Supplementary Online Content

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eTable 1. Characteristics of the prospective studies contributing to the current analysis

Cohort abbreviation	Country	Median year of baseline	Date of last follow-up	No. of individuals	Age at survey (yrs) mean (sd)	Male (%)	Individuals with diabetes (%)	Individuals with previous stroke (%)	Individuals with previous MI (%)	Median years of follow-up (5th & 95th percentiles)	All-cause deaths*	Cardiovascular deaths	Cancer deaths	Nonvascular, noncancer deaths	Person-years of follow-up
ARIC[1]	USA	1988	2002	14121	55 (6)	6551 (46)	1643 (11.6)	422 (3.0)	647 (4.6)	14.1 (6.7 to 15.7)	1987	753	744	450	184166
ATENA[2]	Italy	1995	2001	4774	50 (7)	0 (0)	120 (2.5)	8 (0.2)	15 (0.3)	6.7 (5.2 to 8.1)	44	12	22	9	31891
AUSDIAB[3]	Australia	2000	2012	9542	54 (13)	4298 (45)	507 (5.3)	279 (2.9)	487 (5.1)	12.6 (7.1 to 13.5)	1068	229	276	205	59178
BHS[4]	Australia	1972	2004	6287	45 (16)	2988 (48)	102 (1.6)	33 (0.5)	76 (1.2)	24.7 (6.4 to 33.2)	2123	1019	583	503	150450
BRHS[5]	UK	1979	2005	7134	50 (6)	7134 (100)	91 (1.3)	49 (0.7)	291 (4.1)	24.5 (6.6 to 25.4)	2679	1253	853	401	141142
BRUN[6]	Italy	1990	2010	823	58 (11)	409 (50)	27 (3.3)	11 (1.3)	19 (2.3)	20.3 (5.4 to 20.5)	272	97	84	87	13797
BWHHS[7]	UK	2000	2011	3377	69 (5)	0 (0)	156 (4.6)	150 (4.4)	236 (7.0)	11.0 (4.0 to 12.2)	704	222	259	216	23234
CAPS[8]	UK	1981	1996	2435	52 (5)	2435 (100)	44 (1.8)	43 (1.8)	253 (10.4)	13.0 (5.2 to 13.0)	481	260	147	74	28181
CASTEL[9]	Italy	1984	1996	2807	74 (5)	1103 (39)	381 (13.6)	129 (4.6)	117 (4.2)	11.2 (2.1 to 14.0)	1334	676	309	329	26879
CHARL[10]	USA	1961	2000	2179	50 (11)	1031 (47)	94 (4.3)	35 (1.6)	119 (5.5)	26.6 (3.5 to 40.0)	1630	862	338	364	50305
CHS[11]	USA	1990	2005	4973	72 (5)	2053 (41)	793 (15.9)	209 (4.2)	560 (11.3)	12.6 (2.7 to 15.9)	2789	1069	686	1002	46153
COPEN[13]	Denmark	1993	2013	9083	58 (15)	3969 (44)	287 (3.2)	193 (2.1)	311 (3.4)	19.1 (2.8 to 21.2)	4274	1198	811	1486	121634
DESIR[14]	France	1995	2010	3841	48 (10)	1891 (49)	125 (3.3)	11 (0.3)	13 (0.3)	14.4 (13.5 to 15.0)	75	22	31	14	33937
DISCO[15]	Italy	1987	1992	1897	50 (11)	857 (45)	86 (4.5)	30 (1.6)	41 (2.2)	5.5 (5.5 to 9.5)	30	13	10	7	12846
DUBBO[16]	Australia	1989	2003	2462	69 (7)	1085 (44)	199 (8.1)	131 (5.3)	309 (12.6)	14.1 (2.1 to 15.0)	1082	550	230	265	25933
EAS[17]	Scotland	1988	2008	1110	64 (6)	569 (51)	59 (5.3)	39 (3.5)	70 (6.3)	20.0 (3.2 to 21.3)	579	204	188	143	16891
EMOFRI[2]	Italy	1996	2002	399	55 (6)	199 (50)	22 (5.5)	29 (7.3)	12 (3.0)	6.7 (6.5 to 7.2)	12	7	2	2	2649
EPESEBOS[18]	USA	1982	1993	1180	72 (5)	428 (36)	152 (12.9)	37 (3.1)	119 (10.1)	11.4 (7.6 to 11.9)	265	125	40	75	11487
EPESEIOW[18]	USA	1982	2008	1865	73 (5)	654 (35)	142 (7.6)	94 (5.0)	205 (11.0)	15.4 (7.3 to 26.5)	1709	794	188	528	18599
EPESENCA[18]	USA	1986	2006	1633	72 (5)	568 (35)	241 (14.8)	90 (5.5)	227 (13.9)	13.6 (7.7 to 20.7)	1071	487	173	345	15709
EPESENHA[18]	USA	1982	1992	971	73 (6)	377 (39)	110 (11.3)	55 (5.7)	115 (11.8)	10.5 (7.2 to 10.8)	256	149	13	47	9346
EPICNOR[19]	UK	1996	2005	21601	59 (9)	9854 (46)	477 (2.2)	290 (1.3)	671 (3.1)	9.8 (6.2 to 12.0)	357	357	0	0	205064
ESTHER[20]	Germany	2001	2008	8308	62 (7)	3740 (45)	1109 (13.3)	263 (3.2)	506 (6.1)	5.1 (2.0 to 5.9)	370	108	174	65	37970
FINE_FIN[21]	Finland	1989	1999	360	77 (5)	360 (100)	32 (8.9)	27 (7.5)	70 (19.4)	7.8 (0.9 to 10.0)	221	115	52	53	1937
FINE_IT[21]	Italy	1985	2006	541	73 (5)	541 (100)	47 (8.7)	36 (6.7)	34 (6.3)	11.0 (1.7 to 21.4)	464	226	129	64	5612
FINNMARK[12]	Norway	2002	2009	5777	59 (10)	2719 (47)	284 (4.9)	172 (3.0)	403 (7.0)	7.5 (4.0 to 7.5)	498	173	180	107	41508
FINRISK92[22]	Finland	1992	2008	5984	45 (11)	2820 (47)	109 (1.8)	92 (1.5)	147 (2.5)	16.9 (10.4 to 16.9)	373	137	104	131	94514
FINRISK97[22]	Finland	1997	2008	7560	50 (12)	3805 (50)	256 (3.4)	178 (2.4)	269 (3.6)	11.8 (11.7 to 11.9)	339	131	89	116	85293
FRAMOFF[23]	USA	1999	2005	2804	60 (9)	1242 (44)	312 (11.1)	21 (0.7)	41 (1.5)	5.2 (3.1 to 7.0)	131	16	59	34	14621
GOTO13[24]	Sweden	1963	1998	779	50 (0)	779 (100)	6 (0.8)	2 (0.3)	7 (0.9)	29.7 (10.9 to 34.5)	552	289	143	67	19302
GOTO33[24]	Sweden	1984	1998	740	51 (0)	740 (100)	25 (3.4)	7 (0.9)	14 (1.9)	12.8 (6.8 to 13.1)	87	28	27	29	8898
GOTO43[24]	Sweden	1993	2003	788	50 (0)	788 (100)	19 (2.4)	3 (0.4)	16 (2.0)	10.0 (9.6 to 10.7)	28	6	16	5	8478
GOTOW[25]	Sweden	1969	2009	1392	47 (6)	0 (0)	14 (1.0)	3 (0.2)	2 (0.1)	37.8 (11.9 to 41.1)	852	354	221	214	38659
GRIPS[26]	Germany	1982	1992	5846	48 (5)	5846 (100)	116 (2.0)	9 (0.2)	51 (0.9)	9.8 (8.5 to 10.0)	339	155	109	74	54086
HCS[27]	UK	2001	2010	2917	66 (3)	1503 (52)	395 (13.5)	112 (3.8)	111 (3.8)	8.8 (4.9 to 11.6)	312	80	165	66	25434
HIMS[28]	Australia	1997	2010	10942	72 (4)	10942 (100)	1218 (11.1)	801 (7.3)	1711 (15.6)	12.6 (2.3 to 14.2)	5020	1683	1851	1436	90642
HONOL[29]	USA	1992	1999	3266	78 (4)	3266 (100)	950 (29.1)	172 (5.3)	694 (21.2)	6.3 (1.7 to 7.6)	871	287	243	216	18519
HOORN[30]	Netherlands	1991	2005	2314	61 (7)	1046 (45)	218 (9.4)	33 (1.4)	65 (2.8)	13.6 (4.0 to 14.7)	525	191	151	55	18930
HUBRO[12]	Norway	2001	2009	16456	52 (14)	7328 (45)	510 (3.1)	365 (2.2)	477 (2.9)	8.5 (6.0 to 9.5)	1224	348	467	321	141618
KIHD[33]	Finland	1987	2009	2319	53 (5)	2319 (100)	116 (5.0)	49 (2.1)	215 (9.3)	21.7 (5.1 to 25.2)	751	355	207	182	39821
LASA[34]	Netherlands	1993	2003	2269	70 (9)	1110 (49)	180 (7.9)	140 (6.2)	263 (11.6)	9.9 (1.7 to 10.5)	788	0	0	0	17467
LEADER[35]	UK	1997	2001	1359	68 (9)	1359 (100)	227 (16.7)	157 (11.6)	310 (22.8)	4.3 (1.1 to 6.1)	335	172	90	64	5284
MATISS83[2]	Italy	1984	2002	2605	52 (10)	1227 (47)	127 (4.9)	20 (0.8)	33 (1.3)	18.7 (6.0 to 19.5)	514	268	96	68	44183
MATISS87[2]	Italy	1987	2002	2107	52 (9)	942 (45)	85 (4.0)	19 (0.9)	26 (1.2)	15.6 (7.2 to 16.2)	266	131	46	41	30948
MATISS93[2]	Italy	1994	2002	1239	49 (9)	610 (49)	60 (4.8)	12 (1.0)	20 (1.6)	8.3 (7.0 to 9.3)	42	22	5	10	10110
MCVDRFP[37]	Netherlands	1989	2007	24000	42 (10)	11260 (47)	266 (1.1)	185 (0.8)	314 (1.3)	16.7 (10.0 to 18.9)	1920	527	894	381	385982

