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Association of cardiometabolic multimorbidity with mortality

The Emerging Risk Factors Collaboration

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97

98 Investigators of the Emerging Risk Factors Collaboration are listed in **eAppendix 1**

99 **ABSTRACT**

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

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

103 **Design, Setting, and Participants:** We calculated age-and sex-adjusted mortality rates and
104 hazard ratios (HRs) using individual-participant data from the Emerging Risk Factors Collaboration
105 (ERFC; 689,300 participants; 91 cohorts; years of baseline surveys: 1960-2007; latest follow-up:
106 2013; 128,843 deaths). We compared HRs with those from UK Biobank (499,808 participants;
107 years of baseline survey: 2006-2010; latest follow-up: 2013; 7995 deaths). We estimated
108 cumulative survival by applying calculated age-specific HRs for mortality to contemporary US age-
109 specific death rates.

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

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

112 **Results:** In ERFC participants without diabetes, stroke, or MI at baseline (“reference group”), the
113 all-cause mortality rate adjusted to age 60 years was 6.8 per 1000 person-years. Mortality rates
114 were 15.6 with diabetes only, 16.1 with stroke only, 16.8 with MI only, 32.0 with both diabetes
115 and MI, 32.5 with both diabetes and stroke, 32.8 with both stroke and MI, and 59.5 with diabetes,
116 stroke, and MI. Compared to the reference group, HRs (95% CI) for all-cause mortality were 1.9
117 (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-
118 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
119 both stroke and MI, and 6.9 (5.7-8.3) with diabetes, stroke and MI. HRs from the ERFC were
120 similar to those from the more recently-recruited UK Biobank. HRs were little changed after
121 further adjustment for markers of established intermediate pathways (e.g., lipids, blood pressure)
122 and lifestyle factors (e.g., smoking, diet). At age 60 years, a history of a combination of any two
123 conditions was associated with 12 years of reduced life expectancy; a history of three conditions
124 was associated with 15 years of reduced life expectancy.

125 **Conclusions and Relevance:** Mortality associated with a history of diabetes, stroke, or MI was
126 similar for each condition. As any combination of these conditions was associated with
127 multiplicative mortality risk, life expectancy was substantially lower in people with multimorbidity.
128

129 **INTRODUCTION**

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

138

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

145

146 **METHODS**

147 **Overall design**

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

156

157 **Data sources**

158 Both the ERFC and UK Biobank have been described previously¹⁵⁻¹⁷. Prospective cohort studies
159 contributing to the ERFC were included in this analysis if they met all the following criteria: 1) had
160 recruited participants on the basis of informed consent, 2) had recorded information about the
161 diagnosis of diabetes, stroke, and MI at the baseline survey, 3) did not select participants on the
162 basis of having previous chronic disease (including cardiovascular disease and diabetes), 4)
163 recorded cause-specific deaths, and 5) had accrued more than 1 year of follow-up. Details of
164 contributing studies in the ERFC are presented in eTable 1 and eAppendix 2. eTable 2 provides
165 information on methods used to characterize diagnosis of diabetes, stroke, and MI at the baseline
166 survey. The contributing studies classified deaths according to the primary cause (or, in its
167 absence, the underlying cause), on the basis of coding from the *International Classification of*
168 *Diseases*, revisions 8 through 10, to at least three digits, or according to study-specific
169 classification systems. Classification of deaths was based on death certificates, supplemented in
170 53 studies by medical records, findings on autopsy, and other sources. The date of latest
171 mortality follow-up was April 2013.

172

173 In UK Biobank, information on a baseline history of diabetes, stroke, and MI was available for
174 499,808 participants recruited from 22 centres throughout the United Kingdom (eAppendix 3).
175 After giving consent, participants provided biological samples and completed a touch-screen
176 questionnaire, a computer-assisted interview, and a physical examination. Participants have been
177 linked with death records of the UK Office for National Statistics through National Health Service
178 identification numbers. Deaths were classified according to the primary cause (or, in its absence,
179 the underlying cause), on the basis of coding from the *International Classification of Diseases 10*,
180 to at least three digits. The date of latest mortality follow-up was November 2013.

