

**Life expectancy associated with different ages at diagnosis
of diabetes: 23 million person-years of observation**

The Emerging Risk Factors Collaboration

Contents list of supplementary material

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eTable 2. Cohort-specific characteristics: Ascertainment of diabetes and deaths

| Cohort | Diabetes ascertainment | | Deaths ascertainment | |
|--------------|------------------------|-------------------|----------------------|-----------------------------|
| | Prevalent diabetes | Incident diabetes | Information source | ICD codes provided to ERFC? |
| ARIC | 3 | 3 | 2 | 1 |
| AUSDIAB | 5 | 5 | 1 | 1 |
| BHS | 3 | 3 | 1 | 1 |
| BRUN | 3 | 7 | 2 | 0 |
| BWHHS | 1 | 7 | 2 | 1 |
| CHARL | 1 | 6 | 2 | 1 |
| CHS | 4 | 4 | 2 | 0 |
| COPEN | 1 | 4 | 2 | 1 |
| DESIR | 4 | 4 | 1 | 1 |
| DRECE | | | 1 | 1 |
| EPESEIOW | 1 | 1 | 1 | 1 |
| EPESENHA | 1 | 1 | 1 | 1 |
| EPICNOR | 1 | 7 | 1 | 0 |
| ESTHER | 2 | 7 | 1 | 1 |
| FINE_FIN | 1 | | 2 | 1 |
| FINRISK92 | 3 | 2 | 2 | 1 |
| FINRISK97 | 3 | 6 | 2 | 1 |
| FRAMOFF | 4 | 4 | 2 | 0 |
| FUNAGATA | 4 | 7 | 1 | 1 |
| GOTO13 | 1 | 3 | 2 | 1 |
| GOTO33 | 1 | 3 | 2 | 1 |
| GOTO43 | 1 | 3 | 2 | 1 |
| GOTOW | 4 | 4 | 1 | 1 |
| HBS | 4 | 2 | 2 | 0 |
| HCS | 1 | 7 | 1 | 1 |
| HIMS | 1 | 7 | 1 | 1 |
| HOORN | 4 | 4 | 1 | 1 |
| HPFS1 | 2 | 4 | 2 | 1 |
| LASA | 2 | 7 | 1 | 0 |
| MDC | 1 | 7 | 2 | 1 |
| MESA | 4 | 4 | 2 | 0 |
| MONICA_KORA3 | 2 | 7 | 2 | 1 |
| MOSWEGOT | 1 | 1 | 2 | 1 |
| MRCOLD | 5 | | 1 | 1 |
| NHANESI | 2 | 7 | 1 | 1 |
| NHS1 | 2 | 4 | 1 | 1 |
| PARIS1 | 3 | 3 | 2 | 1 |
| PREVEND | 3 | 4 | 2 | 1 |
| QUEBEC | 1 | 4 | 2 | 0 |
| RANCHO | 3 | 4 | 1 | 1 |
| SHIP | 2 | 1 | 2 | 1 |
| SHS | 4 | 4 | 2 | 1 |
| TOYAMA | | | 1 | 1 |
| TROMSØ | 2 | 7 | 1 | 1 |
| ULSAM | 3 | 7 | 2 | 1 |
| USPHS2 | 1 | 1 | 1 | 0 |
| WHIOS | 2 | 2 | 2 | 0 |
| WHS | 4 | 4 | 2 | 0 |
| ZUTE | 1 | 4 | 2 | 1 |
| ATENA | 3 | | 2 | 1 |
| BRHS1 | 1 | 4 | 1 | 1 |
| FINNMARK | 1 | 6 | 1 | 1 |
| HISAYAMA | 4 | 4 | 2 | 1 |
| HUBRO | 1 | 1 | 1 | 1 |
| KARELIA | | | 2 | 1 |
| MCVDRFP | 1 | 1 | 1 | 1 |
| MIDFAM | 1 | 7 | 1 | 1 |
| MORGEN | 1 | 7 | 1 | 1 |
| MPP | 1 | 6 | 2 | 1 |
| NHANESIII | 1 | 1 | 1 | 1 |
| NSHS | | | 2 | 1 |
| OPPHED | 1 | 1 | 1 | 1 |
| OSLO2 | 1 | 1 | 1 | 1 |
| RS_II | 3 | 7 | 2 | 1 |
| RS_III | 3 | 7 | 2 | 1 |
| TROMS | 2 | 7 | 1 | 1 |
| AFTCAPS | 1 | 4 | 2 | 0 |
| ATTICA | | | 1 | 0 |
| EAS | 4 | 4 | 2 | 1 |
| EPESEBOS | 1 | 1 | 1 | 1 |
| EPESENCA | 1 | 1 | 1 | 1 |
| FINE_IT | 1 | | 2 | 1 |
| GOH | 4 | 6 | 2 | 1 |
| IKNS | 4 | 4 | 2 | 1 |
| ISRAEL | 3 | 3 | 2 | 0 |
| KIHDP | 3 | 7 | 2 | 1 |
| MATISS83 | 3 | | 2 | 1 |
| MATISS87 | 3 | | 2 | 1 |
| MIDCOLL | 1 | 7 | 1 | 1 |
| MIDRP | 1 | 7 | 1 | 1 |
| MONFR186 | 3 | | 2 | 1 |
| MRFIT | 1 | 4 | 2 | 1 |
| NCS1 | 1 | | 1 | 1 |
| NCS2 | 1 | | 1 | 1 |
| NCS3 | 1 | | 1 | 1 |
| NPHSII | 1 | 6 | 2 | 1 |
| OSAKA | 5 | 4 | 2 | 1 |
| PRHHP | 3 | 4 | 2 | 1 |
| PROCAM | 3 | 3 | 2 | 0 |
| PROSPER | 4 | 4 | 2 | 0 |
| REYK | 4 | 4 | 2 | 1 |
| RS_I | 3 | 7 | 2 | 1 |
| TARFS | 4 | 4 | 1 | 1 |
| WCWC | 1 | 1 | 1 | 1 |
| WHITEII | 3 | 4 | 1 | 1 |
| WOSCOPS | 1 | 4 | 2 | 0 |
| UKBB | 2 | 7 | 1 | 1 |

Prevalent diabetes:

- 0 Not recorded
- 1 Self report only
- 2 Self report and medications
- 3 Self report and biochemical
- 4 Self report + biochemical + medications
- 5 Biochemical only

Incident diabetes:

- 0 Not recorded
- 1 Self report only
- 2 Self report and medications
- 3 Self report and biochemical
- 4 Self report + biochemical + medications
- 5 Biochemical only
- 6 Medical records only
- 7 Self report and medical records

Deaths information source:

- 1 Death certificate only
- 2 Death certificate plus additional checks*

Deaths ICD codes provided to ERFC?:

- 0 Not provided
- 1 Provided

* e.g. supplemented by medical records, findings on autopsy, and other sources.

eTable 4. Outcome definitions used in current analyses

(a) Definitions of main outcomes

| Outcome | ICD-10 codes |
|--|--|
| All-cause mortality | A00 – R99 |
| Cardiovascular disease (CVD) mortality | G45, I01, I03 – I82, I87, I95 – I99, F01, Q20 – Q28, R96 |
| Cancer mortality | C00 – C97, D00 – D48 |
| Non-CVD, non-cancer mortality | A00 – A99, B00 – B99, D50 – D99, E00 – E99, F00, F02 – F99, G00 – G44, G46 – G99, H00 – H99, I00, I02, I83 – I86, I88 – I89, J00 – J99, K00 – K99, L00 – L99, M00 – M99, N00 – N99, O00 – O99, P00 – P99, Q00 – Q18, Q30 – Q99, S00 – S99, T00 – T99, U04, V00 – V99, W00 – W99, X00 – X99, Y00 – Y99, Z00 – Z99 |
| Unknown/Ill-defined mortality [†] | R00 – R95, R97 – R99 |

(b) Definitions of cause-specific non-CVD mortality

| Outcome | ICD-10 codes |
|--|--|
| Cancer mortality | |
| Digestive related cancer | C15-C26 |
| Lung cancer | C34 |
| Genitourinary related cancer | C51-C68 |
| Breast cancer | C50 |
| Non-CVD, non-cancer mortality | |
| Respiratory system disease | J00-J99 |
| External (violence/suicide/trauma) | S00-S99, T00-T98, U04, V01-V99, W00-W99, X00-X99, Y00-Y98, Z00-Z99 |
| Nervous system disorder | F00, F02, F03, G00-G44, G46-G99 |
| Digestive system disease | K00-K69, K78-K93 |
| Liver disease | B15-B19, K70-K77 |
| Mental disorder | F04-F99 |
| Infectious/bacterial/parasitic disease | A00-A99, B00-B14, B20-B99, U07 |
| Renal disease | N00-N19 |

Note: Attribution of death refers to the primary cause (or, in its absence, the underlying cause) provided by individual studies. Corresponding ICD-9 codes were used in studies that recorded outcomes using this earlier version of ICD.

