05$.

Results

Emerging Risk Factors Collaboration

At baseline, the mean (SD) age was 53 (9) years and 51% were women (**Table 1**). The large majority of participants were enrolled in Europe (69%) or North America (24%) (eTable 1 in the Supplement). Of 689 300 participants, 24 677 (3.6%) had a history of diabetes at enrollment, 8583 (1.2%) had stroke, 21 591

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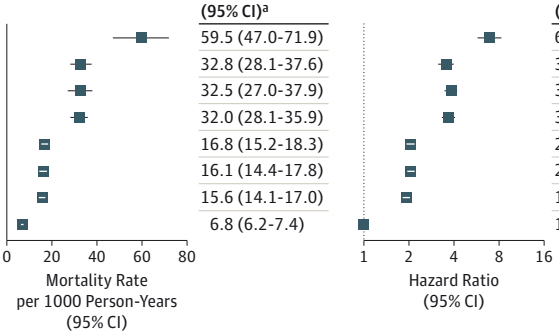
Figure 1. All-Cause Mortality for the Emerging Risk Factors Collaboration by Disease Status of Participants at Baseline

Disease Status at Baseline	No of. Participants	No. of Deaths	Person-Years	Mortality Rate (95% CI)[a]	Hazard Ratio (95% CI)	I^2 (95% CI)
Diabetes, stroke, and MI	541	379	3584	59.5 (47.0-71.9)	6.9 (5.7-8.3)	51 (38-62)
Stroke and MI	1836	1174	14 210	32.8 (28.1-37.6)	3.5 (3.1-4.0)	61 (52-69)
Diabetes and stroke	1321	778	10 234	32.5 (27.0-37.9)	3.8 (3.5-4.2)	18 (0-38)
Diabetes and MI	3233	1794	25 321	32.0 (28.1-35.9)	3.7 (3.3-4.1)	69 (62-75)
MI	21 591	9636	216 081	16.8 (15.2-18.3)	2.0 (1.9-2.2)	84 (80-86)
Stroke	8583	3814	82 208	16.1 (14.4-17.8)	2.1 (2.0-2.2)	50 (36-61)
Diabetes	24 677	8087	254 608	15.6 (14.1-17.0)	1.9 (1.8-2.0)	76 (70-80)
None	627 518	103 181	8 772 977	6.8 (6.2-7.4)	1 [Reference]	



The mortality rates were calculated using a Poisson regression model and are sex-adjusted rates to the age of 60 years. The 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. MI indicates myocardial infarction.

[a] Mortality rate is per 1000 person-years.

(3.1%) had MI, 3233 (0.5%) had a history of both diabetes and MI, 1321 (0.2%) had both diabetes and stroke, 1836 (0.3%) had both stroke and MI, and 541 (0.1%) had diabetes, stroke, and MI. There were 128 843 deaths (50 595 due to vascular causes; 39 266, cancer; 30 664, other causes; and 8318, unknown or ill-defined causes) during 8.83 million person-years at risk (median follow-up, 12.8 years; 5th-95th percentile, 4.0-29.5 years) (eTable 1).

In the reference group, the sex-adjusted mortality rate at the age of 60 years was 6.8 (95% CI, 6.2-7.4) per 1000 person-years at risk. By contrast, the age- and sex-adjusted mortality rates were 15.6 (95% CI, 14.1-17.0) in participants with a history of diabetes, 16.1 (95% CI, 14.4-17.8) in those with stroke, 16.8 (95% CI, 15.2-18.3) in those with MI, 32.0 (95% CI, 28.1-35.9) in those with a history of both diabetes and MI, 32.5 (95% CI, 27.0-37.9) in those with both diabetes and stroke, 32.8 (95% CI, 28.1-37.6) in those with both stroke and MI, and 59.5 (95% CI, 47.0-71.9) in those with diabetes, stroke, and MI (**Figure 1**).

Compared with the reference group, the age- and sex-adjusted HRs for mortality were 1.9 (95% CI, 1.8-2.0) for participants with a history of diabetes, 2.1 (95% CI, 2.0-2.2) in those with stroke, 2.0 (95% CI, 1.9-2.2) in those with MI, 3.7 (95% CI, 3.3-4.1) in those with a history of both diabetes and MI, 3.8 (95% CI, 3.5-4.2) in those with both diabetes and stroke, 3.5 (95% CI, 3.1-4.0) in those with both stroke and MI, and 6.9 (95% CI, 5.7-8.3) in those with diabetes, stroke, and MI (Figure 1).