181

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

187

188 Approval was provided by the Cambridgeshire ethics review committee.

189

190 **Statistical analysis**

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

196

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

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

213

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

220

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

228 age 60, the period of life when multimorbidity becomes increasingly common²². Analyses involved
229 Stata (version 12.0), 2-sided P-values, and used a significance level of $P < 0.05$.

230 RESULTS

231 Emerging Risk Factors Collaboration

232 The mean age of participants at baseline was 53 (SD 9) years; 51% were women (Table 1). The
233 large majority were enrolled in Europe (69%) or North America (24%) (eTable 1). At enrollment,
234 24,677 (3.6%) participants had a history of diabetes only, 8583 (1.2%) stroke only, 21,591
235 (3.1%) MI only, 3233 (0.5%) both diabetes and MI, 1321 (0.2%) both diabetes and stroke, 1836
236 (0.3%) both stroke and MI, and 541 (0.1%) with diabetes, stroke, and MI. During 8.83 million
237 person-years at risk (median follow-up 12.8 [5th and 95th percentile: 4.0-29.5] years), there were
238 128,843 deaths (50,595 vascular, 39,266 cancer, 30,664 other causes, 8318 unknown or ill-
239 defined; eTable 1).

240

241 In the reference group, the sex-adjusted mortality rate at age 60 years was 6.8 (95% CI 6.2-7.4)
242 per 1000 person-years at risk. By contrast, age- and sex-adjusted mortality rates were 15.6
243 (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,
244 32.0 (28.1-35.9) with both diabetes and MI, 32.5 (27.0-37.9) with both diabetes and stroke, 32.8
245 (28.1-37.6) with both stroke and MI, and 59.5 (47.0-71.9) with diabetes, stroke, and MI.
246 Compared with the reference group, HRs for mortality, adjusted for age and sex only, were 1.9
247 (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-
248 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
249 both stroke and MI, and 6.9 (5.7-8.3) in people with diabetes, stroke, and MI (Figure 1). HRs
250 with a history of ≥ 2 conditions were generally consistent with multiplicative effects ($P > 0.05$ for
251 deviation from multiplicative effects), with the exception of the HR with a history of stroke and MI
252 ($P < 0.001$). HRs were stronger among women than in men for patients with diabetes only, stroke
253 only, or the combination of diabetes and MI ($P < 0.001$; eFigure 3). HRs were little changed after
254 additional adjustment for smoking (Table 2). HRs attenuated slightly after further adjustment for
255 total and HDL cholesterol, systolic blood pressure, and body-mass index. In people with all three
256 conditions at baseline, HRs, adjusted for age and sex only, were: 11.8 (9.6-14.6) for

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

259

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

265

266 **UK Biobank**

267 The mean age at baseline was 57 (SD 8) years; 55% were women (Table 1). At enrollment,
268 18,549 (3.7%) participants had a history of diabetes only, 6835 (1.4%) stroke only, 8770 (1.8%)
269 MI only, 2036 (0.4%) both diabetes and MI, 966 (0.2%) both diabetes and stroke, 688 (0.1%)
270 both stroke and MI, and 230 (0.05%) with diabetes, stroke, and MI. During 2.39 million person-
271 years at risk (median follow-up 4.8 [IQR: 4.1-5.5] years), there were 7995 deaths. Compared
272 with the reference group, HRs for mortality, adjusted for age and sex only, were: 1.6 (1.5-1.8)
273 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
274 both diabetes and MI, 3.9 (3.1-4.9) with both diabetes and stroke, 3.8 (2.9-4.9) with both stroke
275 and MI, and 6.0 (4.2-8.7) in people with diabetes stroke, and MI (Figure 2 & eTable 3). HRs
276 were little changed after additional adjustment for smoking, systolic blood pressure, body-mass
277 index, diet, and socioeconomic status (Table 2).