[†]Ill-defined causes of death were non-vascular deaths defined according to study-specific read-codes for mortality, and not the standard ICD codes.

eTable 5. Hazard ratios for all-cause and cause-specific mortality per decade earlier age at diagnosis of diabetes without and with adjustment for markers of glycemia, renal function, inflammation and lipids.

| Outcome \ Adjustment* | Cohorts | Participants | Events | HR (95% CI) | p | I ² (95% CI) |
|---|---------|--------------|--------|-------------------|---------|-------------------------|
| All-cause mortality | | | | | | |
| Adjusted for conventional risk factors | 54 | 258179 | 57568 | 1.14 (1.05, 1.23) | 0.001 | 67 (56, 75) |
| Plus fasting glucose | 54 | 258179 | 57568 | 1.10 (1.01, 1.19) | 0.027 | 65 (53, 74) |
| Adjusted for conventional risk factors | 27 | 584337 | 51356 | 1.20 (1.12, 1.29) | <0.0001 | 74 (62, 82) |
| Plus HbA1c | 27 | 584337 | 51356 | 1.13 (1.05, 1.20) | <0.001 | 65 (48, 77) |
| Adjusted for conventional risk factors | 40 | 709009 | 84134 | 1.12 (1.04, 1.22) | 0.003 | 78 (70, 84) |
| Plus log eGFR | 40 | 709009 | 84134 | 1.11 (1.03, 1.20) | 0.008 | 78 (70, 83) |
| Adjusted for conventional risk factors | 37 | 624554 | 59810 | 1.13 (1.04, 1.24) | 0.004 | 71 (60, 79) |
| Plus log CRP | 37 | 624554 | 59810 | 1.14 (1.04, 1.24) | 0.003 | 71 (60, 79) |
| Adjusted for conventional risk factors | 61 | 771173 | 78258 | 1.15 (1.08, 1.23) | <0.0001 | 69 (60, 76) |
| Plus non-HDL, HDL, triglycerides [†] | 61 | 771173 | 78258 | 1.15 (1.07, 1.23) | <0.0001 | 70 (61, 77) |
| CVD mortality | | | | | | |
| Adjusted for conventional risk factors | 51 | 256898 | 21704 | 1.24 (1.12, 1.36) | <0.0001 | 50 (31, 64) |
| Plus fasting glucose | 51 | 256898 | 21704 | 1.19 (1.09, 1.31) | <0.001 | 41 (17, 58) |
| Adjusted for conventional risk factors | 27 | 584337 | 13745 | 1.27 (1.15, 1.40) | <0.0001 | 64 (46, 76) |
| Plus HbA1c | 27 | 584337 | 13745 | 1.18 (1.08, 1.28) | <0.001 | 46 (14, 65) |
| Adjusted for conventional risk factors | 37 | 707336 | 25841 | 1.19 (1.07, 1.32) | 0.001 | 69 (57, 78) |
| Plus log eGFR | 37 | 707336 | 25841 | 1.18 (1.06, 1.31) | 0.002 | 68 (55, 77) |
| Adjusted for conventional risk factors | 34 | 620848 | 17108 | 1.21 (1.07, 1.38) | 0.003 | 67 (52, 77) |
| Plus log CRP | 34 | 620848 | 17108 | 1.22 (1.07, 1.38) | 0.003 | 68 (54, 77) |
| Adjusted for conventional risk factors | 59 | 770091 | 24027 | 1.20 (1.09, 1.32) | <0.001 | 59 (46, 69) |
| Plus non-HDL, HDL, triglycerides [†] | 59 | 770091 | 24027 | 1.20 (1.09, 1.32) | <0.001 | 60 (46, 70) |
| Cancer mortality | | | | | | |
| Adjusted for conventional risk factors | 50 | 242787 | 18144 | 0.91 (0.80, 1.03) | 0.135 | 34 (7, 54) |
| Plus fasting glucose | 50 | 242787 | 18144 | 0.89 (0.80, 1.00) | 0.059 | 23 (0, 46) |
| Adjusted for conventional risk factors | 25 | 567738 | 21919 | 1.01 (0.92, 1.11) | 0.863 | 33 (0, 59) |
| Plus HbA1c | 25 | 567738 | 21919 | 0.96 (0.88, 1.04) | 0.307 | 17 (0, 49) |
| Adjusted for conventional risk factors | 36 | 693693 | 32747 | 0.93 (0.86, 1.00) | 0.059 | 11 (0, 41) |
| Plus log eGFR | 36 | 693693 | 32747 | 0.91 (0.84, 0.99) | 0.033 | 16 (0, 45) |
| Adjusted for conventional risk factors | 28 | 579753 | 24117 | 0.97 (0.85, 1.10) | 0.589 | 37 (1, 60) |
| Plus log CRP | 28 | 579753 | 24117 | 0.97 (0.86, 1.10) | 0.651 | 34 (0, 59) |
| Adjusted for conventional risk factors | 55 | 733508 | 30014 | 0.97 (0.88, 1.07) | 0.607 | 31 (3, 51) |
| Plus non-HDL, HDL, triglycerides [†] | 55 | 733508 | 30014 | 0.97 (0.88, 1.07) | 0.598 | 31 (3, 50) |
| Non-CVD, non-cancer mortality | | | | | | |
| Adjusted for conventional risk factors | 45 | 239784 | 14248 | 1.19 (1.07, 1.31) | <0.001 | 40 (14, 58) |
| Plus fasting glucose | 45 | 239784 | 14248 | 1.15 (1.03, 1.27) | 0.010 | 41 (15, 58) |
| Adjusted for conventional risk factors | 24 | 566615 | 13878 | 1.25 (1.13, 1.39) | <0.0001 | 61 (39, 75) |
| Plus HbA1c | 24 | 566615 | 13878 | 1.19 (1.08, 1.31) | <0.001 | 50 (19, 69) |
| Adjusted for conventional risk factors | 34 | 692544 | 21768 | 1.18 (1.06, 1.31) | 0.002 | 63 (47, 75) |
| Plus log eGFR | 34 | 692544 | 21768 | 1.16 (1.05, 1.29) | 0.004 | 62 (45, 74) |
| Adjusted for conventional risk factors | 26 | 576653 | 15342 | 1.13 (1.00, 1.28) | 0.047 | 56 (32, 72) |
| Plus log CRP | 26 | 576653 | 15342 | 1.14 (1.01, 1.28) | 0.035 | 55 (30, 71) |
| Adjusted for conventional risk factors | 51 | 725027 | 19965 | 1.21 (1.12, 1.32) | <0.0001 | 39 (14, 57) |
| Plus non-HDL, HDL, triglycerides [†] | 51 | 725027 | 19965 | 1.21 (1.11, 1.31) | <0.0001 | 39 (14, 56) |

* Conventional risk factors included: cohort, sex, age, smoking status, BMI, systolic blood pressure, and total cholesterol.

Fasting glucose, HbA1c, and log eGFR were adjusted for as a continuous variables with linear and quadratic terms.

[†] Replacing total cholesterol with the trio of non-HDL cholesterol, HDL cholesterol, and log triglycerides.

eTable 6. Assessment of additive interactions by category of age at diagnosis of diabetes (<50 years vs >50 years) for all-cause mortality risk adjusted for conventional risk factors*.