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eTable 1. cont'd

Cohort abbreviation	Country	Median year of baseline	Date of last follow-up	No. of individuals	Age at survey (yrs) mean (sd)	Male (%)	Individuals with diabetes (%)	Individuals with previous stroke (%)	Individuals with previous MI (%)	Median years of follow-up (5th & 95th percentiles)	All-cause deaths*	Cardiovascular deaths	Cancer deaths	Nonvascular, noncancer deaths	Person-years of follow-up
MDC[38]	Sweden	1994	2010	19292	58 (7)	8430 (44)	832 (4.3)	236 (1.2)	463 (2.4)	16.3 (6.0 to 19.1)	4098	1379	1795	836	281551
MIDFAM[39]	UK	1996	2011	2310	45 (6)	1032 (45)	27 (1.2)	11 (0.5)	117 (5.1)	15.4 (14.2 to 15.8)	129	24	62	38	34857
MIDRP[40]	UK	1975	2010	12106	55 (6)	5573 (46)	153 (1.3)	147 (1.2)	1106 (9.1)	24.2 (4.4 to 36.8)	9826	4747	2728	2296	266241
MONFRI86[2]	Italy	1986	2002	1159	49 (9)	568 (49)	12 (1.0)	7 (0.6)	15 (1.3)	16.7 (6.4 to 16.9)	156	63	34	20	18181
MONFRI89[2]	Italy	1989	2002	1135	49 (8)	566 (50)	15 (1.3)	6 (0.5)	28 (2.5)	13.6 (8.4 to 13.7)	93	44	13	17	14709
MONFRI94[2]	Italy	1994	2002	1364	49 (8)	677 (50)	61 (4.5)	53 (3.9)	23 (1.7)	8.5 (8.2 to 8.8)	57	22	7	8	11298
MONICA_KORA1[41]	Germany	1985	1998	923	54 (6)	923 (100)	45 (4.9)	17 (1.8)	35 (3.8)	13.0 (4.5 to 13.5)	176	90	53	32	10641
MONICA_KORA2[41]	Germany	1990	1998	4193	53 (12)	2103 (50)	234 (5.6)	63 (1.5)	117 (2.8)	7.9 (5.3 to 8.4)	338	148	107	79	30045
MONICA_KORA3[41]	Germany	1995	2009	4710	50 (14)	2326 (49)	223 (4.7)	95 (2.0)	96 (2.0)	14.0 (6.0 to 14.7)	692	279	224	167	59051
MORGEN[42]	Netherlands	1995	2007	18860	46 (9)	8674 (46)	275 (1.5)	186 (1.0)	269 (1.4)	10.8 (6.0 to 13.0)	647	182	332	103	195521
MOSWEGOT[43]	Sweden	1990	2003	4249	47 (11)	2040 (48)	107 (2.5)	52 (1.2)	59 (1.4)	13.0 (8.0 to 18.6)	308	105	133	65	57496
MPP[36]	Sweden	1980	2010	31911	46 (7)	21920 (69)	349 (1.1)	113 (0.4)	245 (0.8)	29.3 (10.1 to 34.1)	9812	3574	3672	2307	802712
MRCOLD[44]	UK	1996	2007	13248	80 (4)	5237 (40)	1039 (7.8)	1152 (8.7)	1494 (11.3)	7.8 (0.9 to 11.7)	8824	3977	1702	2872	94742
MRFIT[45]	USA	1974	1985	12270	47 (6)	12270 (100)	108 (0.9)	5 (0.0)	7 (0.1)	11.0 (8.3 to 11.8)	981	529	278	168	85170
NCS1[46]	Norway	1976	1993	24316	42 (4)	12014 (49)	183 (0.8)	25 (0.1)	86 (0.4)	16.1 (14.2 to 16.7)	1481	578	565	256	382133
NCS2[46]	Norway	1975	1993	13171	42 (4)	6741 (51)	72 (0.5)	34 (0.3)	50 (0.4)	17.3 (15.3 to 17.8)	844	304	336	147	223176
NCS3[46]	Norway	1974	1993	10249	42 (4)	5347 (52)	35 (0.3)	27 (0.3)	66 (0.6)	18.2 (11.7 to 18.8)	1056	517	292	145	179604
NFR[15]	Italy	1980	1991	3293	55 (5)	3293 (100)	222 (6.7)	32 (1.0)	146 (4.4)	10.2 (5.7 to 11.2)	392	159	168	47	32169
NHANESI[47]	USA	1973	1993	11728	50 (15)	4773 (41)	701 (6.0)	296 (2.5)	747 (6.4)	18.3 (4.0 to 21.0)	3550	1802	863	828	186808
NHANESIII[48]	USA	1990	2008	16017	52 (18)	7547 (47)	1439 (9.0)	599 (3.7)	998 (6.2)	14.2 (3.0 to 17.7)	4640	2088	1053	1413	209386
OPPHED[12]	Norway	2001	2009	9783	53 (13)	4552 (47)	300 (3.1)	214 (2.2)	350 (3.6)	8.5 (6.0 to 9.5)	734	239	274	167	81986
OSAKA[50]	Japan	1992	2008	12523	52 (10)	8529 (68)	623 (5.0)	114 (0.9)	29 (0.2)	10.2 (3.9 to 18.8)	707	141	230	168	140564
OSLO[51]	Norway	1973	2003	17586	44 (6)	17586 (100)	151 (0.9)	31 (0.2)	165 (0.9)	29.5 (10.6 to 30.5)	6089	2755	2055	1088	462041
OSLO2[12]	Norway	2000	2009	6037	69 (6)	6037 (100)	383 (6.3)	364 (6.0)	668 (11.1)	9.5 (2.0 to 9.5)	1475	459	587	298	50937
PREVEND[52]	Netherlands	1998	2010	7890	50 (12)	3960 (50)	317 (4.0)	75 (1.0)	381 (4.8)	12.7 (7.4 to 13.2)	795	221	373	172	77701
PRHHP[53]	Caribbean	1967	1980	6832	54 (6)	6832 (100)	682 (10.0)	88 (1.3)	398 (5.8)	12.0 (5.5 to 12.0)	1112	530	263	294	56492
PRIME[54]	France / NI	1992	2000	9998	55 (3)	9998 (100)	344 (3.4)	73 (0.7)	344 (3.4)	5.2 (5.0 to 7.3)	223	61	106	39	54563
PROCAM[55]	Germany	1983	2003	20484	44 (10)	14861 (73)	433 (2.1)	61 (0.3)	169 (0.8)	9.8 (3.8 to 18.9)	1071	351	454	215	241682
PROSPER[56]	Scotland/Irel	1998	2002	4201	75 (3)	1987 (47)	499 (11.9)	205 (4.9)	776 (18.5)	3.3 (1.7 to 3.9)	430	200	154	76	12810
ProspectEPIC[57]	Netherlands	1995	2012	16069	57 (6)	0 (0)	339 (2.1)	310 (1.9)	54 (0.3)	14.4 (9.5 to 17.2)	1329	324	658	266	221730
QUEBEC[58]	Canada	1974	2002	3415	46 (8)	3415 (100)	63 (1.8)	8 (0.2)	5 (0.1)	27.8 (11.1 to 28.2)	993	188	0	0	74109
RANCHO[59]	USA	1985	2002	2188	70 (11)	986 (45)	127 (5.8)	75 (3.4)	303 (13.8)	14.2 (2.2 to 18.1)	1093	527	241	320	25273
RS_I[60]	Netherlands	1992	2005	5608	68 (8)	2301 (41)	470 (8.4)	157 (2.8)	753 (13.4)	12.0 (2.7 to 14.2)	2037	777	570	447	58177
RS_II[60]	Netherlands	2000	2011	2466	64 (8)	1107 (45)	276 (11.2)	86 (3.5)	117 (4.7)	10.0 (4.2 to 10.9)	392	127	153	86	23038
RS_III[60]	Netherlands	2007	2011	3429	57 (7)	1472 (43)	268 (7.8)	35 (1.0)	87 (2.5)	3.6 (1.9 to 4.8)	61	19	34	6	11888
SHHEC[61]	UK	1986	1999	13081	50 (7)	6545 (50)	207 (1.6)	90 (0.7)	2068 (15.8)	10.0 (7.6 to 10.0)	956	409	380	143	124751
SHIP[62]	Germany	1999	2011	3285	55 (14)	1634 (50)	421 (12.8)	73 (2.2)	121 (3.7)	11.3 (5.3 to 12.4)	507	178	185	116	21296
SPEED[8]	UK	1980	1997	2308	55 (4)	2308 (100)	45 (1.9)	27 (1.2)	132 (5.7)	16.8 (3.8 to 18.2)	674	347	234	90	32979
TARFS[64]	Turkey	1990	2010	3451	45 (13)	1689 (49)	113 (3.3)	1 (0.0)	4 (0.1)	20.0 (4.6 to 20.0)	550	301	42	29	44834
TROMS[12]	Norway	2002	2009	2017	51 (12)	895 (44)	68 (3.4)	37 (1.8)	62 (3.1)	7.5 (7.5 to 7.5)	91	33	40	14	14922
TROMSØ[65]	Norway	1987	2009	19917	43 (14)	9868 (50)	229 (1.1)	175 (0.9)	421 (2.1)	22.0 (10.2 to 22.4)	2562	891	830	554	315667
ULSAM[66]	Sweden	1972	2008	2038	51 (4)	2038 (100)	120 (5.9)	6 (0.3)	16 (0.8)	28.0 (8.7 to 37.7)	1369	616	464	254	49634
WHIOS[67]	USA	1994	2012	85493	63 (7)	0 (0)	4326 (5.1)	1224 (1.4)	2260 (2.6)	12.1 (5.1 to 14.8)	10580	2764	4124	2687	931744
WHITEI[68]	UK	1997	2010	4890	77 (5)	4890 (100)	275 (5.6)	345 (7.1)	607 (12.4)	11.0 (1.7 to 13.3)	2841	1177	758	869	46175
ZUTE[21]	Netherlands	1960	2000	641	64 (13)	641 (100)	22 (3.4)	6 (0.9)	32 (5.0)	25.0 (6.5 to 40.1)	429	189	135	71	13192
TOTAL				689300	53 (9)	340930 (49)	29772 (4.3)	12281 (1.8)	27201 (3.9)	12.8 (4.0 to 29.5)	128843	50595	39266	30664	8832963

*All-cause mortality includes 8318 unknown or ill-defined deaths. Numbers of deaths are based on data without censoring for non-fatal outcomes.
Superscripted numbers listed after the study acronyms refer to publications in the list of references in the Supplement.

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eTable 2. Study-specific definition of known history of diabetes, myocardial infarction and stroke at baseline

Study name	Previous diabetes	Previous MI	Previous stroke
ARIC[1]	○●	++	+
AUSDIAB[3]	○	+	+
BHS[4]	○	++	+
BRHS[5]	○	++	++
BRUN[6]	○●●	++	+
BWHHS[7]	○	++	++
CAPS[8]	○	++	+
CASTEL[9]	○	++	+
CHARL[10]	○	++	+
CHS[a 11]	○●	++	+
CONOR[b 12]	○	+	+
COPEN[13]	○	++	++
CUORE[c 2]	○●	++	+
DESIR[14]	○●●	++	++
DUBBO[16]	○●	++	+
EAS[17]	○	++	+
EPESEBOS[1]	○	+	+
EPESEIOW[1]	○	+	+
EPESENCA[1]	○	+	+
EPESENHA[1]	○	+	+
EPICNOR[19]	○	+	+
ESTHER[20]	○●	++	+
FINE[d 21]	○	++	++
FINRISK[e 22]	○●	++	++
FRAMOFF[23]	○●●	++	++
GOTO13[24]	○	++	++
GOTO33[24]	○	++	++
GOTO43[24]	○	++	++
GOTOW[25]	○●●	++	++
GRIPS[26]	○	++	++
HCS[27]	○	++	++
HIMS[28]	○	++	++
HONOL[29]	○●●	++	++
HOORN[30]	○●●	++	+
KIHD[33]	●	++	++
LASA[34]	○●	++	+

Study name	Previous diabetes	Previous MI	Previous stroke
LEADER[35]	○	++	++
MCVDRFP[37]	○	+	+
MDC[38]	○	++	++
MIDFAM[39]	○	++	++
MIDRP[40]	○	++	+
MONICA_KORA1	○●	+	+
MONICA_KORA2	○●	+	+
MONICA_KORA3	○●	+	+
MORGEN[42]	○	+	+
MOSWEGOT[43]	○	+	+
MPP[36]	○	+	++
MRCOLD[44]	●	+	+
MRFIT[45]	○	++	++
NCS[f 46]	○	+	+
NHANESI[47]	○●	+	+
NHANESIII[48]	○	+	+
OSAKA[50]	●	++	+
OSLO[51]	○	+	+
PREVEND[52]	○●	++	++
PRHHP[53]	○●	++	++
PRIME[54]	○	++	+
PROCAM[55]	○●	++	+
ProspectEPIC[57]	○	+	+
PROSPER[56]	○	++	++
QUEBEC[58]	○	++	++
RANCHO[59]	○●	++	+
RIFLE[g 15]	○	++	++
ROTT[h 60]	○●	++	+
SHHEC[61]	○	++	+
SHIP[62]	○●	++	++
SPEED[8]	○	++	+
TARFS[64]	○●●	++	++
TROMSO[65]	○●	+	+
ULSAM[66]	○●	++	++
WHIOS[67]	○●	+	+
WHITEI[68]	○●	+	+

○: Self-report only; ●: Diabetes medications data; ●: Biochemical criteria; +: Self-report only; ++: Self-report supplemented by objective criteria (eg, Electrocardiogram, Physical examination)

[a] CHS was analysed as 2 different studies (ie, CHS-1 and CHS-2).

[b] CONOR was analysed as 5 different studies (ie, FINNMARK, HUBRO, OPPHED, OSLO2, and TROMS).

[c] CUORE was analysed as 8 different studies (ie, ATENA, EMOFRI, MATISS-83, MATISS-87, MATISS-93, MONFRI-86, MONFRI-89 and MONFRI-94).

[d] FINE was analysed as 3 different studies (FINE_FIN, FINE_IT, and ZUTE). FINE_IT ascertained baseline history of diabetes using self-report and diabetes medications data.

[e] FINRISK was analysed as 2 different studies (FINRISK92 and FINRISK97).

[f] NCS was analysed as 3 different studies (ie, NCS1, NCS2 and NCS3).

[g] RIFLE was analysed as 2 different studies (ie, DISCO and NFR).

[h] ROTT was analysed as 3 different studies (ie, RS_I, RS_II, RS_III).

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eTable 3. Hazard ratios for all-cause mortality according to participants' disease status at baseline in UK Biobank

Disease status at baseline	*No. of participants*	*No. of deaths*	*Pearson-years*	*Hazard ratio (95% CI)*
Diabetes & Stroke & MI	230	29	1,039	6.0 (4.2, 8.7)
Stroke & MI	668	57	3,151	3.8 (2.9, 4.9)
Diabetes & Stroke	966	79	4,511	3.9 (3.1, 4.9)
Diabetes & MI	2,036	201	9,341	4.3 (3.7, 5.0)
MI only	8,770	421	41,717	2.1 (1.9, 2.3)
Stroke only	6,835	277	32,563	2.1 (1.9, 2.4)
Diabetes only	18,549	534	87,474	1.6 (1.5, 1.8)
None	461,754	6,397	2,214,549	[Reference]

Hazard ratios are adjusted by age and sex.