278

279 **Estimated reductions in life expectancy**

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

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

296

297 **Systematic review**

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

305

306 **DISCUSSION**

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

311

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

320

321 Second, our results suggest that estimated reductions in life expectancy associated with
322 cardiometabolic multimorbidity are of similar magnitude to those previously noted for exposures
323 of major concern to public health, such as lifelong smoking (10 years of reduced life
324 expectancy²⁷) and infection with human immunodeficiency virus (11 years of reduced life
325 expectancy^{28;29}). For example, cardiometabolic multimorbidity at age 60 years was associated
326 with an average reduction in life expectancy of about 15 years. We estimated even greater
327 reductions in life expectancy in patients with multimorbidity at younger ages, such as 23 years of
328 life lost in patients with three conditions at age 40 years.

329

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

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

339

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

348

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

361

362 The generalizability of our results was enhanced by involvement in the ERFC of individual-
363 participant data from 91 cohorts in 18 different countries that recruited participants during 1960-
364 2007. To what extent do the HRs from the ERFC reflect the contemporary situation? Our study
365 addressed this concern in several ways. We analyzed data in the ERFC by calendar decade, and
366 we did not find evidence of large differences in HRs by calendar period of recruitment. We noted
367 broadly similar findings between the ERFC and UK Biobank, which recruited participants during
368 2006-2010. Our systematic review found that HRs reported in previous relevant publications were
369 compatible to those in the ERFC, although previous data were sparse. Finally, in survival
370 modeling, we applied HRs observed in the ERFC to death rates derived from the contemporary US
371 (and, secondarily, European Union) population.

372

373 **CONCLUSIONS**

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

377

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389

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394

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

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<i>Disease status at baseline</i>	<i>None</i>	<i>Diabetes only</i>	<i>Stroke only</i>	<i>MI only</i>	<i>Diabetes & MI</i>	<i>Diabetes & Stroke</i>	<i>Stroke & MI</i>	<i>Diabetes, Stroke & MI</i>
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)

490 Values are mean (SD) or No. (%)
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Table 2. Hazard ratios for all-cause mortality in subsets of participants with information on cardiovascular risk factors and other characteristics.

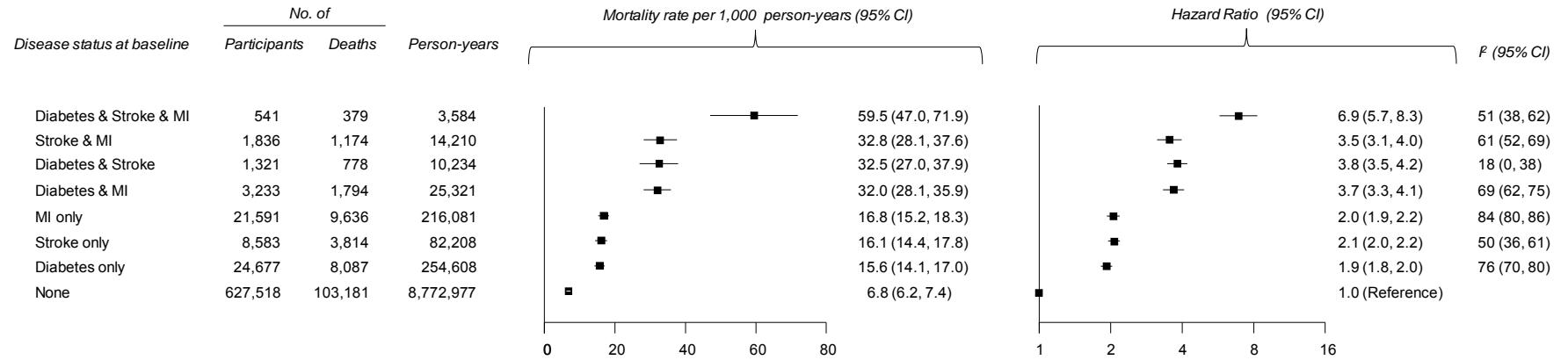
Disease status at baseline	No. of participants	No. of deaths	Hazard ratio (95% CI)			
			Age and sex	Age, sex, and smoking	Age, sex, smoking, and intermediate risk factors*	Age, sex, smoking, intermediate risk factors, and other lifestyle factors†
ERFC						
(68 studies, 355,639 participants, 47,067 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)

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* 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.