| Characteristic \ Subgroup | Statistic | Diabetes diagnosed < 50 years | | Diabetes diagnosed ≥ 50 years | |
|--|-----------|-------------------------------|---------|-------------------------------|---------|
| | | Statistic (95% CI) | p | Statistic (95% CI) | p |
| Sex | | | | | |
| Male vs Female sex (without diabetes) | RR | 1.63 (1.58, 1.68) | <0.0001 | 1.63 (1.58, 1.68) | <0.0001 |
| With diabetes AND Male sex | RR | 2.57 (2.35, 2.81) | <0.0001 | 1.66 (1.56, 1.77) | <0.0001 |
| With diabetes AND Female sex | RR | 3.38 (3.10, 3.69) | <0.0001 | 2.49 (2.34, 2.65) | <0.0001 |
| Relative excess risk due to interaction (RERI) | RERI_RR | 0.186 (-0.066, 0.438) | 0.148 | 0.196 (0.105, 0.287) | <0.0001 |
| Attributable proportion (AP) | AP | 0.055 (-0.017, 0.127) | 0.132 | 0.079 (0.045, 0.113) | <0.0001 |
| Synergy index (SI) | SI | 1.08 (0.97, 1.21) | 0.142 | 1.15 (1.08, 1.23) | <0.0001 |
| Smoking status | | | | | |
| Current vs Other status (without diabetes) | RR | 1.96 (1.87, 2.05) | <0.0001 | 1.96 (1.87, 2.05) | <0.0001 |
| With diabetes AND Other status | RR | 2.39 (2.21, 2.59) | <0.0001 | 1.61 (1.52, 1.70) | <0.0001 |
| With diabetes AND Current smoker | RR | 3.89 (3.47, 4.36) | <0.0001 | 2.73 (2.52, 2.95) | <0.0001 |
| Relative excess risk due to interaction (RERI) | RERI_RR | 0.542 (0.192, 0.892) | 0.002 | 0.164 (0.011, 0.316) | 0.036 |
| Attributable proportion (AP) | AP | 0.139 (0.063, 0.216) | <0.001 | 0.060 (0.008, 0.112) | 0.025 |
| Synergy index (SI) | SI | 1.23 (1.09, 1.39) | 0.001 | 1.10 (1.01, 1.21) | 0.027 |
| Age at risk | | | | | |
| Age ≥ 60 vs Age < 60 years (without diabetes) | RR | 3.95 (3.51, 4.44) | <0.0001 | 3.95 (3.51, 4.44) | <0.0001 |
| With diabetes AND Age < 60 years | RR | 2.35 (2.11, 2.61) | <0.0001 | 2.88 (2.52, 3.29) | <0.0001 |
| With diabetes AND Age ≥ 60 years | RR | 6.85 (5.90, 7.96) | <0.0001 | 6.48 (5.60, 7.50) | <0.0001 |
| Relative excess risk due to interaction (RERI) | RERI_RR | 1.555 (0.851, 2.259) | <0.0001 | 0.653 (0.242, 1.063) | 0.002 |
| Attributable proportion (AP) | AP | 0.227 (0.148, 0.305) | <0.0001 | 0.101 (0.046, 0.155) | <0.001 |
| Synergy index (SI) | SI | 1.36 (1.21, 1.53) | <0.0001 | 1.14 (1.06, 1.22) | 0.001 |
| History of CVD (HxCVD) | | | | | |
| HxCVD=Yes vs HxCVD=No (without diabetes) | RR | 1.67 (1.59, 1.74) | <0.0001 | 1.67 (1.59, 1.74) | <0.0001 |
| With diabetes AND HxCVD=No | RR | 2.20 (2.04, 2.38) | <0.0001 | 1.55 (1.47, 1.64) | <0.0001 |
| With diabetes AND HxCVD=Yes | RR | 3.82 (3.35, 4.35) | <0.0001 | 2.36 (2.18, 2.55) | <0.0001 |
| Relative excess risk due to interaction (RERI) | RERI_RR | 0.945 (0.513, 1.377) | <0.0001 | 0.138 (0.016, 0.260) | 0.027 |
| Attributable proportion (AP) | AP | 0.248 (0.163, 0.332) | <0.0001 | 0.059 (0.010, 0.107) | 0.018 |
| Synergy index (SI) | SI | 1.51 (1.29, 1.76) | <0.0001 | 1.11 (1.02, 1.22) | 0.019 |

* Conventional risk factors included: cohort, sex, age, smoking status, BMI, systolic blood pressure, and total cholesterol.

For each subgroup characteristic, the table summarises (a) relative risks (RR) for groups of the characteristic with/without diabetes diagnosed before and after age 50 years; and (b) summary indices of additive interactions that are functions of the preceding relative risks (for details see VanderWeele TJ et al A Tutorial on Interaction Epidemiol Methods 2014(3)33–72).

eTable 7. Hazard ratios for all-cause and cause-specific mortality according to duration of diabetes with adjustment for conventional risk factors*

| Outcome \ Duration of diabetes | Events | HR (95% CI) adjusted for... | | |
|--------------------------------------|---------------|-----------------------------|--------------------------|--|
| | | Age and sex | Age, sex, and smoking | Age, sex, smoking, and other risk factors* |
| All-cause mortality | | | | |
| No Diabetes | 153068 | 1 (Ref) | 1 (Ref) | 1 (Ref) |
| <5 yrs | 3908 | 1.58 (1.45, 1.73) | 1.62 (1.49, 1.76) | 1.58 (1.45, 1.72) |
| 5 to <10 yrs | 2867 | 1.56 (1.46, 1.67) | 1.60 (1.50, 1.71) | 1.54 (1.45, 1.64) |
| 10 to <15 yrs | 2657 | 1.69 (1.57, 1.82) | 1.72 (1.60, 1.85) | 1.66 (1.56, 1.78) |
| 15 to <20 yrs | 2029 | 2.00 (1.86, 2.14) | 2.04 (1.90, 2.18) | 1.94 (1.82, 2.06) |
| ≥20 yrs | 2633 | 2.01 (1.85, 2.19) | 2.07 (1.90, 2.25) | 2.00 (1.84, 2.16) |
| Per decade higher | 167162 | 1.14 (1.08, 1.19) | 1.13 (1.08, 1.19) | 1.13 (1.07, 1.19) |
| P-value | | <0.0001 | <0.0001 | <0.0001 |
| I ² (95% CI) | | 67 (59, 74) | 68 (60, 74) | 67 (60, 74) |
| CVD mortality | | | | |
| No Diabetes | 53857 | 1 (Ref) | 1 (Ref) | 1 (Ref) |
| <5 yrs | 1538 | 1.85 (1.66, 2.06) | 1.89 (1.70, 2.10) | 1.73 (1.56, 1.92) |
| 5 to <10 yrs | 1097 | 2.01 (1.81, 2.22) | 2.06 (1.85, 2.29) | 1.89 (1.72, 2.09) |
| 10 to <15 yrs | 988 | 2.13 (1.91, 2.38) | 2.17 (1.95, 2.42) | 1.98 (1.80, 2.18) |
| 15 to <20 yrs | 817 | 2.61 (2.33, 2.92) | 2.66 (2.38, 2.97) | 2.40 (2.19, 2.63) |
| ≥20 yrs | 1054 | 2.56 (2.25, 2.92) | 2.63 (2.31, 2.99) | 2.41 (2.15, 2.69) |
| Per decade higher | 59351 | 1.19 (1.11, 1.27) | 1.19 (1.11, 1.27) | 1.20 (1.12, 1.28) |
| P-value | | <0.0001 | <0.0001 | <0.0001 |
| I ² (95% CI) | | 58 (47, 67) | 58 (48, 67) | 59 (48, 67) |
| Cancer mortality | | | | |
| No Diabetes | 53217 | 1 (Ref) | 1 (Ref) | 1 (Ref) |
| <5 yrs | 1063 | 1.40 (1.27, 1.55) | 1.43 (1.30, 1.57) | 1.42 (1.29, 1.55) |
| 5 to <10 yrs | 816 | 1.27 (1.17, 1.38) | 1.29 (1.19, 1.40) | 1.24 (1.15, 1.33) |
| 10 to <15 yrs | 760 | 1.43 (1.28, 1.60) | 1.46 (1.32, 1.62) | 1.43 (1.33, 1.54) |
| 15 to <20 yrs | 431 | 1.34 (1.20, 1.50) | 1.37 (1.24, 1.52) | 1.31 (1.19, 1.44) |
| ≥20 yrs | 469 | 1.26 (1.13, 1.40) | 1.30 (1.17, 1.43) | 1.24 (1.13, 1.36) |
| Per decade higher | 56756 | 0.95 (0.89, 1.02) | 0.95 (0.89, 1.02) | 0.95 (0.89, 1.01) |
| P-value | | 0.154 | 0.143 | 0.113 |
| I ² (95% CI) | | 16 (0, 37) | 15 (0, 36) | 17 (0, 37) |
| Non-CVD, non-cancer mortality | | | | |
| No Diabetes | 35986 | 1 (Ref) | 1 (Ref) | 1 (Ref) |
| <5 yrs | 954 | 1.84 (1.61, 2.10) | 1.87 (1.64, 2.13) | 1.92 (1.68, 2.19) |
| 5 to <10 yrs | 764 | 1.79 (1.61, 1.99) | 1.83 (1.65, 2.03) | 1.82 (1.65, 2.00) |
| 10 to <15 yrs | 775 | 2.03 (1.84, 2.24) | 2.07 (1.88, 2.28) | 2.02 (1.84, 2.21) |
| 15 to <20 yrs | 696 | 2.73 (2.49, 2.99) | 2.78 (2.54, 3.04) | 2.64 (2.42, 2.87) |
| ≥20 yrs | 984 | 2.76 (2.43, 3.13) | 2.85 (2.50, 3.24) | 2.82 (2.49, 3.19) |
| Per decade higher | 40159 | 1.18 (1.10, 1.27) | 1.18 (1.10, 1.27) | 1.16 (1.08, 1.25) |
| P-value | | <0.0001 | <0.0001 | <0.0001 |
| I ² (95% CI) | | 48 (32, 60) | 49 (33, 61) | 48 (33, 60) |

*Analyses based on ERFC and UK Biobank, including 92 cohorts and 1,132,277 participants with complete information on age at diagnosis of diabetes, age, sex, smoking and other risk factors.