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eTable 4. Estimated future years of life lost according to participants' age, sex and disease status at baseline

Disease status at baseline	*Age (years)*									
	40	45	50	55	60	65	70	75	80	85
Male										
Diabetes & Stroke & MI	22.9	21.7	19.8	17.3	14.4	11.2	8.1	5.2	2.9	1.2
Stroke & MI	21.5	20.1	18.1	15.6	12.9	10.1	7.4	4.8	2.7	1.2
Diabetes & Stroke	16.3	15.6	14.5	13.1	11.2	9.1	6.8	4.6	2.6	1.2
Diabetes & MI	16.8	16.0	14.8	13.1	11.2	9.0	6.7	4.5	2.6	1.2
MI only	10.0	9.6	8.9	8.0	7.0	5.7	4.4	3.1	1.9	0.9
Stroke only	8.8	8.6	8.1	7.5	6.6	5.6	4.4	3.1	1.9	0.9
Diabetes only	7.9	7.6	7.2	6.5	5.7	4.8	3.7	2.7	1.6	0.8
Female										
Diabetes & Stroke & MI	20.1	19.8	19.1	17.7	15.7	13.0	9.9	6.7	3.9	1.8
Stroke & MI	13.0	12.8	12.3	11.5	10.4	9.0	7.2	5.2	3.3	1.6
Diabetes & Stroke	16.5	16.2	15.5	14.5	13.0	11.1	8.7	6.2	3.8	1.9
Diabetes & MI	19.9	19.2	18.1	16.4	14.3	11.8	9.1	6.4	3.8	1.8
MI only	6.5	6.4	6.2	5.9	5.5	4.9	4.1	3.1	2.0	1.0
Stroke only	7.4	7.4	7.2	7.0	6.5	5.9	5.0	3.8	2.5	1.3
Diabetes only	8.2	8.1	7.8	7.3	6.7	5.9	4.8	3.6	2.4	1.2

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.

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eTable 5. Summary of prospective studies included in the literature-based systematic review

Study acronym	*Country*	*Population source*	*Baseline year*	*Date of last follow-up*	*Age, range*	*Sex, % male*	*Exposed group*	*No. of participants, exposed / reference group*	*No. of deaths, exposed / reference group*
EPESE[23]	USA	Population register	1993-1994	1999	65+	43	Diabetes & Stroke	76 / 2,246	35 / 375
Schramm et al.[9]	Denmark	Data linkage	1997	2002	30+	48	Diabetes & MI	6,419 / 3,129,516	2,997 / 244,775
PHS[10]	USA	Occupational	1982-1983	1988	40-84	100	Diabetes & CHD	815 / 82,247	210 / 2,425
FINRISK[11]	Finland	Population register	1972-1997	2001	25-74	49	Diabetes & MI	146 / 49,319	93 / 8,082
HPFS[12]	USA	Occupational	1986	1996	40-75	100	Diabetes & CHD	230 / 47,763	98 / 3,195
NHS[14]	USA	Occupational	1976	1996	30-55	0	Diabetes & CHD	234 / 109,231	30 / 7,853

Abbreviations: CHD, coronary heart disease; EPESE, Hispanic Established Population for the Epidemiological Study of the Elderly; HPFS, Health Professionals Follow-up Study; MI, myocardial infarction; NHS, Nurses' Health Study; PHS, Physicians' Health Study. Superscripted numbers listed after the study acronyms refer to publications in the list of references in the main text.

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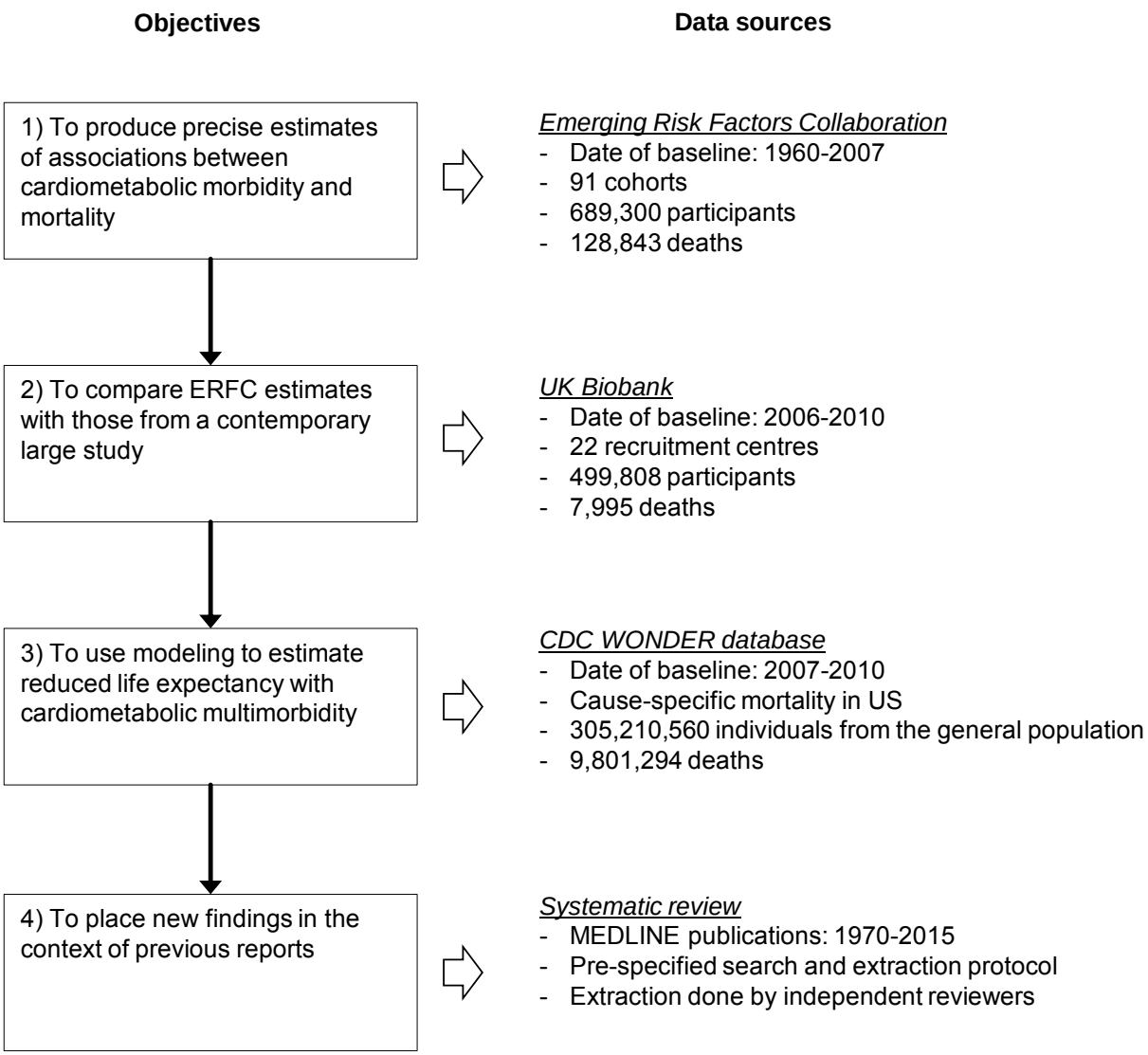
eFigure 1. Study design



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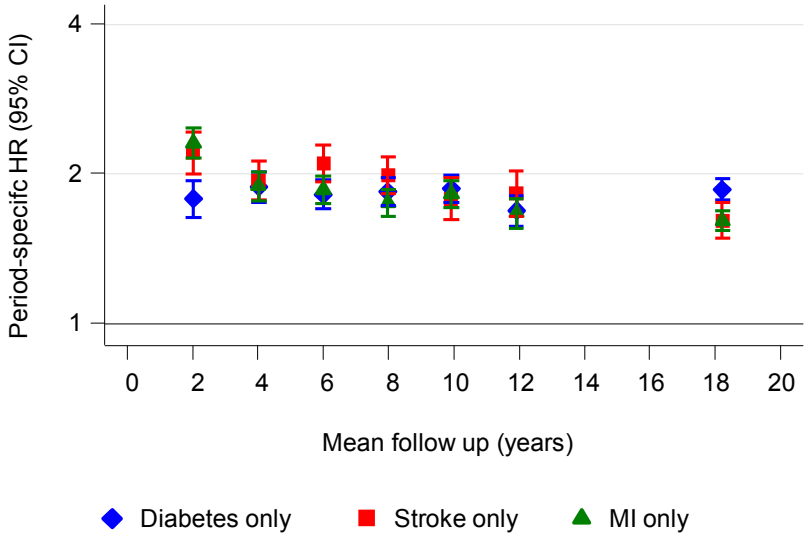
eFigure 2. Hazard ratios for all-cause mortality according to participants' disease status at baseline, against follow-up time



Hazard-ratios (HRs) were adjusted for age and sex. HRs were calculated within bins of follow-up times defined as 0 to <2, 2 to <4, 4 to <6, 6 to <8, 8 to <10, 10 to <12, and ≥12 years.

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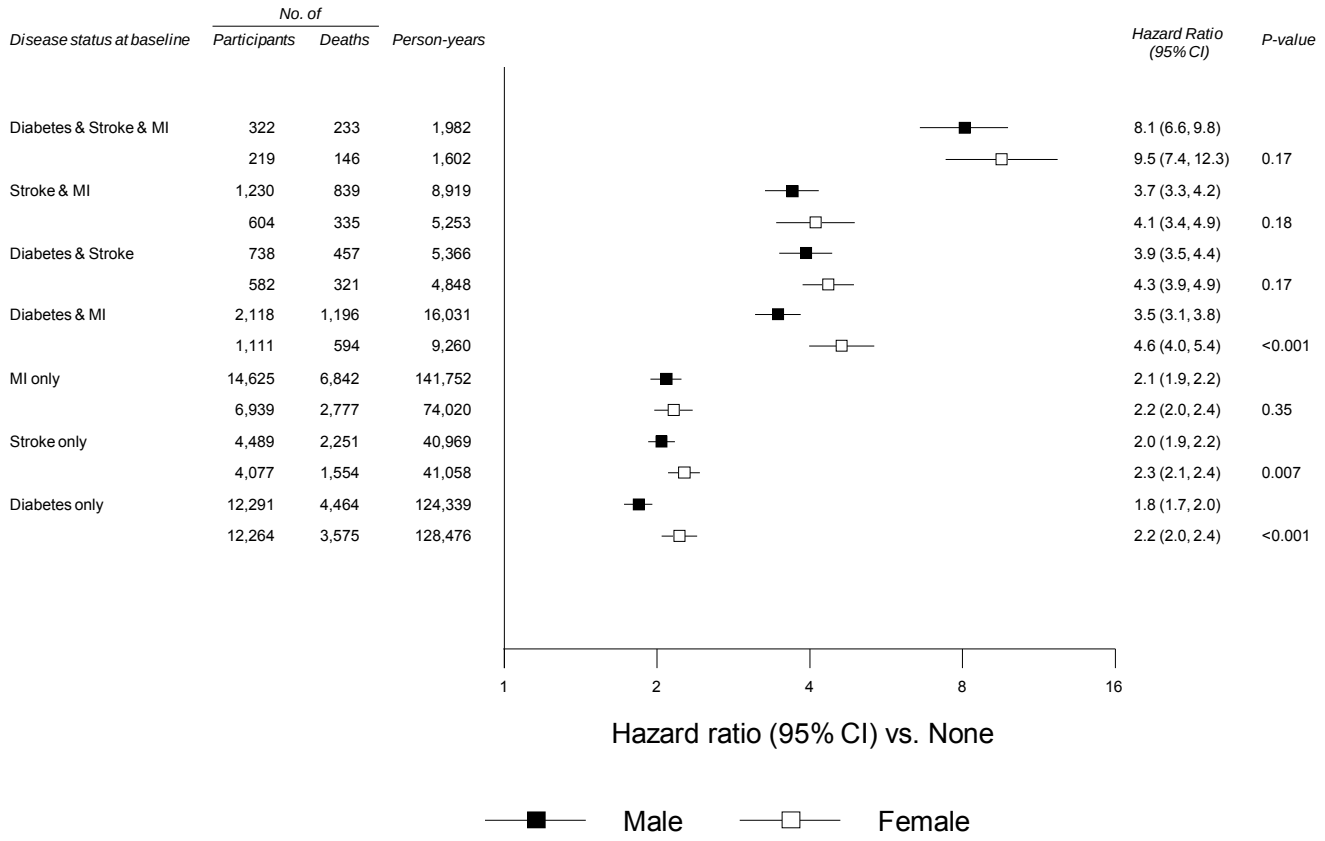
eFigure 3. Sex-specific hazard ratios for all-cause mortality according to participants' disease status at baseline



Hazard ratios are stratified by sex and adjusted by age at baseline. Analyses were based on data without censoring for non-fatal outcomes. Analyses were based on participants from 91 studies.