The HRs for participants with a history of 2 or more conditions were generally consistent with multiplicative effects ($P > .05$ for deviation from multiplicative effects), with the exception of the HR for those with a history of both stroke and MI ($P < .001$). The HRs were stronger among women than men for participants with diabetes only, stroke only, and those with both diabetes and MI ($P < .001$; eFigure 3 in the Supplement). The HRs were little changed after additional adjustment for smoking (**Table 2**). The HRs attenuated slightly after further adjustment for total and high-density lipoprotein cholesterol, systolic blood pressure, and body mass index. In participants with all 3 conditions at baseline, the age- and sex-adjusted HRs were 11.8 (95% CI, 9.6-14.6) for cardiovascular mortality, 2.1 (95% CI, 1.5-2.9) for cancer mortality, and 7.9 (95% CI, 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 (1) used alternative definitions of baseline disease (eFigure 5 in the Supplement), (2) were restricted to studies that supplemented death certificates with additional information (eFigure 6), (3) excluded the initial 5 years of follow-up (eFigure 7), or (4) used fixed-effect meta-analysis (eFigure 8). The HRs for mortality appeared to decline somewhat with increasing calendar year of baseline study enrollment (eFigure 9).

UK Biobank

At baseline, the mean (SD) age was 57 (8) years and 55% were women (Table 1). Of 499 808 participants, 18 549 (3.7%) had a history of diabetes at enrollment, 6835 (1.4%) had stroke, 8770 (1.8%) had MI, 2036 (0.4%) had a history of both diabetes and MI, 966 (0.2%) had both diabetes and stroke, 688 (0.1%) had both stroke and MI, and 230 (0.05%) had diabetes, stroke, and MI. There were 7995 deaths during 2.39 million person-years at risk (median follow-up, 4.8 years; interquartile range, 4.1-5.5 years).

Compared with the reference group, the age- and sex-adjusted HRs for mortality were 1.6 (95% CI, 1.5-1.8) for participants with diabetes, 2.1 (95% CI, 1.9-2.4) for those with stroke, 2.1 (95% CI, 1.9-2.3) for those with MI, 4.3 (95% CI, 3.7-5.0) for those with both diabetes and MI, 3.9 (95% CI, 3.1-4.9) for those with both diabetes and stroke, 3.8 (95% CI, 2.9-4.9) for those with both stroke and MI, and 6.0 (95% CI, 4.2-8.7) for those with diabetes, stroke, and MI (**Figure 2** and eTable 3 in the Supplement). The HRs were little changed after additional adjustment for smoking, systolic blood pressure, body mass index, diet, and socioeconomic status (Table 2).

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Table 2. All-Cause Mortality in 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
Emerging Risk Factors Collaboration (68 Studies, 355 639 Participants, 47 067 Deaths)[a]						
Diabetes, stroke, and MI	260	165	6.2 (5.1-7.4)	6.3 (5.2-7.5)	6.0 (5.0-7.1)	
Stroke and MI	921	517	3.7 (3.1-4.3)	3.8 (3.2-4.4)	3.7 (3.2-4.4)	
Diabetes and stroke	654	334	3.7 (3.3-4.2)	3.9 (3.4-4.4)	3.6 (3.2-4.1)	
Diabetes and MI	1827	930	3.6 (3.1-4.0)	3.8 (3.3-4.4)	3.6 (3.2-4.1)	
MI	12 141	4270	2.0 (1.9-2.1)	2.0 (1.9-2.2)	2.0 (1.9-2.2)	
Stroke	4357	1530	2.1 (1.9-2.2)	2.0 (1.9-2.2)	2.0 (1.8-2.1)	
Diabetes	12 887	3629	1.9 (1.7-2.0)	1.9 (1.8-2.0)	1.8 (1.7-1.9)	
None	322 592	35 692	1 [Reference]	1 [Reference]	1 [Reference]	
UK Biobank (491 424 Participants, 7688 Deaths)[b]						
Diabetes, stroke, and 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 and 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 and 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 and MI	1943	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	8572	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	6632	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	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	6176	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviation: MI, myocardial infarction.

[a] The intermediate risk factors available were body mass index; systolic blood pressure; and high-density lipoprotein and total cholesterol.