* Other risk factors were body mass index, systolic blood pressure and total cholesterol.

eTable 8. Hazard ratios for all-cause and cause-specific mortality per decade higher duration of diabetes without and with adjustment for markers of glycemia, renal function, inflammation and lipids.

| Outcome \ Adjustment* | Cohorts | Participants | Events | HR (95% CI) | p | I ² (95% CI) |
|---|---------|--------------|--------|-------------------|---------|-------------------------|
| All-cause mortality | | | | | | |
| Adjusted for conventional risk factors | 54 | 258179 | 57568 | 1.14 (1.06, 1.24) | <0.001 | 66 (55, 74) |
| Plus fasting glucose | 54 | 258179 | 57568 | 1.10 (1.01, 1.19) | 0.021 | 63 (51, 72) |
| Adjusted for conventional risk factors | 27 | 584337 | 51356 | 1.20 (1.12, 1.29) | <0.0001 | 74 (63, 82) |
| Plus HbA1c | 27 | 584337 | 51356 | 1.13 (1.05, 1.20) | <0.001 | 66 (48, 77) |
| Adjusted for conventional risk factors | 40 | 709009 | 84134 | 1.12 (1.04, 1.22) | 0.003 | 78 (70, 84) |
| Plus log eGFR | 40 | 709009 | 84134 | 1.11 (1.03, 1.20) | 0.008 | 78 (70, 83) |
| Adjusted for conventional risk factors | 37 | 624554 | 59810 | 1.13 (1.04, 1.24) | 0.004 | 71 (60, 79) |
| Plus log CRP | 37 | 624554 | 59810 | 1.14 (1.04, 1.24) | 0.003 | 71 (60, 79) |
| Adjusted for conventional risk factors | 61 | 771173 | 78258 | 1.15 (1.08, 1.23) | <0.0001 | 69 (60, 76) |
| Plus non-HDL, HDL, triglycerides [†] | 61 | 771173 | 78258 | 1.15 (1.07, 1.23) | <0.0001 | 70 (61, 77) |
| CVD mortality | | | | | | |
| Adjusted for conventional risk factors | 51 | 256898 | 21704 | 1.24 (1.12, 1.36) | <0.0001 | 49 (30, 63) |
| Plus fasting glucose | 51 | 256898 | 21704 | 1.19 (1.09, 1.31) | <0.001 | 40 (17, 58) |
| Adjusted for conventional risk factors | 27 | 584337 | 13745 | 1.27 (1.15, 1.40) | <0.0001 | 64 (45, 76) |
| Plus HbA1c | 27 | 584337 | 13745 | 1.18 (1.09, 1.28) | <0.001 | 45 (14, 65) |
| Adjusted for conventional risk factors | 37 | 707336 | 25841 | 1.19 (1.07, 1.32) | 0.001 | 69 (57, 78) |
| Plus log eGFR | 37 | 707336 | 25841 | 1.18 (1.06, 1.31) | 0.002 | 68 (55, 77) |
| Adjusted for conventional risk factors | 34 | 620848 | 17108 | 1.20 (1.06, 1.36) | 0.004 | 65 (50, 76) |
| Plus log CRP | 34 | 620848 | 17108 | 1.21 (1.06, 1.37) | 0.003 | 66 (51, 76) |
| Adjusted for conventional risk factors | 59 | 770091 | 24027 | 1.19 (1.09, 1.31) | <0.001 | 59 (45, 69) |
| Plus non-HDL, HDL, triglycerides [†] | 59 | 770091 | 24027 | 1.19 (1.09, 1.32) | <0.001 | 59 (45, 69) |
| Cancer mortality | | | | | | |
| Adjusted for conventional risk factors | 50 | 242787 | 18144 | 0.92 (0.80, 1.04) | 0.184 | 36 (10, 55) |
| Plus fasting glucose | 50 | 242787 | 18144 | 0.90 (0.79, 1.02) | 0.089 | 30 (1, 51) |
| Adjusted for conventional risk factors | 25 | 567738 | 21919 | 1.01 (0.92, 1.11) | 0.859 | 35 (0, 60) |
| Plus HbA1c | 25 | 567738 | 21919 | 0.96 (0.88, 1.05) | 0.351 | 20 (0, 51) |
| Adjusted for conventional risk factors | 36 | 693693 | 32747 | 0.93 (0.86, 1.00) | 0.060 | 10 (0, 40) |
| Plus log eGFR | 36 | 693693 | 32747 | 0.92 (0.84, 0.99) | 0.034 | 15 (0, 44) |
| Adjusted for conventional risk factors | 28 | 579753 | 24117 | 0.97 (0.86, 1.10) | 0.626 | 32 (0, 57) |
| Plus log CRP | 28 | 579753 | 24117 | 0.98 (0.87, 1.10) | 0.699 | 29 (0, 55) |
| Adjusted for conventional risk factors | 55 | 733508 | 30014 | 0.98 (0.89, 1.07) | 0.620 | 28 (0, 49) |
| Plus non-HDL, HDL, triglycerides [†] | 55 | 733508 | 30014 | 0.98 (0.89, 1.07) | 0.610 | 28 (0, 48) |
| Non-CVD, non-cancer mortality | | | | | | |
| Adjusted for conventional risk factors | 44 | 231659 | 14222 | 1.19 (1.07, 1.31) | <0.001 | 41 (15, 59) |
| Plus fasting glucose | 44 | 231659 | 14222 | 1.15 (1.03, 1.28) | 0.011 | 42 (16, 59) |
| Adjusted for conventional risk factors | 24 | 566615 | 13878 | 1.25 (1.13, 1.39) | <0.0001 | 61 (39, 75) |
| Plus HbA1c | 24 | 566615 | 13878 | 1.19 (1.08, 1.31) | <0.001 | 49 (18, 68) |
| Adjusted for conventional risk factors | 34 | 692544 | 21768 | 1.18 (1.06, 1.31) | 0.002 | 63 (47, 75) |
| Plus log eGFR | 34 | 692544 | 21768 | 1.17 (1.05, 1.29) | 0.004 | 62 (45, 74) |
| Adjusted for conventional risk factors | 26 | 576653 | 15342 | 1.13 (1.00, 1.28) | 0.045 | 56 (31, 72) |
| Plus log CRP | 26 | 576653 | 15342 | 1.14 (1.01, 1.28) | 0.033 | 55 (29, 71) |
| Adjusted for conventional risk factors | 51 | 725027 | 19965 | 1.21 (1.12, 1.32) | <0.0001 | 39 (14, 56) |
| Plus non-HDL, HDL, triglycerides [†] | 51 | 725027 | 19965 | 1.21 (1.11, 1.31) | <0.0001 | 38 (13, 56) |

* Conventional risk factors included: cohort, sex, age, smoking status, BMI, systolic blood pressure, and total cholesterol.

Fasting glucose, HbA1c, and log eGFR were adjusted for as a continuous variables with linear and quadratic terms.