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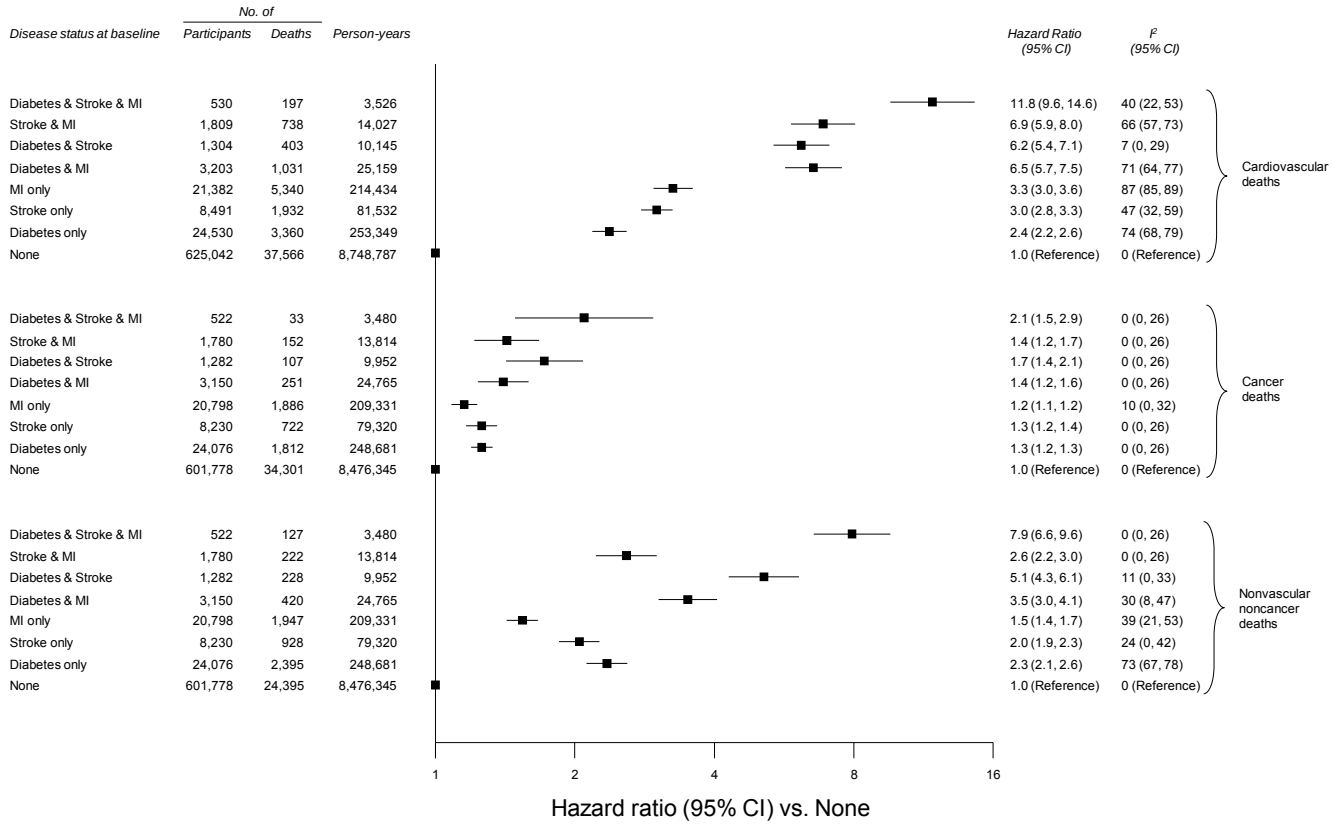
eFigure 4. Hazard ratios for cardiovascular mortality, cancer mortality, and nonvascular noncancer mortality according to participants' disease status at baseline



Hazard ratios are stratified by sex and adjusted by age at baseline. Analyses were based on data without censoring for non-fatal outcomes. Analyses were based on 89 studies for cardiovascular mortality, 87 studies for cancer mortality, and 87 studies for nonvascular noncancer mortality.

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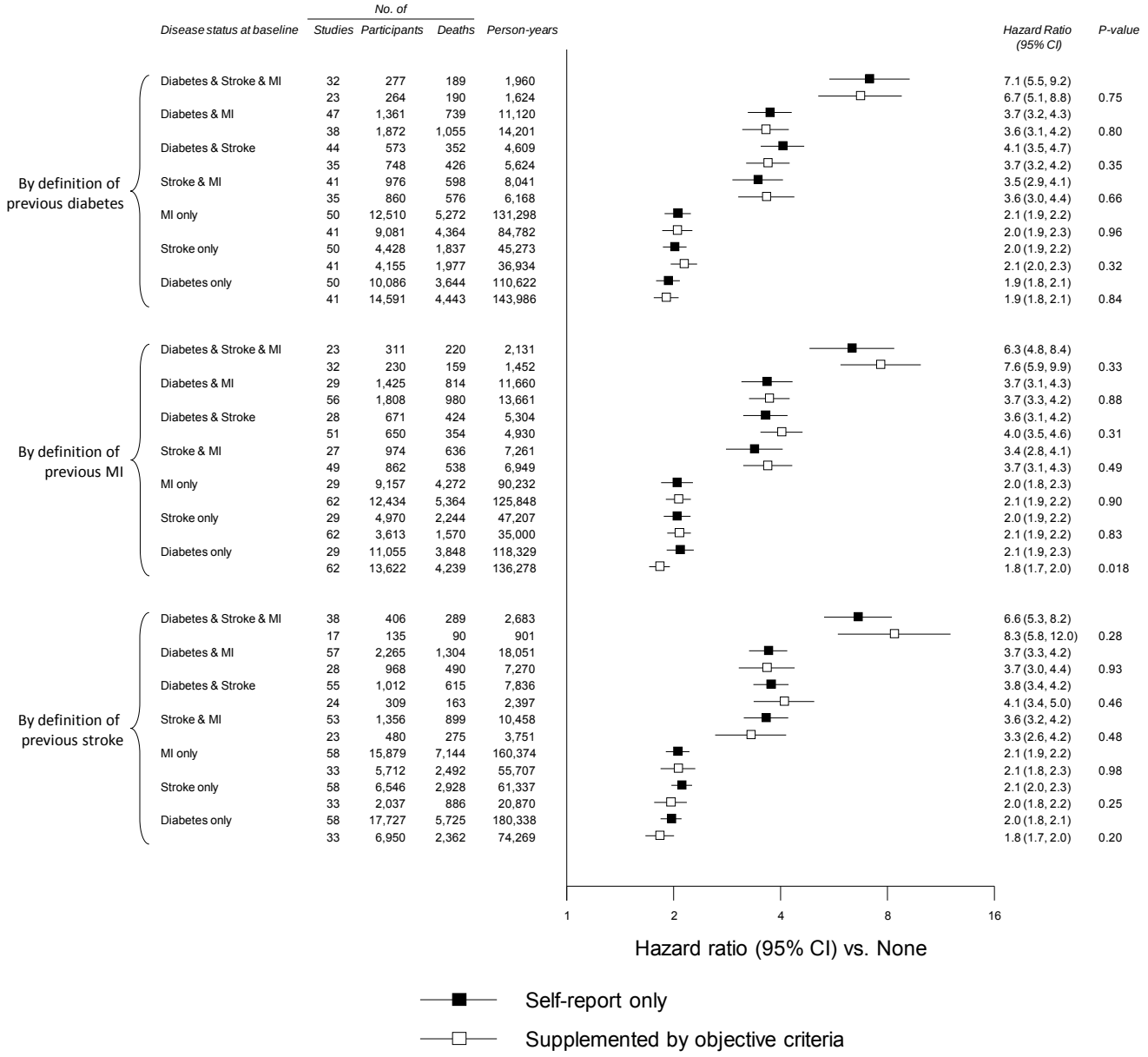
eFigure 5. Hazard ratios for all-cause mortality according to participants' disease status at baseline, by study-specific definitions of baseline diseases



Hazard ratios are stratified by sex and adjusted by age at baseline. Study-specific definitions of baseline diseases are provided in eTable 2.

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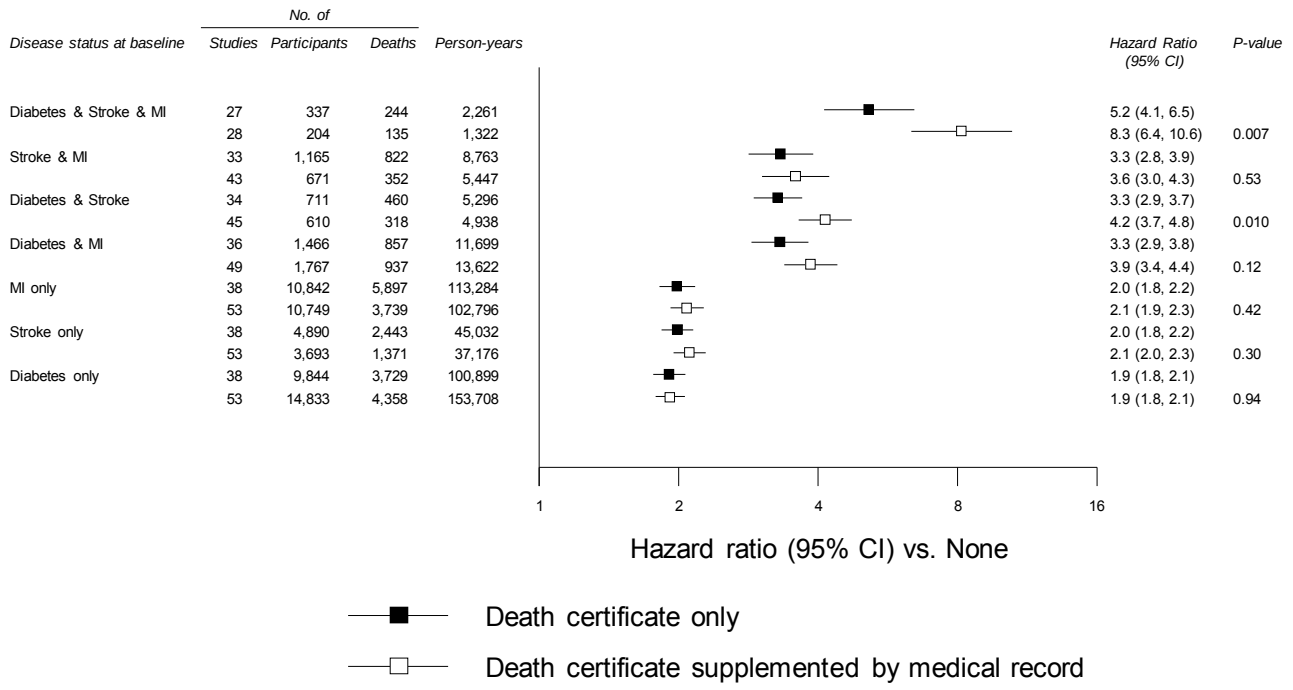
eFigure 6. Hazard ratios for all-cause mortality according to participants' disease status at baseline, by study-specific methods of ascertainment of death



Hazard ratios are stratified by sex and adjusted by age at baseline.

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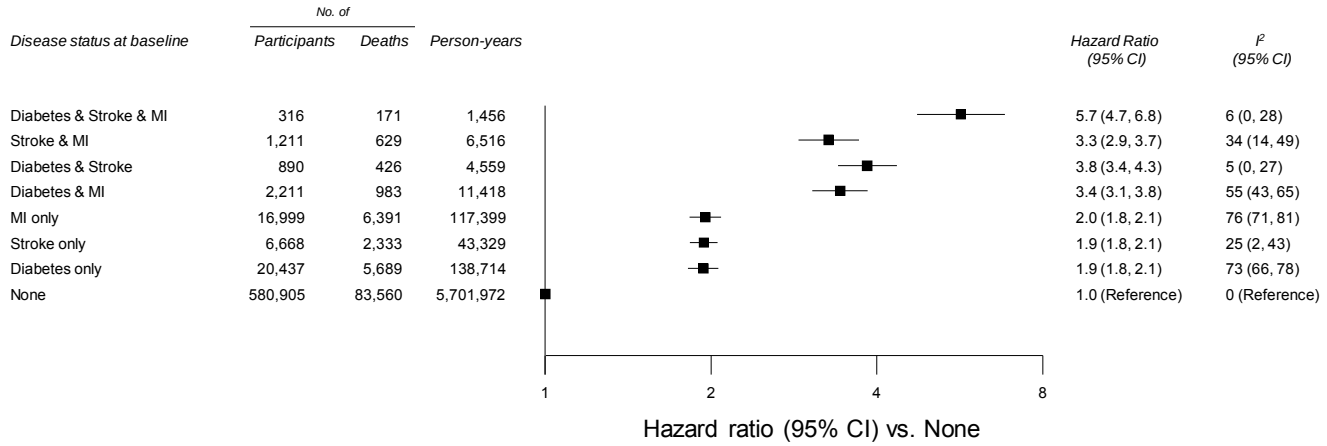
eFigure 7. Hazard ratios for all-cause mortality according to participants' disease status at baseline, after excluding the first 5 years of follow-up



Hazard ratios are stratified by sex and adjusted by age at baseline. Analyses of all-cause mortality were based on data without censoring for non-fatal outcomes. Analyses were based on participants from 87 studies.