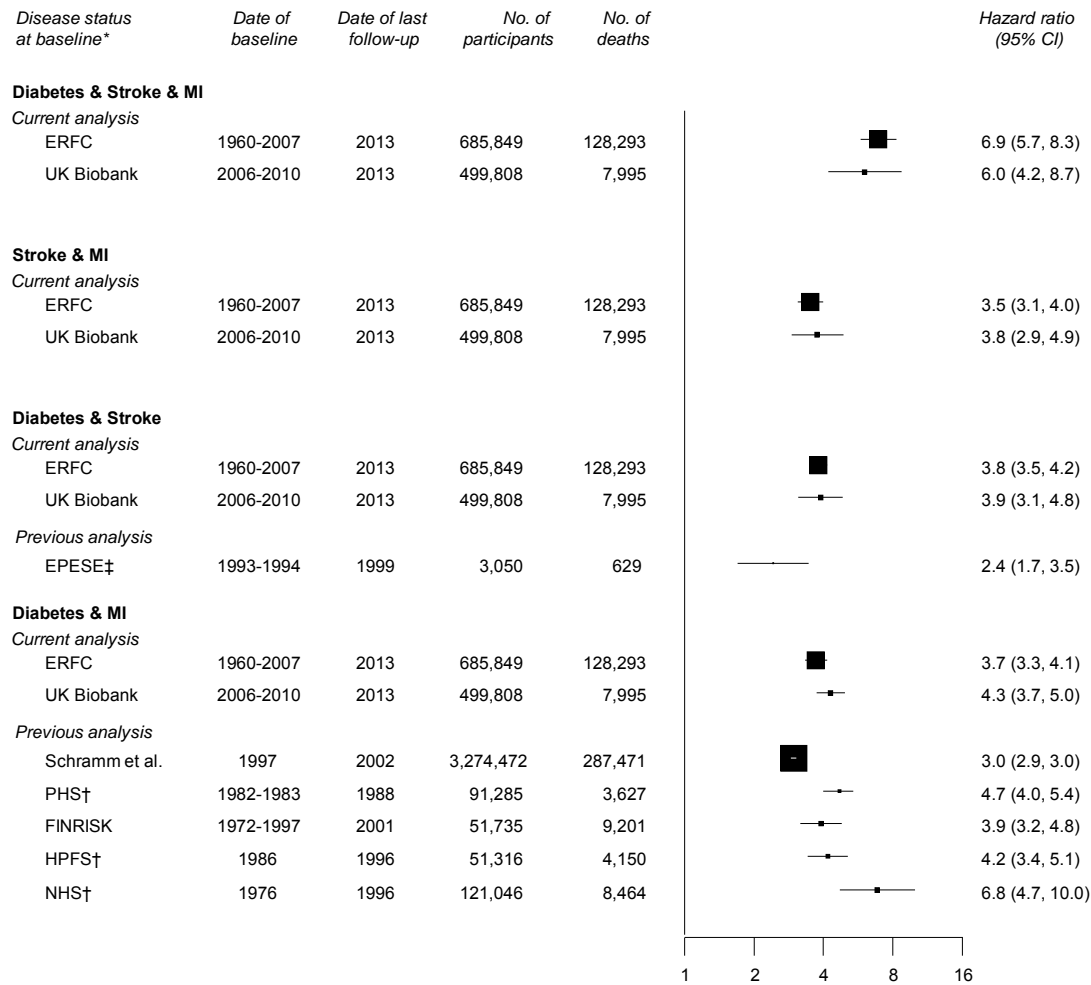
† Other lifestyle factors in the UK Biobank were: socioeconomic status (defined as education level) and diet (defined as self-reported meat and fruit consumption)