[†] Replacing total cholesterol with the trio of non-HDL cholesterol, HDL cholesterol, and log triglycerides.

eTable 9. Hazard ratios for components of non-CVD mortality per decade earlier age at diagnosis of diabetes adjusted for conventional risk factors*.

| Outcome | Cohorts | Participants | Events | HR (95% CI) | p | I^2 (95% CI) |
|--|---------|--------------|--------|-------------------|---------|----------------|
| Cancer mortality | | | | | | |
| All cancer mortality | 83 | 1068608 | 56756 | 0.94 (0.88, 1.02) | 0.128 | 24 (0, 43) |
| Digestive related cancer | 70 | 1014958 | 15871 | 0.97 (0.87, 1.09) | 0.646 | 12 (0, 35) |
| Lung cancer | 63 | 954825 | 11687 | 0.93 (0.83, 1.04) | 0.195 | 0 (0, 30) |
| Genitourinary related cancer | 64 | 999797 | 9430 | 0.95 (0.84, 1.07) | 0.389 | 0 (0, 30) |
| Breast cancer | 33 | 855481 | 3197 | 1.07 (0.87, 1.32) | 0.516 | 0 (0, 39) |
| Non-CVD, non-cancer mortality | | | | | | |
| All non-CVD, non-cancer mortality | 80 | 1061784 | 40159 | 1.16 (1.08, 1.25) | <0.0001 | 50 (36, 62) |
| Respiratory system disease | 69 | 1027860 | 12853 | 1.07 (0.96, 1.19) | 0.232 | 19 (0, 40) |
| External (violence/suicide/trauma) | 63 | 1022280 | 5710 | 1.21 (1.04, 1.42) | 0.015 | 3 (0, 25) |
| Nervous system disorder | 39 | 838787 | 5792 | 1.13 (1.01, 1.28) | 0.041 | 0 (0, 37) |
| Digestive system disease | 48 | 926328 | 3149 | 1.20 (1.03, 1.40) | 0.020 | 0 (0, 34) |
| Liver disease | 33 | 829812 | 1699 | 0.77 (0.62, 0.96) | 0.022 | 0 (0, 39) |
| Mental disorder | 27 | 759888 | 1092 | 1.10 (0.84, 1.44) | 0.486 | 0 (0, 43) |
| Infectious/bacterial/parasitic disease | 33 | 838853 | 2162 | 1.28 (1.07, 1.53) | 0.007 | 13 (0, 44) |
| Renal disease | 25 | 731736 | 983 | 1.46 (1.16, 1.84) | 0.001 | 29 (0, 57) |

* Conventional risk factors included: cohort, sex, age, smoking status, BMI, systolic blood pressure, and total cholesterol. Studies with fewer than 10 events of any outcome were excluded from the analysis of that outcome.

eTable 10. Hazard ratios (HR) and subdistribution hazard ratios (SHRs) for all-cause and cause-specific mortality per decade earlier age at diagnosis of diabetes adjusted for conventional risk factors* with/without adjustment for competing risks in analyses restricted to studies with ≥ 80 deaths recorded\$.

| Outcome | Cohorts‡ | Participants | Main events | Competing events† | HR (95% CI) | p | I^2 (95% CI) |
|--|----------|--------------|-------------|-------------------|-------------------|---------|----------------|
| Cox model results (without competing risks) | | | | | | | |
| All-cause mortality | | | | | | | |
| All-cause mortality | 87 | 1119110 | 166929 | - | 1.13 (1.08, 1.19) | <0.0001 | 69 (61, 75) |
| CVD mortality | 76 | 1090897 | 58899 | - | 1.20 (1.12, 1.29) | <0.0001 | 65 (55, 72) |
| Cancer mortality | 67 | 1030099 | 56143 | - | 0.94 (0.87, 1.01) | 0.084 | 27 (0, 46) |
| Non-CVD, non-cancer mortality | 57 | 999429 | 39093 | - | 1.15 (1.06, 1.24) | <0.001 | 58 (44, 69) |
| Fine and Gray model results (competing risk adjusted) | | | | | | | |
| CVD mortality | | | | | | | |
| CVD mortality | 73 | 1078926 | 58340 | 104806 | 1.30 (1.22, 1.38) | <0.0001 | 59 (48, 67) |
| Cancer mortality | 65 | 1019096 | 55515 | 101606 | 0.97 (0.90, 1.03) | 0.287 | 39 (21, 54) |
| Non-CVD, non-cancer mortality | 56 | 991281 | 38880 | 114155 | 1.24 (1.17, 1.32) | <0.0001 | 51 (37, 63) |

* Conventional risk factors included: cohort, sex, age, smoking status, BMI, systolic blood pressure, and total cholesterol. Studies with fewer than 80 events of any outcome were excluded from the analysis of that outcome.

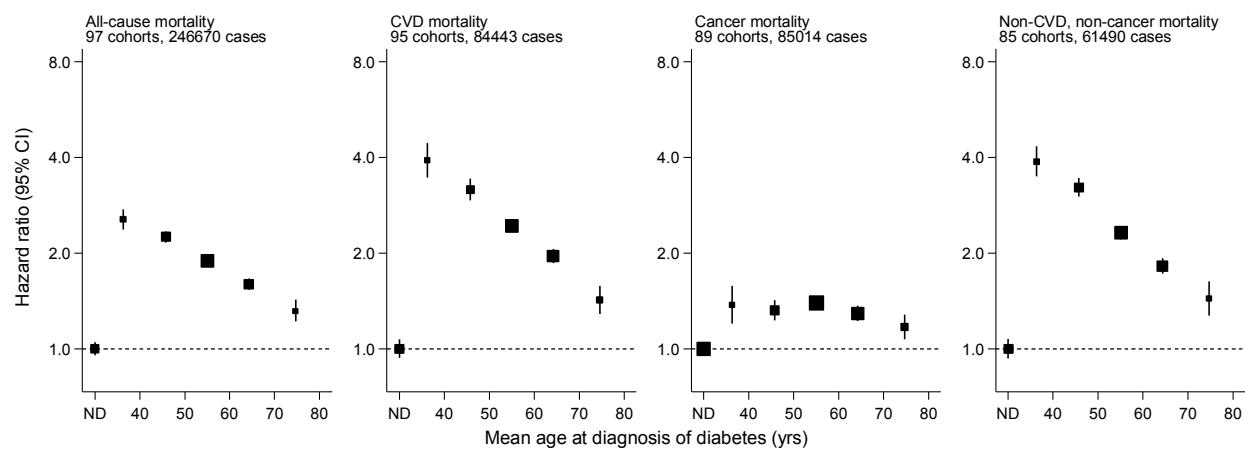
† Competing events in the Fine and Gray model comprised deaths other than the main cause of interest.

‡ The Fine and Gray model did not converge to a solution in a few cohorts hence the slight difference in sample sizes shown.

\$ Analyses were restricted to studies with ≥ 80 deaths recorded as additional sensitivity analyses to check for possible overfitting according to conventional rule of 10 events per variable included in the regression model (here 8 variables \times 10 events = 80 deaths).

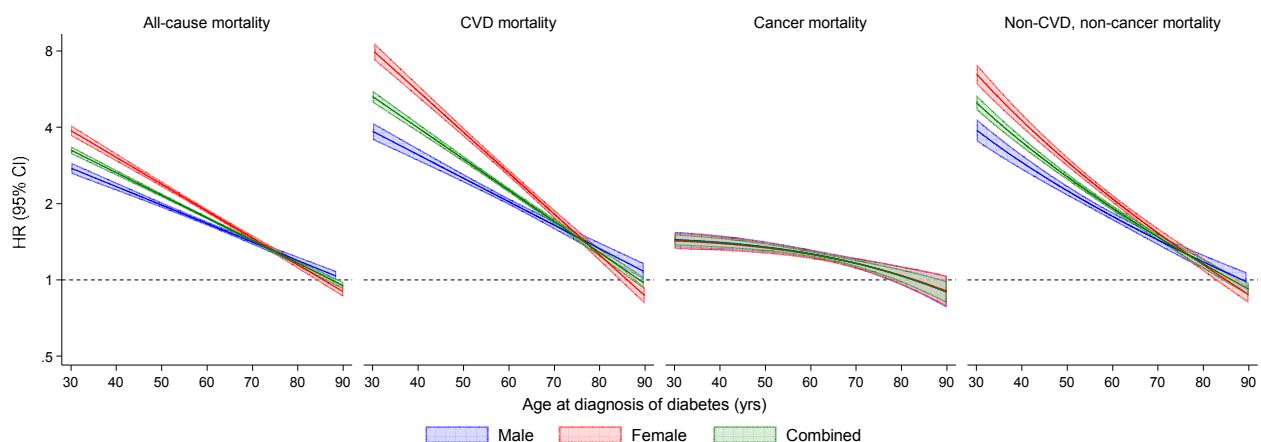
eFigure 1. Associations of age at diagnosis of diabetes with all-cause and cause-specific mortality adjusted for age and sex.