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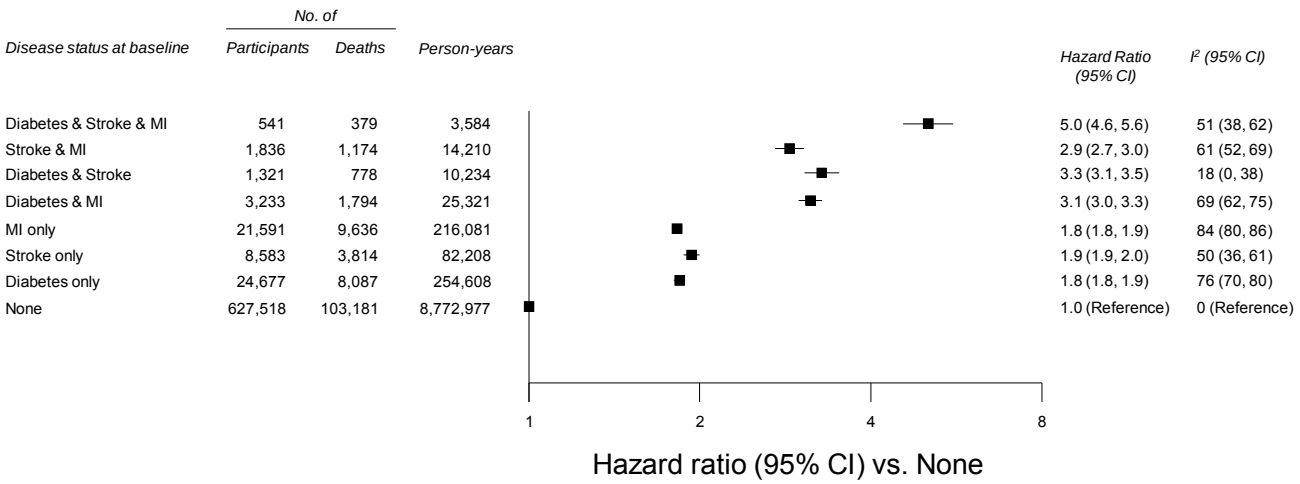
eFigure 8. Hazard ratios for all-cause mortality according to participants' disease status at baseline, with study-specific estimates pooled using fixed-effect meta-analysis.



Hazard ratios are stratified by sex and adjusted by age at baseline. Analyses of all-cause mortality were based on data without censoring for non-fatal outcomes. Analyses were based on participants from 87 studies.

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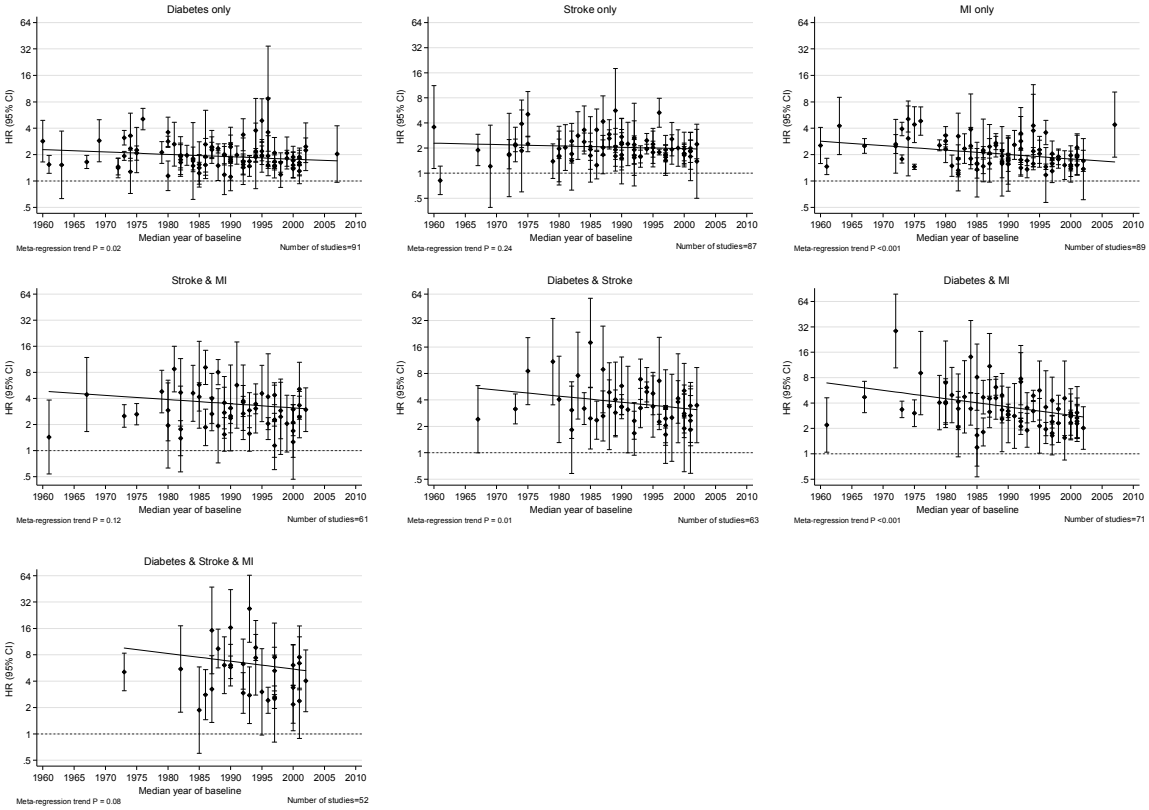
eFigure 9A. Hazard ratios for all-cause mortality according to participants' disease status at baseline and by median year of survey



Hazard ratios (HRs) were stratified by sex and adjusted by age at baseline. Each data marker denotes results from a single study. The number of studies contributing to each panel in this figure is listed under the panel's horizontal axis. Studies with less than 2 events in each exposure category were omitted from the plots. To provide greater visual clarity in instances when more than one study in a panel had the same median year of survey, panels in Figure 9B have been plotted without confidence intervals around the point estimates. The lines in this figure have been fitted by meta-regression using a method described in reference 16 of the reference list in the main text.

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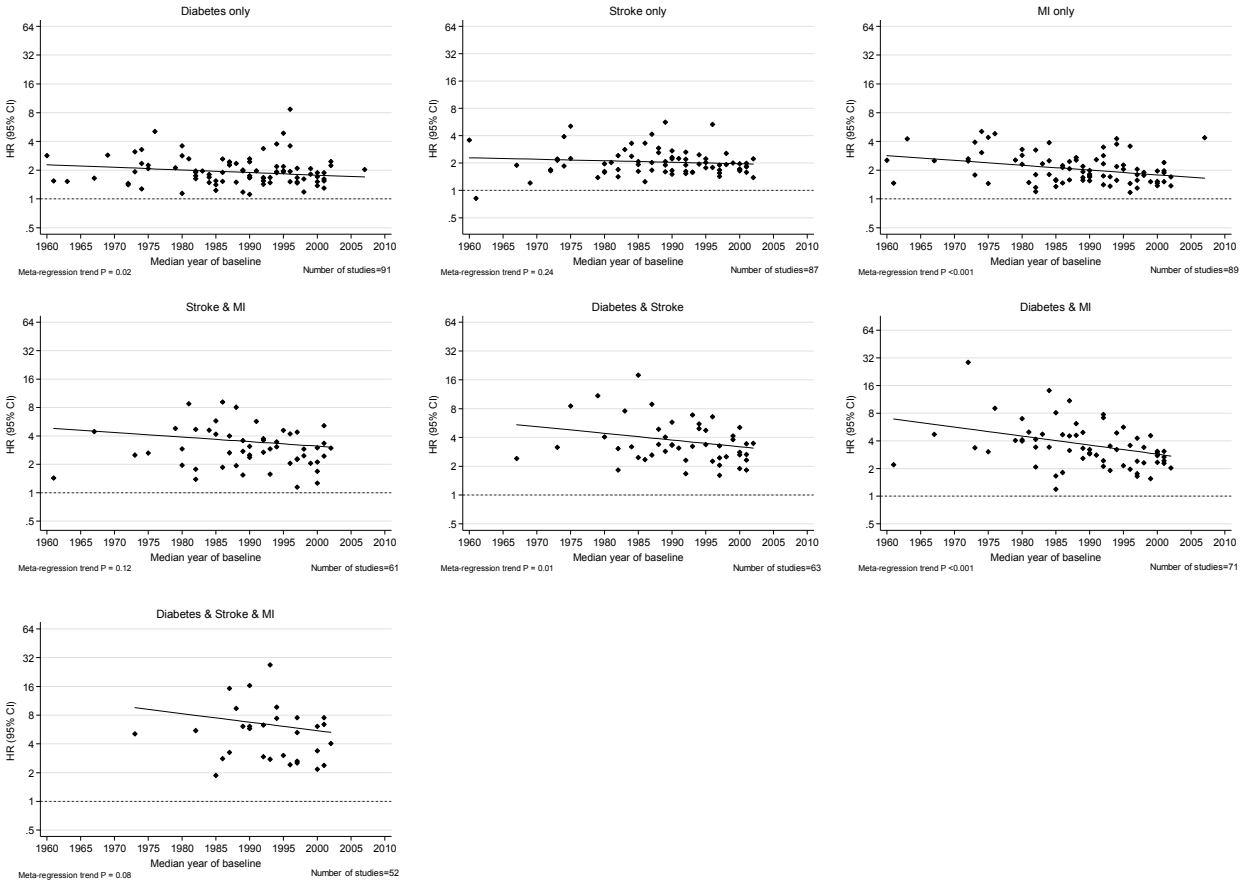
eFigure 9B. Hazard ratios (without confidence intervals) for all-cause mortality according to participants' disease status at baseline and by median year of survey



Hazard ratios (HRs) were stratified by sex and adjusted by age at baseline. Each data marker denotes results from a single study. The number of studies contributing to each panel in this figure is listed under the panel's horizontal axis. Studies with less than 2 events in each group were omitted from the plots. The lines in this figure have been fitted by meta-regression using a method described in reference 16 of the reference list in the main text.