[b] The intermediate risk factors available were body mass index and systolic blood pressure. Other lifestyle factors available were socioeconomic status (defined as education level) and diet (defined as self-reported consumption of meat and fruit).

Estimated Reductions in Life Expectancy

We estimated that at the age of 60 years, men with any 2 of the cardiometabolic conditions we studied would on average have 12 years of reduced life expectancy, and men with all 3 conditions would have 14 years of reduced life expectancy (**Figure 3** and eTable 4 in the Supplement). For women at the age of 60 years, the corresponding estimates were 13 years and 16 years of life lost. 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 years with 3 conditions compared with 20 years of life lost for men at age 50 years with 3 conditions). Estimated reductions in life expectancy in patients with MI only were greater for men than women; estimated reductions in life expectancy in patients with diabetes only were greater for women (Figure 3 and 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 in the Supplement). Broadly similar results were observed when modeling involved cause-specific death rates from the European Union (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, or any previous relevant reports of participants having the combination of stroke and MI. We identified only 1 previous relevant report on the combination of diabetes and stroke, albeit of limited statistical power.[23] By contrast, we identified 5 previous reports on the combination of diabetes and MI, which generally yielded similar HRs as in the current analysis (Figure 2 and eTable 5 in the Supplement), although none estimated reductions in life expectancy associated with such multimorbidity.[9-12,14]

Discussion

Our analysis of more than 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 (ie, a history of diabetes, stroke, and/or MI). Each of our 3 main findings has potential implications.

First, in patients who had only 1 condition that we studied, we observed an HR for mortality of about 2; for a combination of any 2 conditions, the HR was about 4; and for a combination of all 3 conditions, the HR was about 8. These results suggest that associations of cardiovascular disease

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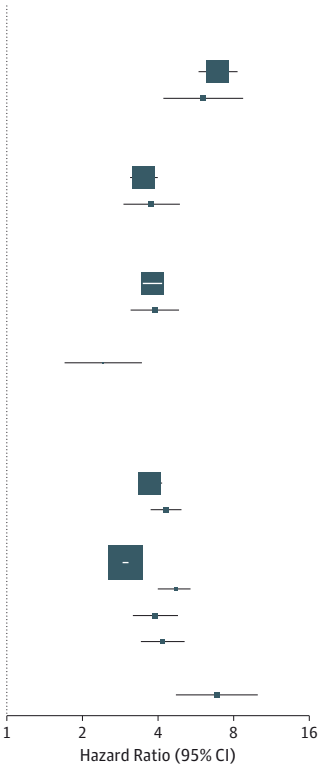
Figure 2. All-Cause Mortality From the Emerging Risk Factors Collaboration Compared With the UK Biobank and Previous Reports

Disease Status at Baseline	Date of Baseline	Date of Last Follow-up	No. of Participants	No. of Deaths	Hazard Ratio (95% CI)
Diabetes, stroke, and MI					
Current analysis					
Emerging Risk Factors Collaboration[a]	1960-2007	2013	685 849	128 293	6.9 (5.7-8.3)
UK Biobank[a]	2006-2010	2013	499 808	7995	6.0 (4.2-8.7)
Stroke and MI					
Current analysis					
Emerging Risk Factors Collaboration[a]	1960-2007	2013	685 849	128 293	3.5 (3.1-4.0)
UK Biobank[a]	2006-2010	2013	499 808	7995	3.8 (2.9-4.9)
Diabetes and stroke					
Current analysis					
Emerging Risk Factors Collaboration[a]	1960-2007	2013	685 849	128 293	3.8 (3.5-4.2)
UK Biobank[a]	2006-2010	2013	499 808	7995	3.9 (3.1-4.9)
Previous analysis[b]					
Hispanic Established Population for the Epidemiological Study of the Elderly[23]	1993-1994	1999	3050	629	2.4 (1.7-3.5)
Diabetes and MI					
Current analysis					
Emerging Risk Factors Collaboration[a]	1960-2007	2013	685 849	128 293	3.7 (3.3-4.1)
UK Biobank[a]	2006-2010	2013	499 808	7995	4.3 (3.7-5.0)
Previous analysis[b]					
Schramm et al[9]	1997	2002	3 274 472	287 471	3.0 (2.9-3.0)
Physicians' Health Study[10,c]	1982-1983	1988	91 285	3627	4.7 (4.0-5.4)
FINRISK Study[11]	1972-1997	2001	51 735	9201	3.9 (3.2-4.8)
Health Professionals Follow-up Study[12,c]	1986	1996	51 316	4150	4.2 (3.4-5.1)
Nurses' Health Study[14,c]	1976	1996	121 046	8464	6.8 (4.7-10.0)



The hazard ratios were adjusted for sex when appropriate and age, except those for the Hispanic Established Population for the Epidemiological Study of the Elderly, which were adjusted for additional variables. MI indicates myocardial infarction. The size of the data markers is proportional to the information content in each study.