(a) Sex adjusted associations by categories of age at diagnosis of diabetes



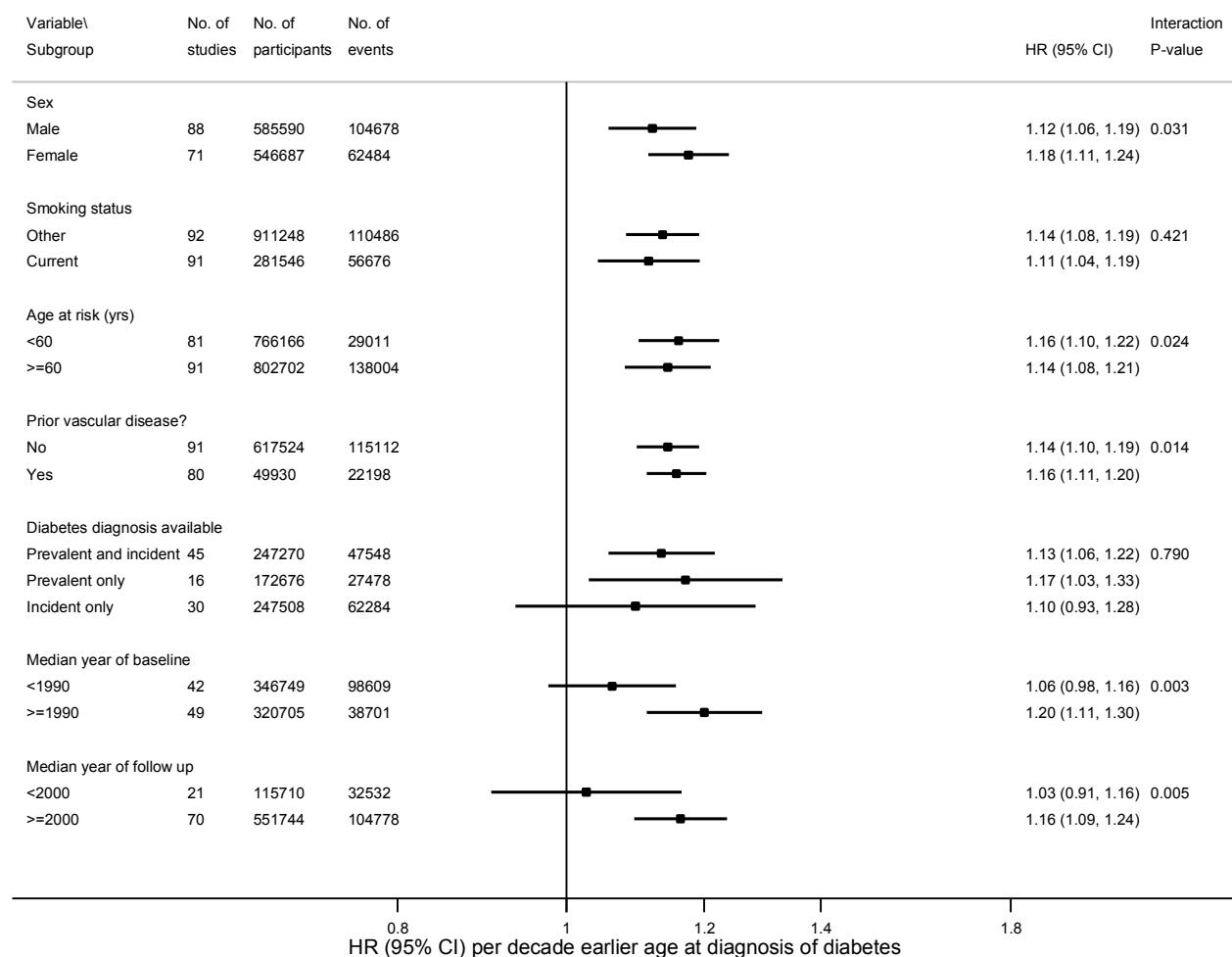
ND, No diabetes. The 6 categories of age at diagnosis correspond to: ND, 30 to <40 yrs, 40 to <50 yrs, 50 to <60 yrs, 60 to <70 yrs, and ≥70 yrs. Hazard ratios adjusted for age and sex. The reference category is no diabetes. Studies with fewer than 10 events of any outcome were excluded from the analysis of that outcome. Sizes of the boxes are proportional to the inverse of the variance of the log-transformed hazard ratios. Vertical lines represent 95% CIs.

(b) Continuous associations by sex and overall using fractional polynomial modelling

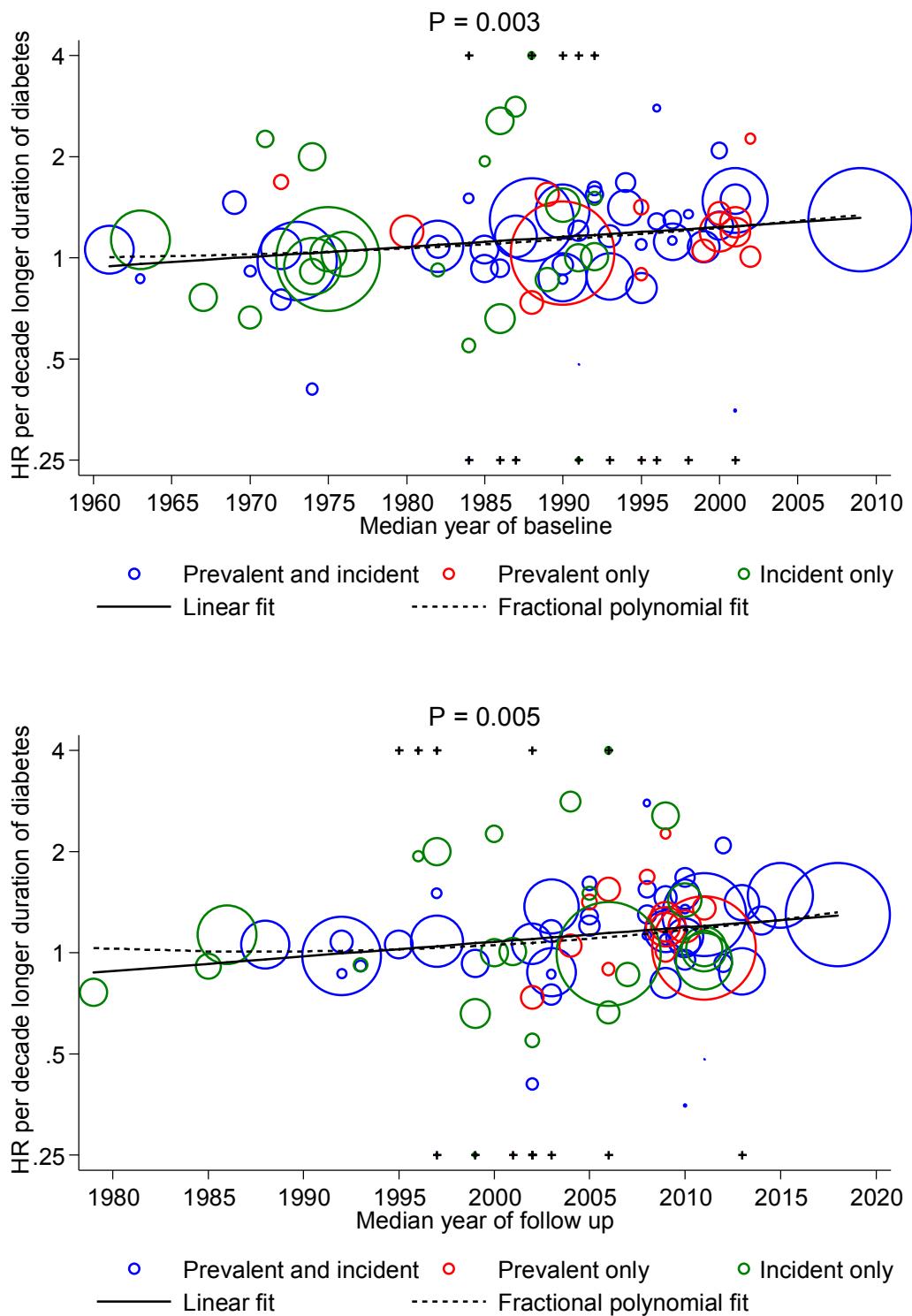


The reference group is no diabetes. Studies with fewer than 10 events of any outcome were excluded from the analysis of that outcome.

eFigure 2. Hazard ratios for all-cause mortality per decade earlier age at diagnosis of diabetes according to selected participant and study-level characteristics.