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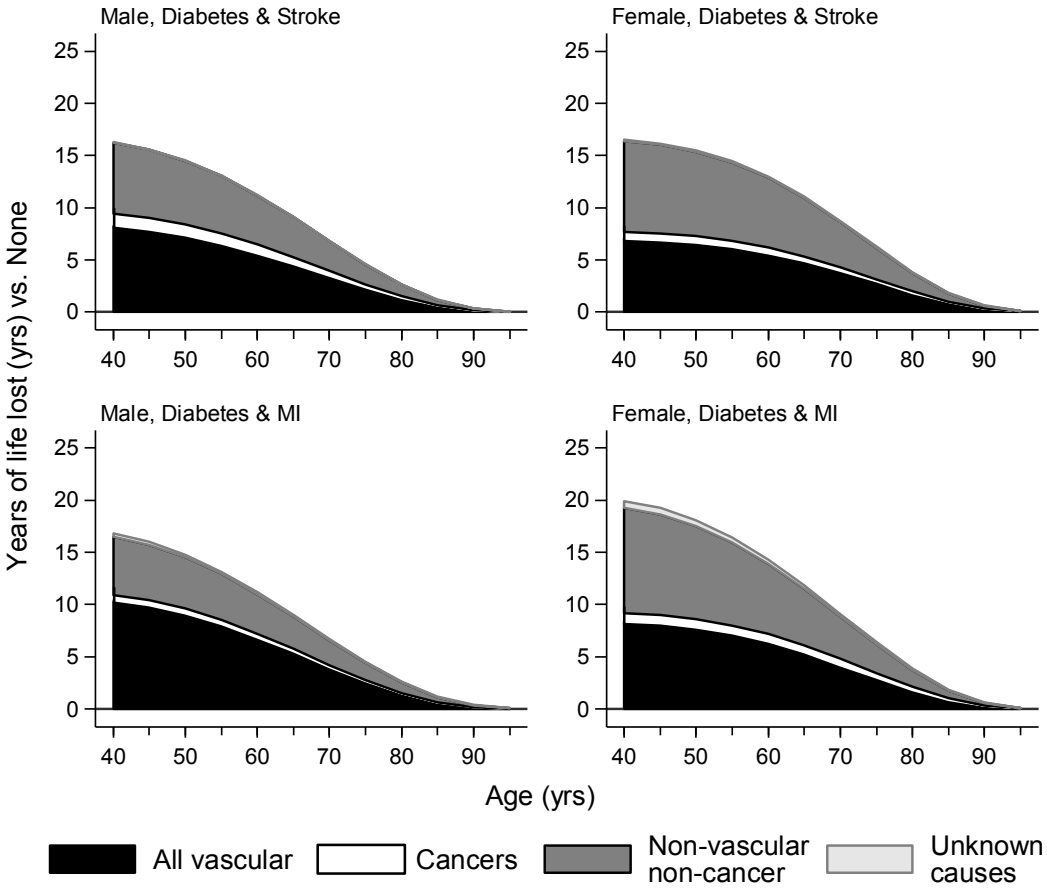
eFigure 10. Estimated future years of life lost due to comorbidity with diabetes and prior MI or stroke, attributable to vascular, cancer and other mortality causes



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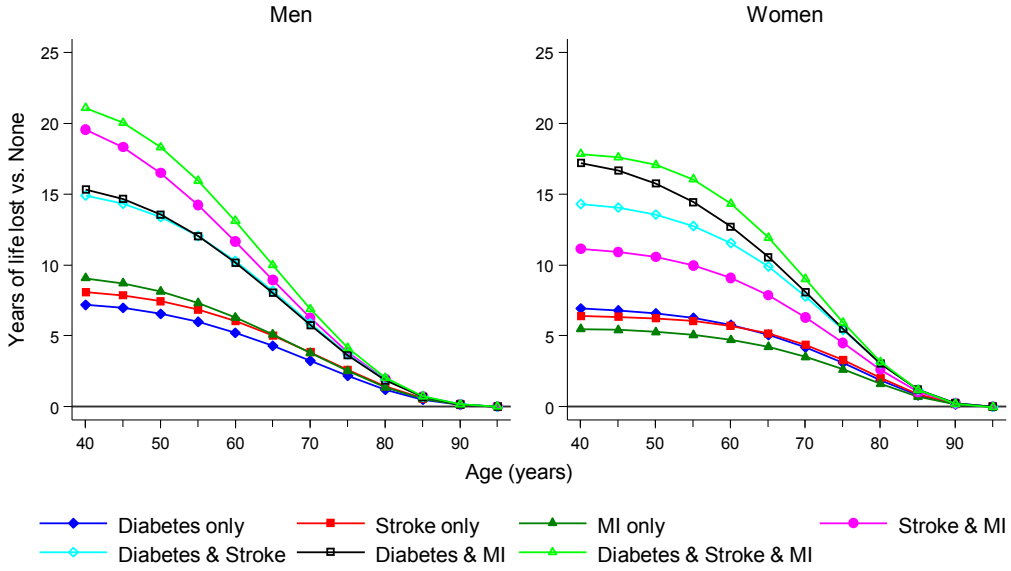
eFigure 11. Estimated future years of life lost according to diabetes, MI and stroke status in the European Union



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 European Union cause-specific death rates at 40 years of age and older. Details are provided in eAppendix 5.

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Data Management Team: M Walker, S Spackman, T Bolton.

Coordinating Centre: T Bolton, N Bansal, S Burgess, A S Butterworth, E Di Angelantonio, D F Freitag, P Gao, E Harshfield, S Kaptoge, L M O'Keeffe, L Pennells, S Spackman, S G Thompson, M Walker, P Willeit, A M Wood, D Wormser, J Danesh (principal investigator).

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eAppendix 2. List of study acronyms

ARIC, Atherosclerosis Risk in Communities Study[1]
ATENA, cohort of Progetto CUORE[2]
AUSDIAB, Australian Diabetes, Obesity and Lifestyle Study[3]
BHS, Busselton Health Study[4]
BRHS, British Regional Heart Study[5]
BRUN, Bruneck Study[6]
BWHHS, British Women's Heart and Health Study[7]
CaPS, Caerphilly Prospective Study[8]
CASTEL, Cardiovascular Study in the Elderly[9]
CHARL, Charleston Heart Study[10]
CHS, CHS-1 original cohort of the Cardiovascular Health Study[11] and CHS-2, supplemental African-American cohort of the Cardiovascular Health Study[11]
CONOR, Cohort of Norway[12]
COPEN, Copenhagen City Heart Study[13]
CUORE, Progetto CUORE[2]
DESIR, Data from an Epidemiological Study on the Insulin Resistance Syndrome[14]
DISCO, cohort of Risk Factors and Life Expectancy Pooling Project[15]
DUBBO, Dubbo Study of the Elderly[16]
EAS, Edinburgh Artery Study[17]
EMOFRI, part of CUORE[2]
EPESEBOS, The Established Populations for the Epidemiologic Study of the Elderly Studies, Boston[18]
EPESEIOW, The Established Populations for the Epidemiologic Study of the Elderly Studies, Iowa[18]
EPESENCA, The Established Populations for the Epidemiologic Study of the Elderly Studies, North Carolina[18]
EPESENHA, The Established Populations for the Epidemiologic Study of the Elderly Studies, New Haven[18]
EPICNOR, European Prospective Investigation of Cancer Norfolk Study[19]
ESTHER, Epidemiologische Studie zu Chancen der Verhutung und optimierten Therapie chronischer Erkrankungen in der alteren Bevolkerung[20]
FINE, Finland, Italy and Netherlands Elderly Study – Italian cohort[21]
FINE_FIN, cohort of FINE[21]
FINE_IT, cohort of FINE[21]
FINMARK, cohort of CONOR[12]
FINRISK-92, Finrisk Cohort 1992[22]
FINRISK-97, Finrisk Cohort 1997[22]
FRAMOFF, Framingham Offspring Cohort[23]
GOTO13, Goteborg Study 1913[24]
GOTO33, Göteborg 1933 Study[24]
GOTO43, Göteborg 1943 Study[24]
GOTOW, Population Study of Women in Göteborg, Sweden[25]
GRIPS, Göttingen Risk Incidence and Prevalence Study[26]
HCS, Hertfordshire Cohort Study[27]
HIMS, Health in Men Study[28]
HONOL, Honolulu Heart Program[29]
HOORN, Hoorn Study[30]
HPFS, Health Professionals Follow-up Study[31]
HUBR0, cohort of CONOR[12]
IKNS, Ikawa, Kyowa, and Noichi Study[32]
KIHD, Kuopio Ischaemic Heart Disease Study[33]
LASA, Longitudinal Aging Study Amsterdam[34]
LEADER, Lower Extremity Arterial Disease Event Reduction Trial[35]
MATISS-83, cohort of Progetto CUORE[2]
MATISS-87, cohort of Progetto CUORE[2]
MATISS-93, cohort of Progetto CUORE[2]
MCVDRFP, Monitoring of CVD Risk Factors Project[37]
MDC-CV, Malmö Diet and Cancer Study[38]
MIDFAM, MIDSPAN Family Study[39]
MIDRP, MIDSPAN Renfrew & Paisley Study[40]
MONFRI-86, cohort of Progetto CUORE[2]
MONFRI-89, cohort of Progetto CUORE[2]
MONFRI-94, cohort of Progetto CUORE[2]
MONICA_KORA1, MONICA/KORA Augsburg Surveys S1[41]
MONICA_KORA2, MONICA/KORA Augsburg Surveys S2[41]
MONICA_KORA3, MONICA/KORA Augsburg Surveys S3[41]
MORGEN, Monitoring Project on Chronic Disease Risk Factors[42]
MOSWEGOT, MONICA Göteborg Study[43]
MPP, Malmö Preventive Project[36]
MRCOLD, MRC Study of Older People[44]
MRFIT, Multiple Risk Factor Intervention Trial 1[45]
NCS 1, 2 and 3, Norwegian Counties Studies[46]
NFR, cohort of Risk Factors and Life Expectancy Pooling Project[15]
NHANES I, First National Health and Nutrition Examination Survey[47]
NHANES III, Third National Health and Nutrition Examination Survey[48]
NSHS, Nova Scotia Health Survey[49]

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OPPHED, cohort of CONOR[12]
OSAKA, Osaka Study[50]
OSLO, Oslo Study[51]
OSLO2, cohort of CONOR[12]
PREVEND, Prevention of Renal and Vascular End Stage Disease Study[52]
PRHHP, Puerto Rico Heart Health Program[53]
PRIME, Prospective Epidemiological Study of Myocardial Infarction[54]
PROCAM, Prospective Cardiovascular Münster Study[55]
Prospect EPIC, Prospect-EPIC Utrecht[57]
PROSPER, Prospective Study of Pravastatin in the Elderly at Risk[56]
QUEBEC, Quebec Cardiovascular Study[58]
RANCHO, Rancho Bernardo Study[59]
RIFLE, Risk Factors and Life Expectancy Pooling Project[15]
ROTT, The Rotterdam Study[60]
RS-1, 2 and 3, cohorts of The Rotterdam Study[60]
SHHEC, Scottish Heart Health Extended Cohort[61]
SHIP, Study of Health in Pomerani[62]
SHS, Strong Heart Study[63]
SPEED, Speedwell Study[8]
TARFS, Turkish Adult Risk Factor Study[64]
TROMS, cohort of CONOR[12]
TROMSØ, Tromsø Study[65]
ULSAM, Uppsala Longitudinal Study of Adult Men[66]
WHIOS, Women's Health Initiative[67]
WHITE I, Whitehall I Study[68]
ZUTE, cohort of FINE[21]

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eAppendix 3. UK Biobank

Details of UK Biobank have been described previously.[1] Briefly, over 500,000 participants aged 40-69 years were recruited during 2006-2010 in 22 geographical centres throughout the United Kingdom. The assessment visit comprised electronic signed consent; a self-completed touch-screen questionnaire; brief computer-assisted interview; physical and functional measures; and collection of biological samples. Participants have been linked with death records of the UK Office for National Statistics through National Health Service identification numbers.[2]

A total of 499,808 participants with complete data on age, sex, and medical history of diabetes, stroke and myocardial infarction were included in the current analysis. Medical history of diabetes, stroke and myocardial infarction was defined using self-reported information recorded at baseline visit in UK Biobank and updated using information on hospitalization before baseline extracted from Hospital Episode Statistics (using the following ICD codes: I21-I22 for history of myocardial infarction; I60, I61, I63, I64 for history of stroke). Information on smoking status, level of education (as measure of socioeconomic status), and fruit and meat consumption were collected using the touchscreen questionnaire at baseline visit. Body mass index was calculated (kg/m^2) using measured height and weight. Weight was measured using the Tanita BC-418 MA body composition analyser (accurate to within 0.1kg) after removal of heavy clothing and shoes. Standing height was measured without shoes using a Seca 202 height measure. Blood pressure was measured using the Omron HEM-7015IT digital blood pressure monitor.[2] The mean of two measurements taken approximately within a minute of each other was used in the analysis. The UK Biobank study was approved by the North West Multi-centre Research Ethics Committee (MREC) and all participants provided written informed consent to participate in the UK Biobank.

Statistical analysis

Participants were categorized 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). Hazard ratios and 95% CI for all-cause mortality were calculated using Cox proportional-hazards regression models. The primary analysis adjusted for age and sex only. Secondary analyses were additionally adjusted for smoking status, education level, body mass index, systolic blood pressure, and diet(fruit intake and meat consumption). Data were analysed using Stata version 12.1

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eAppendix 4. Systematic review

Data Sources and Searches

Studies published between January 1970 and April 2015 were identified, without any language restriction, through electronic searches using MEDLINE, and supplemented by scanning reference lists of articles identified. The computer-based search strategy is detailed below.

Study Selection

Prospective observational studies were included if they had reported on the association of cardiometabolic morbidity (ie, people with a baseline history of at least two of the conditions diabetes, stroke, and myocardial infarction) with all-cause mortality. Observational studies were eligible if had recorded at least one year of follow-up and involved participants from approximately general populations (ie, participants not selected on the basis of pre-existing disease at baseline). Studies were not eligible for the review if they had contributed data to the Emerging Risk Factors Collaboration. A literature search flow chart is provided below.

Data Extraction

Data on the following characteristics were extracted independently by two investigators (PW and LOK) according to a pre-specified protocol: study location, sampling population, year of baseline survey, date of last follow-up, duration of follow-up, age range of participants at baseline, gender, sample size, numbers of deaths, reported hazard ratios for mortality associated with ≥2 cardiometabolic conditions (ie, diabetes, stroke, and myocardial infarction), and degree of statistical adjustment used. Discrepancies were resolved by discussion and by adjudication of a third reviewer (EDA). We used the most up-to-date or comprehensive information in cases of multiple publications.