[a] For participant-level analyses in the Emerging Risk Factors Collaboration and the 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.

[b] For previously published studies, participants with cardiometabolic multimorbidity at baseline were compared with participants without any such conditions.

[c] Used history of coronary heart disease instead of history of MI.

and diabetes with mortality are multiplicative and essentially nonoverlapping. 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 the human immunodeficiency virus (11 years of reduced life expectancy[28,29]). For example, cardiometabolic multimorbidity at the age of 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 3 conditions at the age of 40 years.

Third, we noted modification by sex of associations between cardiometabolic multimorbidity and mortality. For men, the association between baseline cardiovascular disease (ie, 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, about 60% of the years of life lost from cardiometabolic multimorbidity can be attributed to cardiovascular deaths for men compared with 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 the primary prevention and secondary prevention of cardiovascular disease. About 1% of the participants in the cohorts we studied had cardiometabolic multimorbidity compared with an estimate of 3% from recent surveys in the United States.[30,31] There are currently an estimated 10 million adults in the United States and the European Union with cardiometabolic

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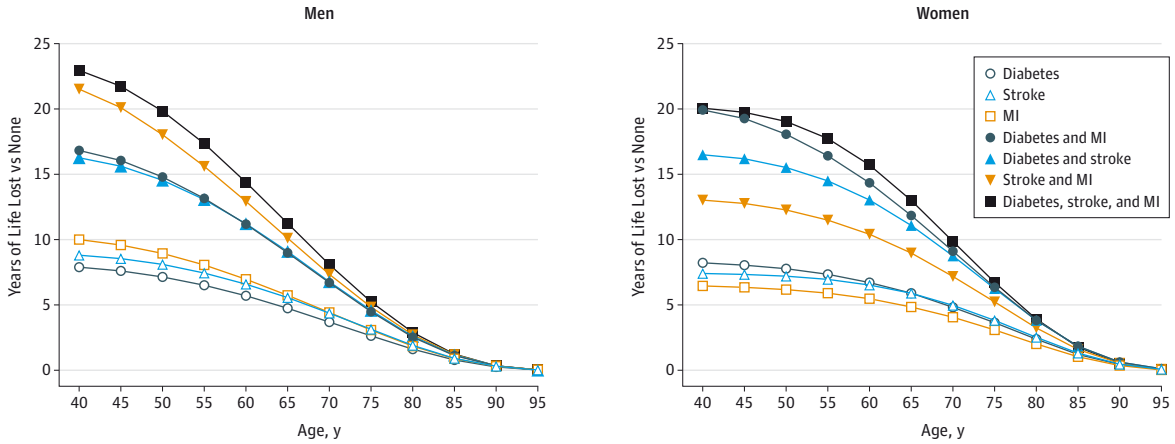
Figure 3. Modeling of Years of Life Lost by Disease Status of Participants at Baseline Compared With Those Free of Diabetes, Stroke, and Myocardial Infarction (MI)



The estimates of cumulative survival from 40 years of age onward among the 8 baseline disease groups were calculated by applying hazard ratios (specific to age at risk and sex) for all-cause mortality associated with baseline disease status to US cause-specific death rates at the age of 40 years or older.

multimorbidity.[1,3,20,21] Nevertheless, an overemphasis 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 effect of blood pressure on chronic disease because 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, which are 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 through 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 the HRs by calendar period of recruitment. We noted broadly similar findings between the ERFC and the UK Biobank, which recruited participants during 2006 through 2010. Our systematic review found that the HRs reported in previous relevant publications were compatible with those in the ERFC, although previous data were sparse. In addition, for the survival modeling, we applied the HRs observed in the ERFC to the death rates derived from the contemporary US population and secondarily to the European Union population.

Conclusions

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

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