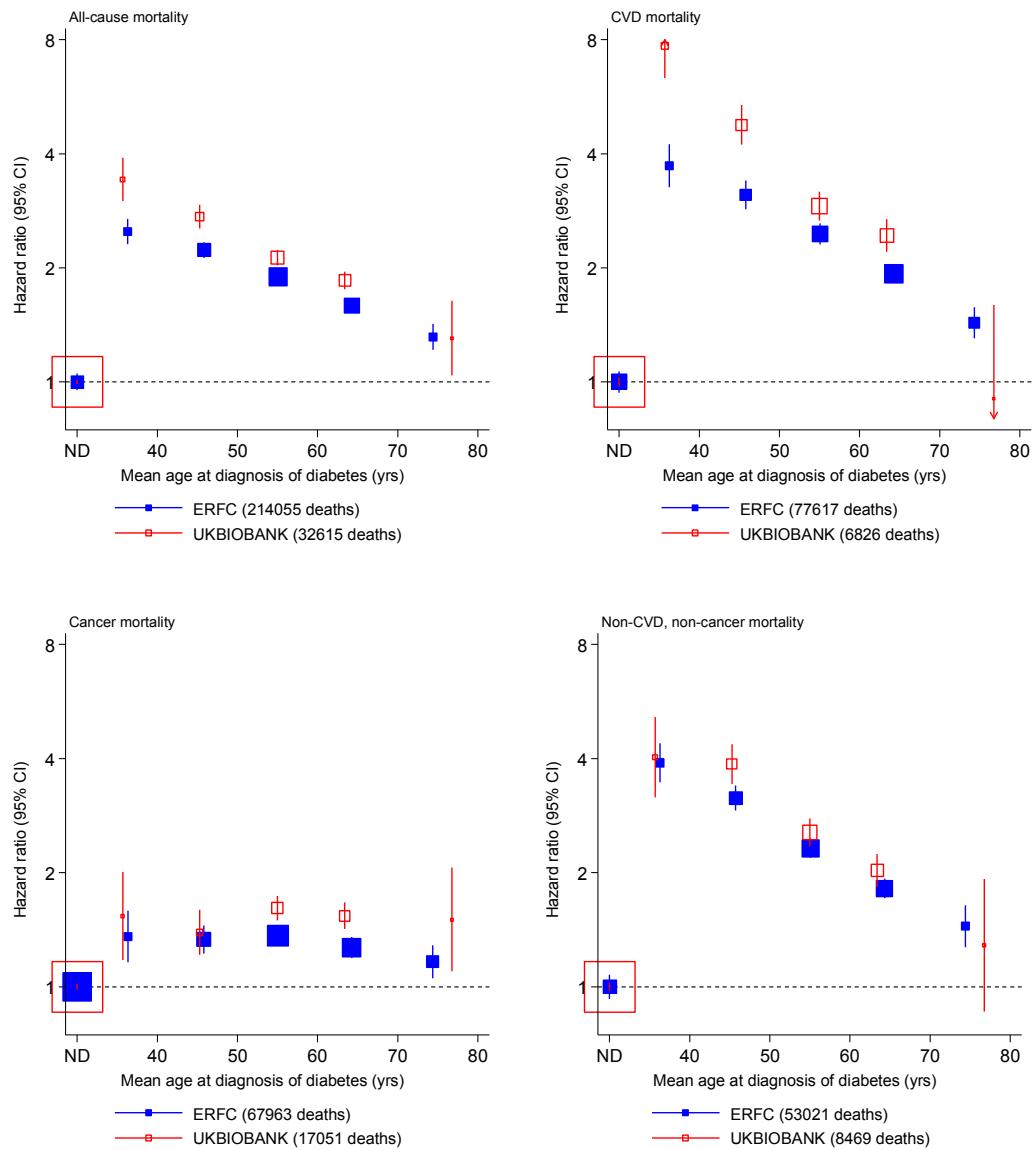


eFigure 3. Cohort-specific hazard ratios for all-cause mortality per decade earlier age at diagnosis of diabetes according to calendar time of study enrolment and follow-up period.



* Multivariate meta-analysis of cohort-specific hazard ratios estimated using Cox-regression models stratified by sex and adjusted for age, smoking status, BMI, systolic blood pressure, and total cholesterol. Cohort-specific hazard ratios exceeding 0.25 or 4.0 are truncated at those values and shown as plus (+) in the meta-regression plots. The line of best-fit corresponds to the meta-regression based relationship of cohort-specific log HRs and calendar time.

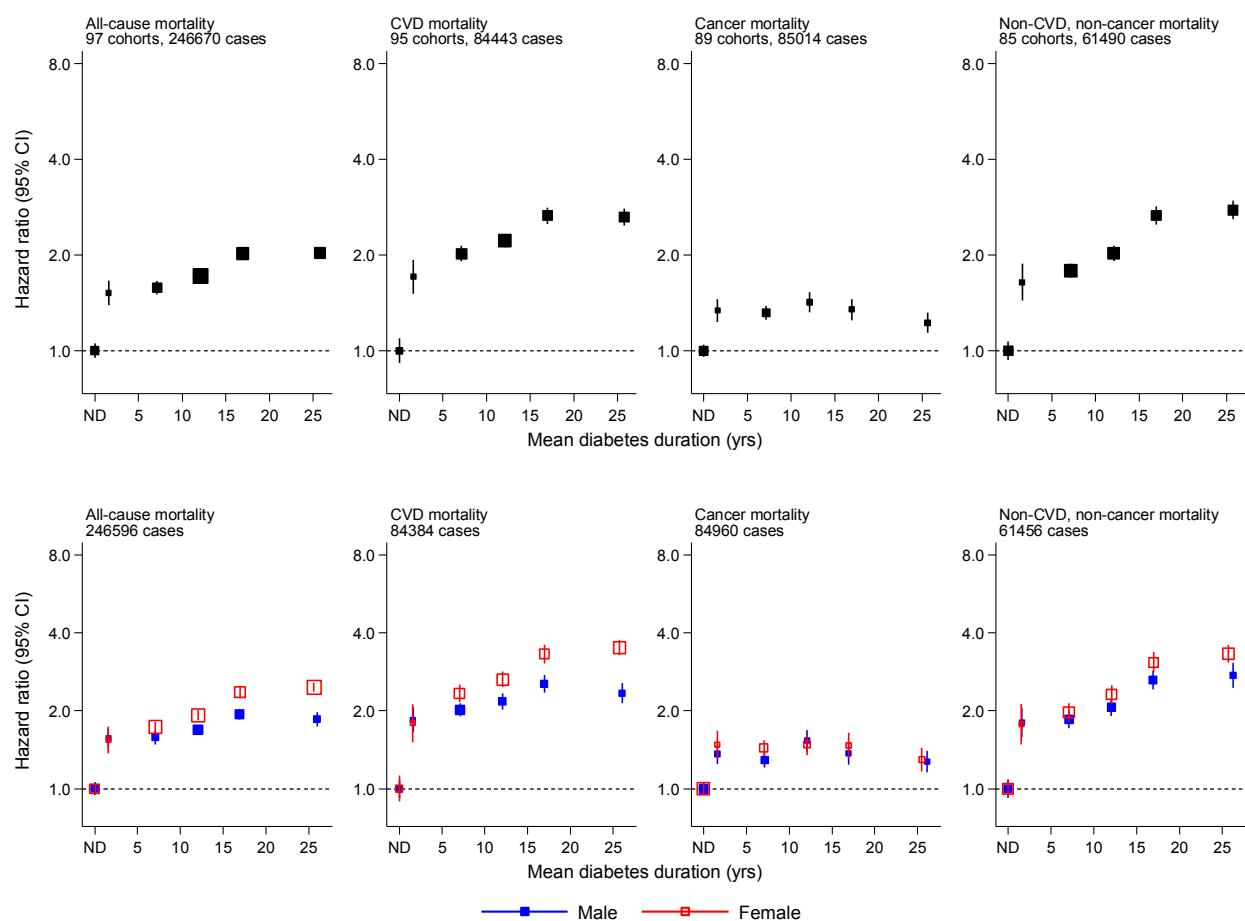
eFigure 4. Hazard ratios for all-cause and cause-specific mortality in ERFC and UK Biobank separately according to age at diagnosis of diabetes adjusted for age and sex.*



* Hazard ratios were estimated using Cox-regression models stratified by centre and sex and adjusted for age. The 5 categories of age at diagnosis correspond to: No diabetes (ND, Reference), 30 to <40 yrs, 40 to <50 yrs, 50 to <60 yrs, 60 to <70 yrs, and ≥70 yrs.