Search strategy

#1	"history of" or "prior" or "pre-existing" or "prevalent" or "existing" or "comorbidity"
#2	"Myocardial infarction" OR "coronary heart disease" OR stroke OR diabetes
#3	Mortality[Mesh] OR mortality OR death OR survival
#4	"Cohort Studies"[Mesh] OR cohort OR prospective OR "risk ratio" OR "relative risk" OR "hazard ratio" OR "rate ratio" OR "risk ratios" OR "relative risks" OR "hazard ratios" OR "rate ratios"
#5	"Animals"[Mesh] NOT "Humans"[Mesh]
Search:	(#1 AND #2 AND #3 AND #4) NOT #5
Restrictions:	None
Publication database:	MEDLINE
Result:	13,422 citations

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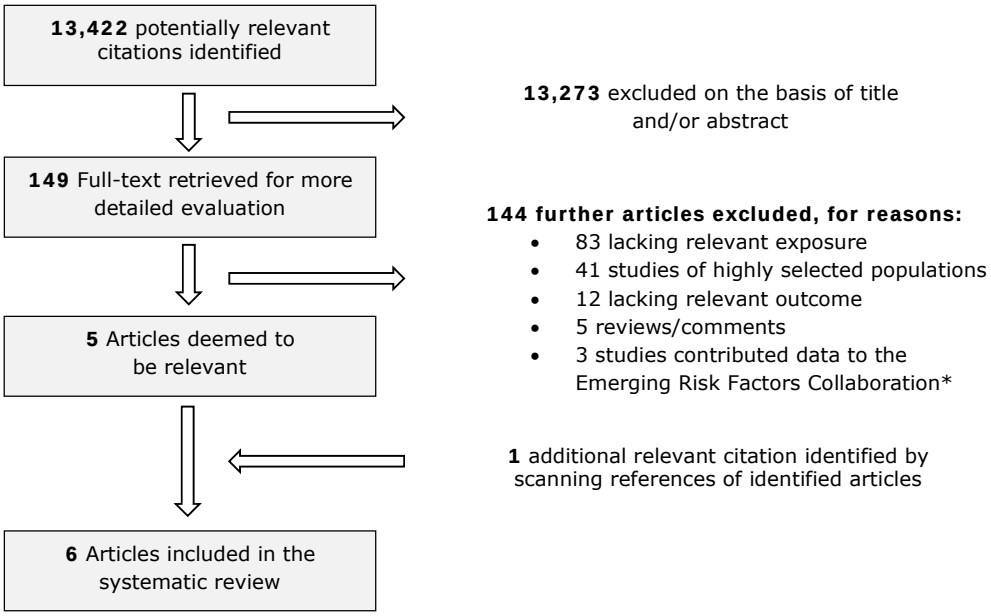
Literature search flow chart



* British Regional Heart Study (BRHS), Cardiovascular Health Study (CHS), and MIDSPAN Renfrew & Paisley Study (MIDRP).

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eAppendix 5. Statistical methods used for estimating years of life lost.

We used three pieces of information to estimate reductions in life expectancy associated with a history of disease at baseline (henceforth "exposure groups"):
(i) age-at-risk specific hazard ratios for all-cause (and cause-specific) mortality in each exposure group versus the reference (derived from the ERFC);
(ii) population all-cause (and cause-specific) mortality rates (derived from the detailed mortality component of the CDC WONDER database of the US Centers for Disease Control and Prevention); and
(iii) prevalence of exposure groups in the population (derived from the ERFC).

We estimated population survival curves for each of 8 exposure groups, utilising estimated age-at-risk specific hazard ratios for mortality by exposure groups in the ERFC and routine statistics on overall population mortality rates. We estimated reductions in life-expectancy as differences in areas under any two survival curves compared. To calculate an appropriate mortality rate for the reference group (i.e. those without disease morbidity), we used ERFC data on exposure prevalence estimates, as described below.

Age-at-risk specific hazard ratios for mortality by exposure groups were estimated from ERFC data separately for each sex. Specifically, a Cox regression model stratified by cohort and trial arm (where applicable) was fitted separately for each sex using a dataset in which participant ages-at-risk were deterministically updated by splitting the follow up times every 5-years and recalculating an age-at-risk variable at the beginning of each 5-year interval of follow up. Interactions between baseline exposure groups and linear and quadratic terms for the age-at-risk variable were included in the model to obtain smoothed hazard ratios. Thus, for participant i in stratum s with exposure group indicator variable $E_{si(j)}$ (i.e. dummy variable equal to 1 if in exposure group is j and zero otherwise) the log hazard rate at time t since baseline was modelled as:

$$\log(h_{si}(t)) = \log(h_{s0}(t)) + \sum_{j=1}^{7} \gamma_{0j} E_{si(j)} + \beta_2 agerisk_{si} + \beta_3 agerisk_{si}^2 + \sum_{j=1}^{7} \gamma_{1j} E_{si(j)} \times agerisk_{si} + \sum_{j=1}^{7} \gamma_{2j} E_{si(j)} \times agerisk_{si}^2 \qquad (1)$$

from which the age-at-risk specific hazard ratios (and 95% CIs) for mortality were obtained as linear combinations of the relevant estimated coefficients, with age-at-risk fixed at values corresponding to midpoints of 5-year age-groups from age 40 onwards (**Figure 1**).

Population all-cause (and cause-specific) mortality rates per 100,000 were obtained in 5-year age-groups for the US population during years 2007-2010 from the Center for Disease Control (CDC) WONDER online database (http://wonder.cdc.gov/controller/datarequest/D76) (**Figure2**), as well as for 15 EU countries during year 2000 (http://ec.europa.eu/eurostat/data/database). Because the mortality rates were provided only up to age-group 80-84 years, but we desired to estimate the overall population survival curves, we used a Poisson regression model with linear and quadratic terms for the midpoints of 5-year age-groups to smooth and extrapolate the mortality rates (**Figure 3**). Next, assuming exponential survival (i.e. constant hazard) within each 5-year age group, we estimated the age-specific survival probability as $S_a = \exp(-5 \times IR_a)$ and derived the overall population survival curves from age 35 onwards as the product of the relevant age-group specific survival probabilities (**Figure 4**).

$$p(survival \mid agerisk \geq 35) = \prod_{agerisk \geq 35} S_a \qquad (2)$$

In order to infer population mortality rates appropriate for the reference exposure group used in our estimation of age-specific hazard ratios (i.e. those without disease morbidity), we used logistic regression to model the age-specific prevalence of (co)morbidity in ERFC cohorts by sex and decade of recruitment (**Figure 5**) We used the age-specific prevalence estimates for the decade commencing in the year 1990 to infer the age-specific mortality rates appropriate for our reference group IR_{a0} as:[1]

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$$IR_{a0} = \frac{IR_a}{p_{a0} + \sum_{j=1}^{7} p_{aj} \times RR_{aj}} \qquad (3)$$

Where IR_a is the population mortality rate for age group a, p_{aj} is the age-specific prevalence of exposure group j, and RR_{aj} is the age-specific hazard ratio in comparison of exposure group j versus reference group ($j = 0$). The age-specific mortality rates in each of the non-reference exposure groups were then inferred in turn by multiplying the age-specific mortality rate for the reference group IR_{a0} by the age-specific hazard ratios RR_{aj} based on ERFC data and equation (2) above used to infer the exposure group-specific population survival curves (**Figure 6**). Finally, reductions in life expectancy according to baseline disease (co)morbidity groups were estimated as difference in the areas under the survival curves for the reference group and each of the disease (co)morbidity groups in turn (**Figure 7**). The areas under curves were calculated by numerical integration.

Appendix References

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eAppendix 5. Figures

Figure 1. Age-at-risk specific hazard ratios for all-cause mortality by sex and exposure groups estimated from ERFC data.

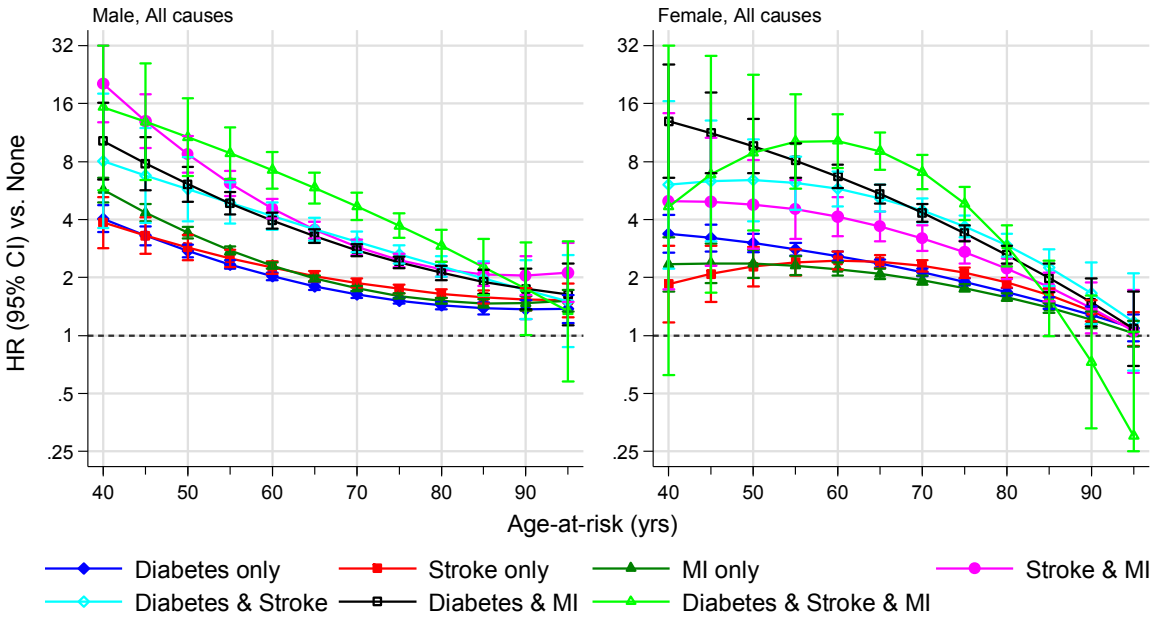
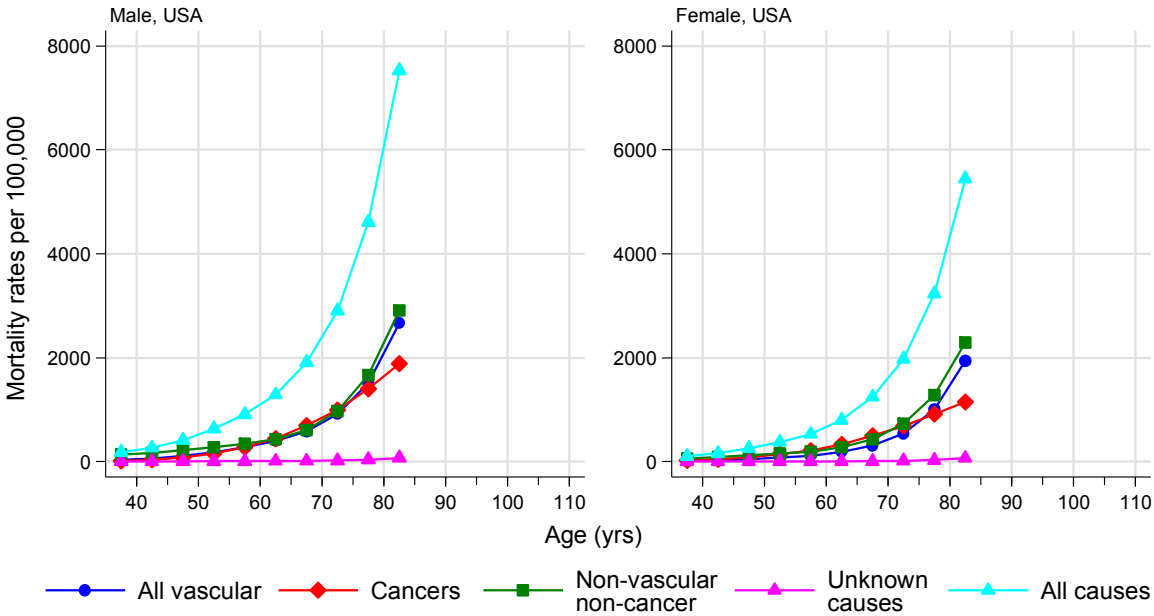


Figure 2. US population mortality rates during year 2007 - 2010 downloaded from CDC WONDER online database.*



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* To maintain consistency with analyses conducted in ERFC, the mortality rate for non-vascular non-cancer causes was recalculated as the difference of all-cause mortality and the sum of vascular mortality (I00-I99), cancer mortality (C00-D48), and unknown causes of mortality (R00-R99).