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



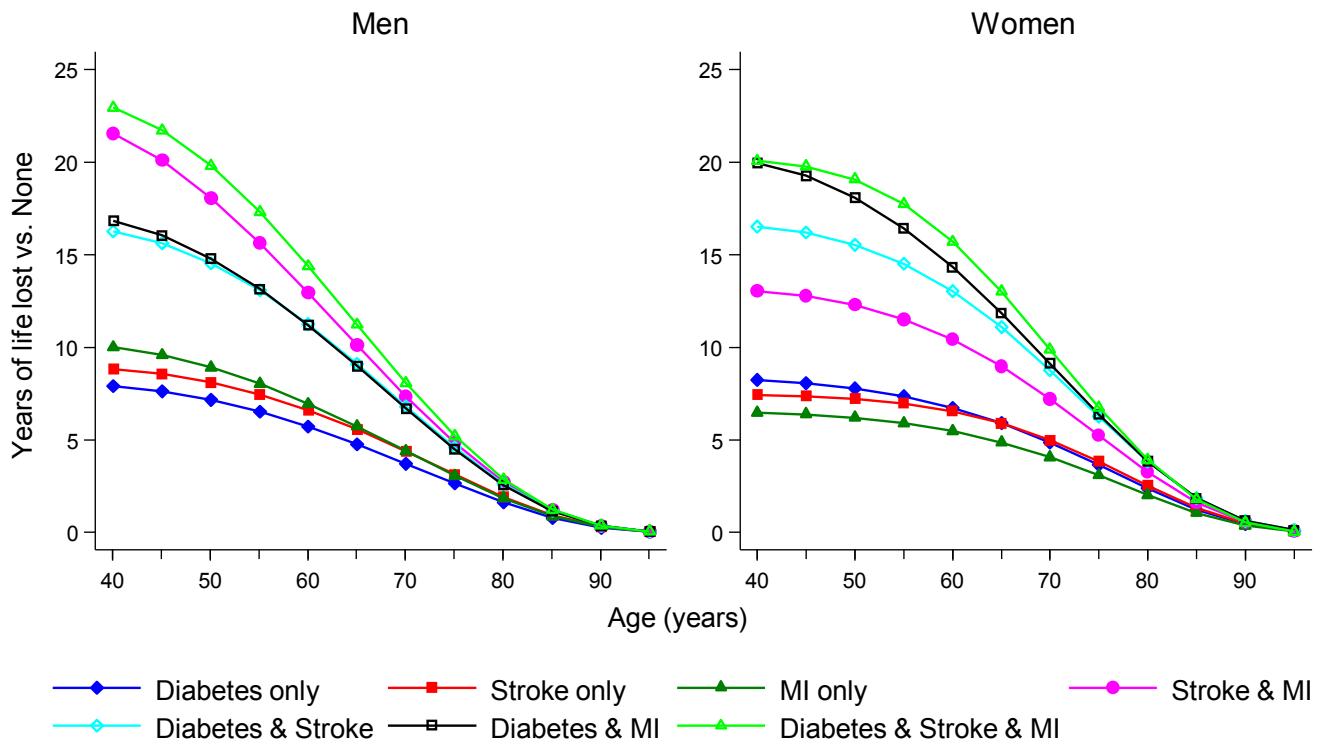
Mortality rates were calculated using a Poisson regression model and are sex-adjusted rates at age 60 years. Hazard ratios were calculated using a Cox proportional-hazards regression model and are stratified by sex and adjusted by age at baseline. Analyses were based on participants from 91 studies.

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; EPSE, 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 EPSE 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.