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Figure 3. Assessment of adequacy of a Poisson model used to smooth and extrapolate US population mortality rates during years 2007 - 2010 downloaded from CDC WONDER online database beyond the database's upper bound age cut-off of 84 years to facilitate modelling.

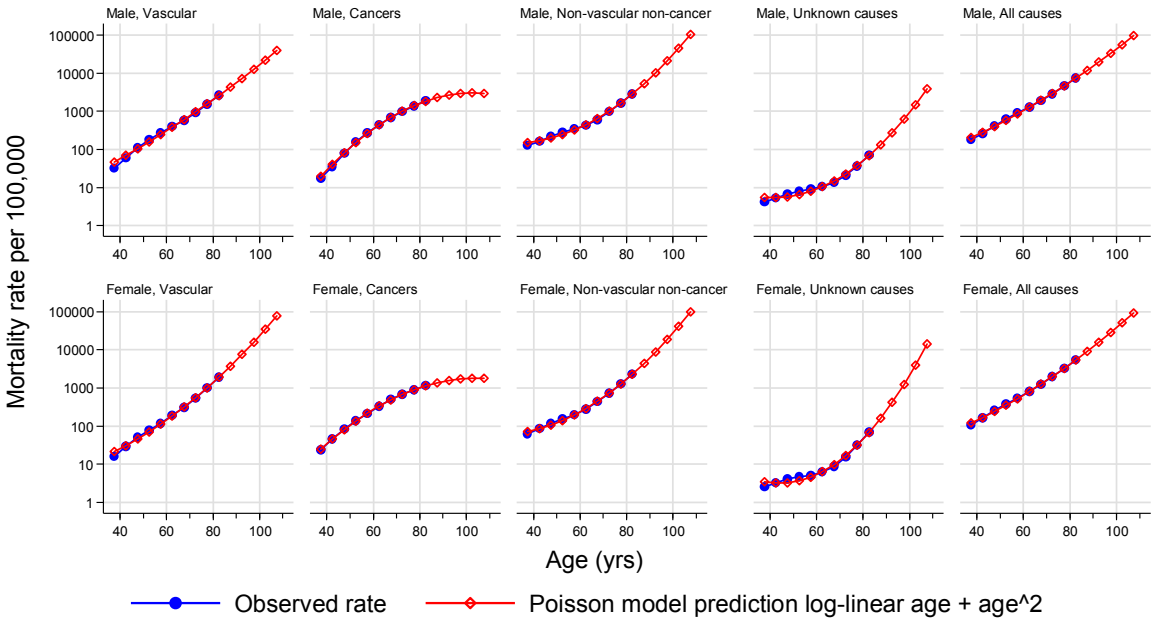

Figure 4. Derived population survival curves for all-cause and cause-specific mortality from age 35 years based on smoothed and extrapolated US population mortality rates 2007 - 2010.

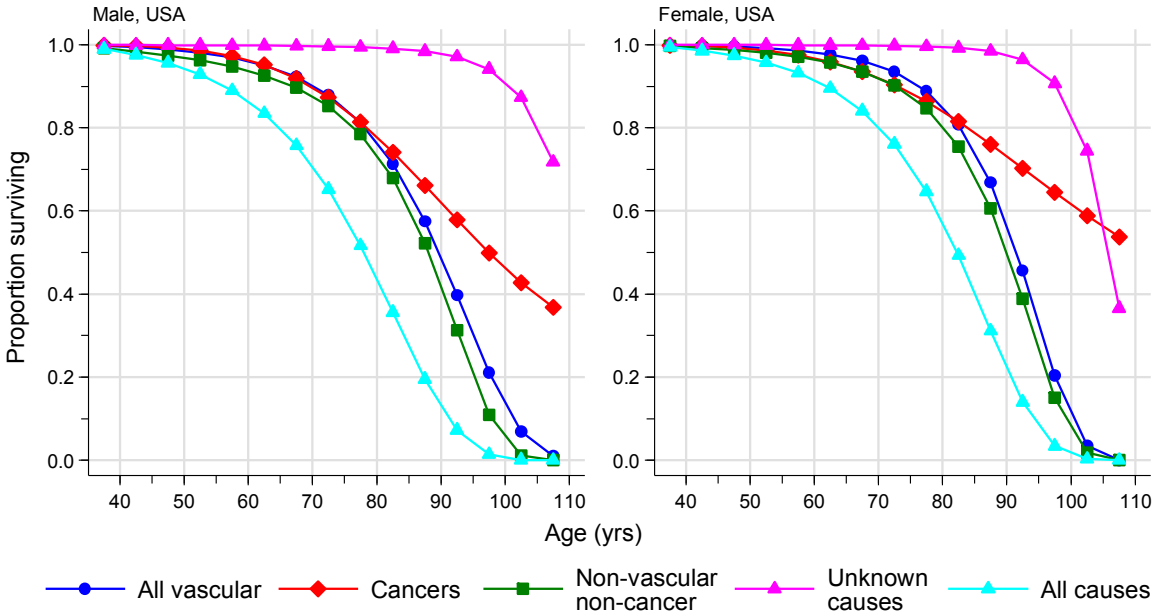

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Figure 5. Modelled age-specific prevalence of (co)morbidity in ERFC cohorts by sex and decade of recruitment.

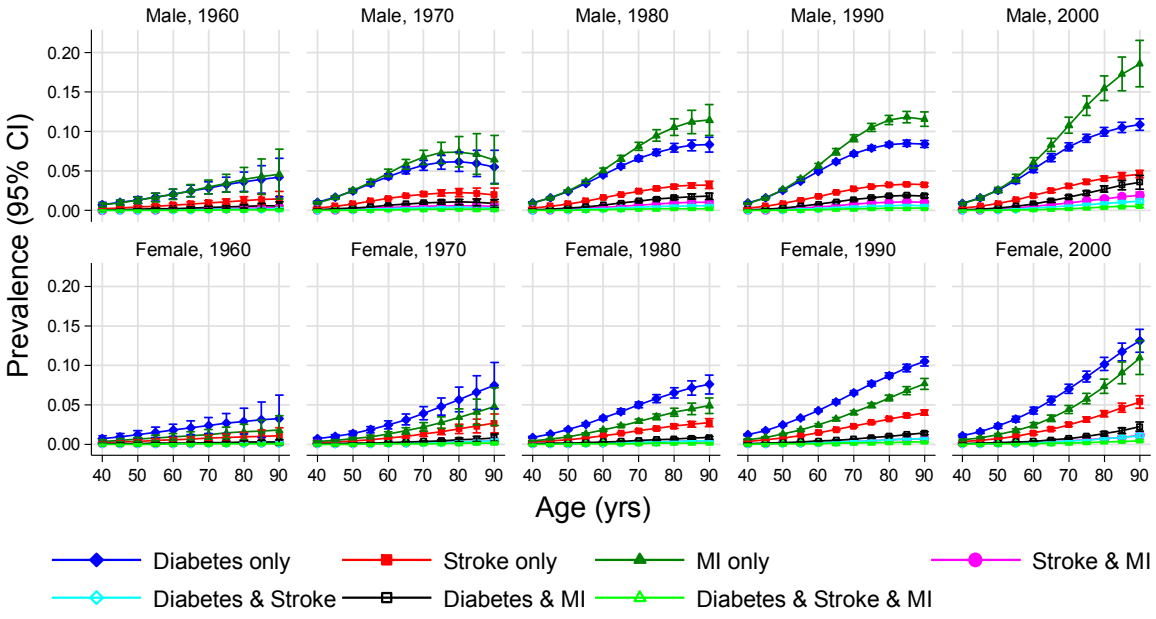

Figure 6. Inferred survival curves for US population by sex and baseline disease morbidity.

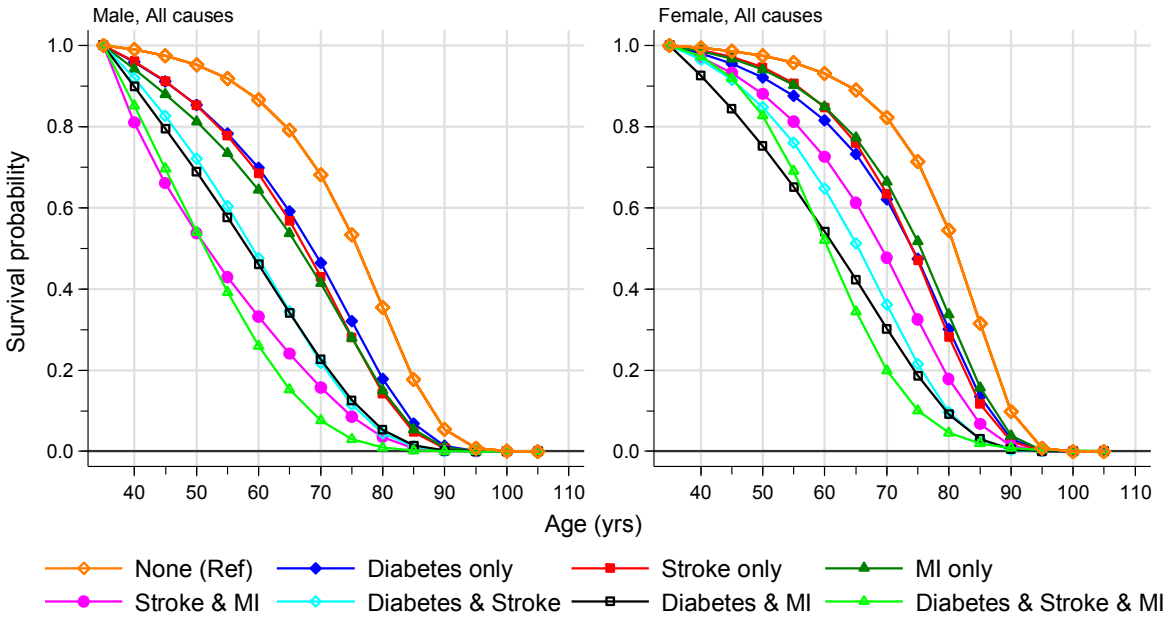

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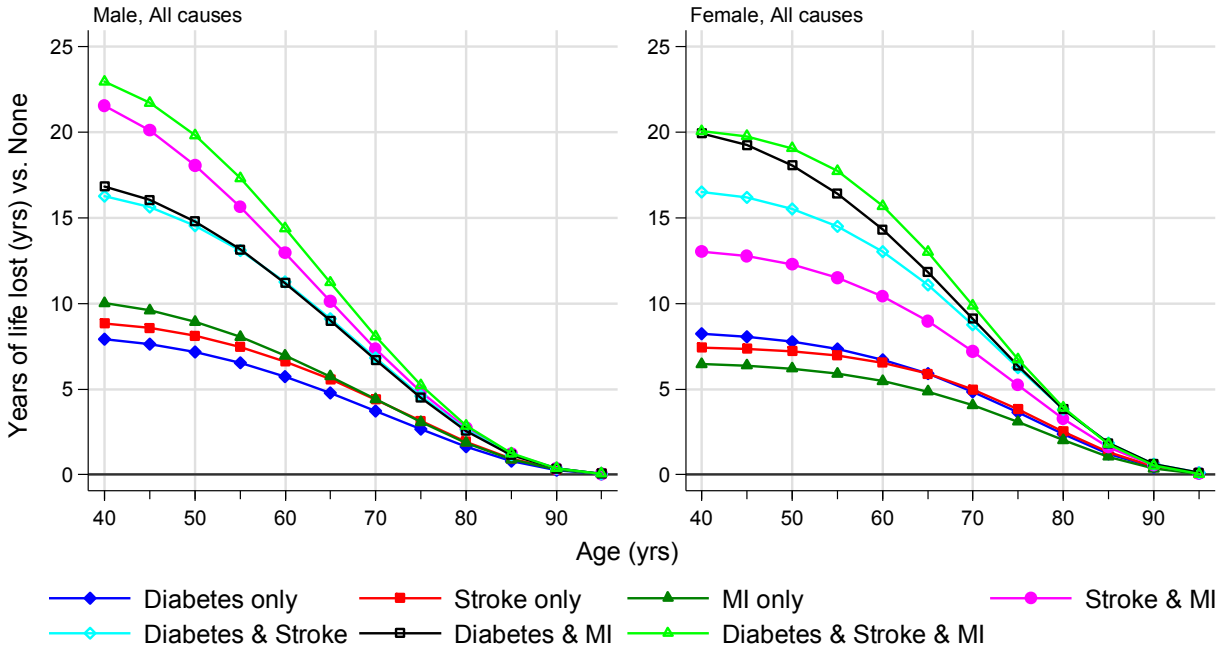
Figure 7. Estimated sex-specific reductions in life expectancy in the US population according to baseline disease morbidity.



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