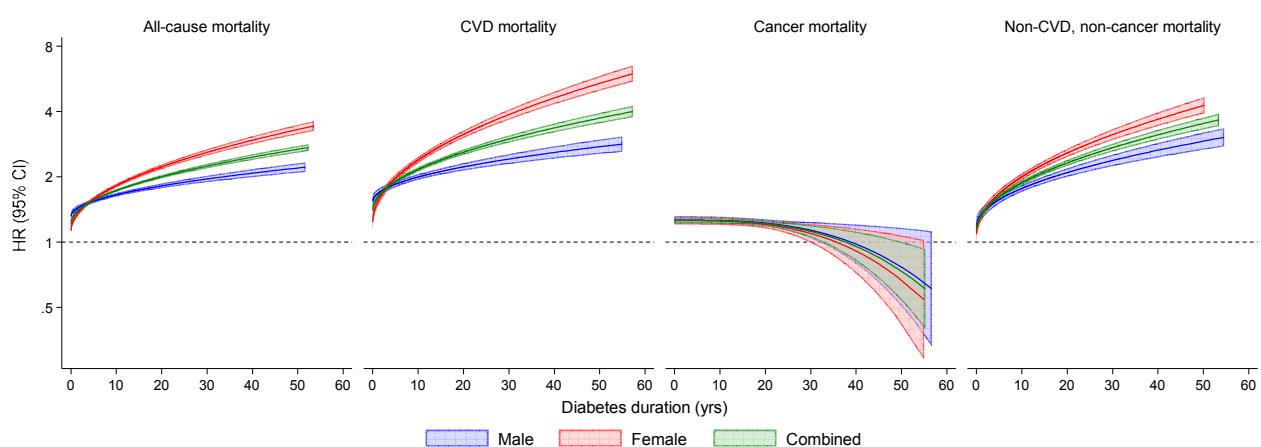
eFigure 5. Hazard ratios for all-cause and cause-specific mortality according to duration of diabetes adjusted for age and sex (top) and sex-specific (bottom).

(a) Sex adjusted and sex-specific associations by categories of age at diagnosis of diabetes

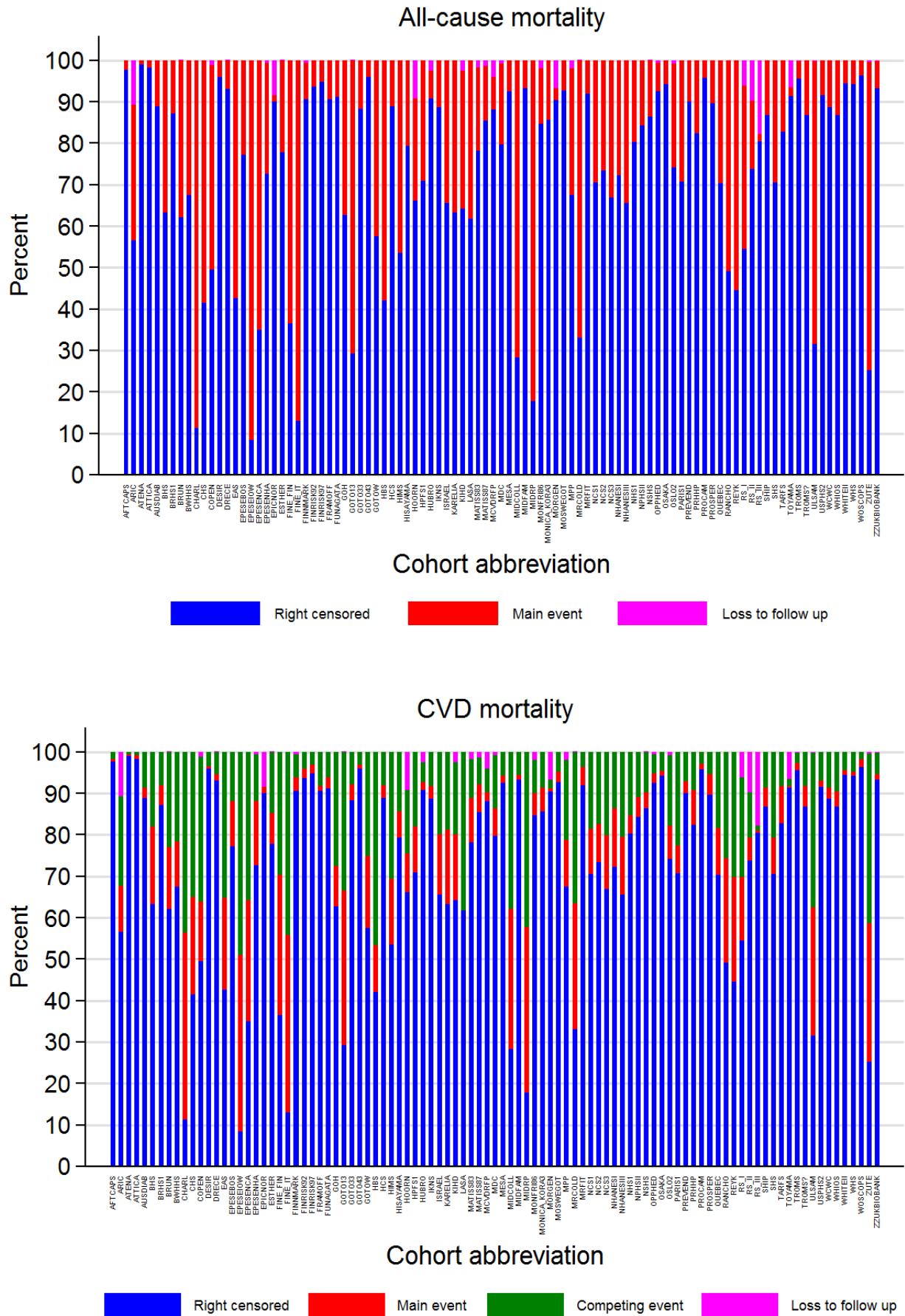


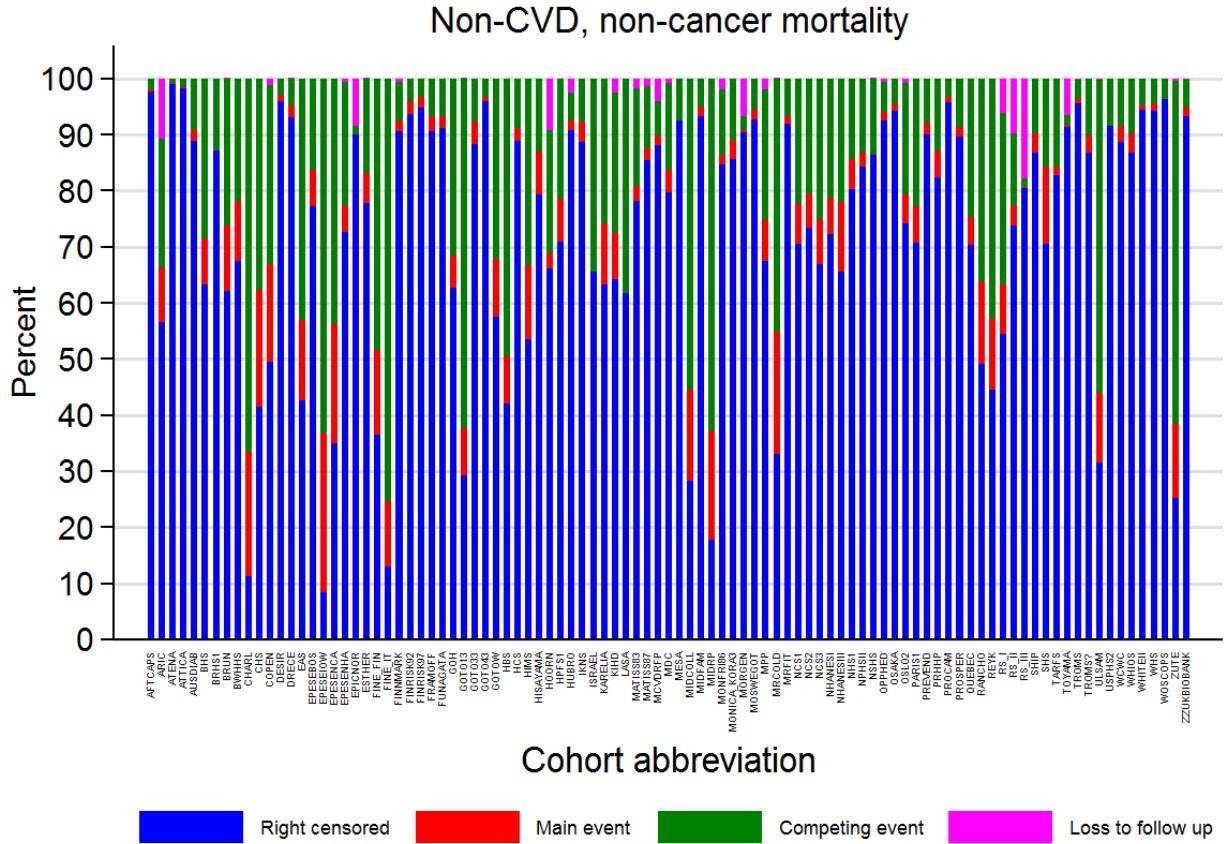
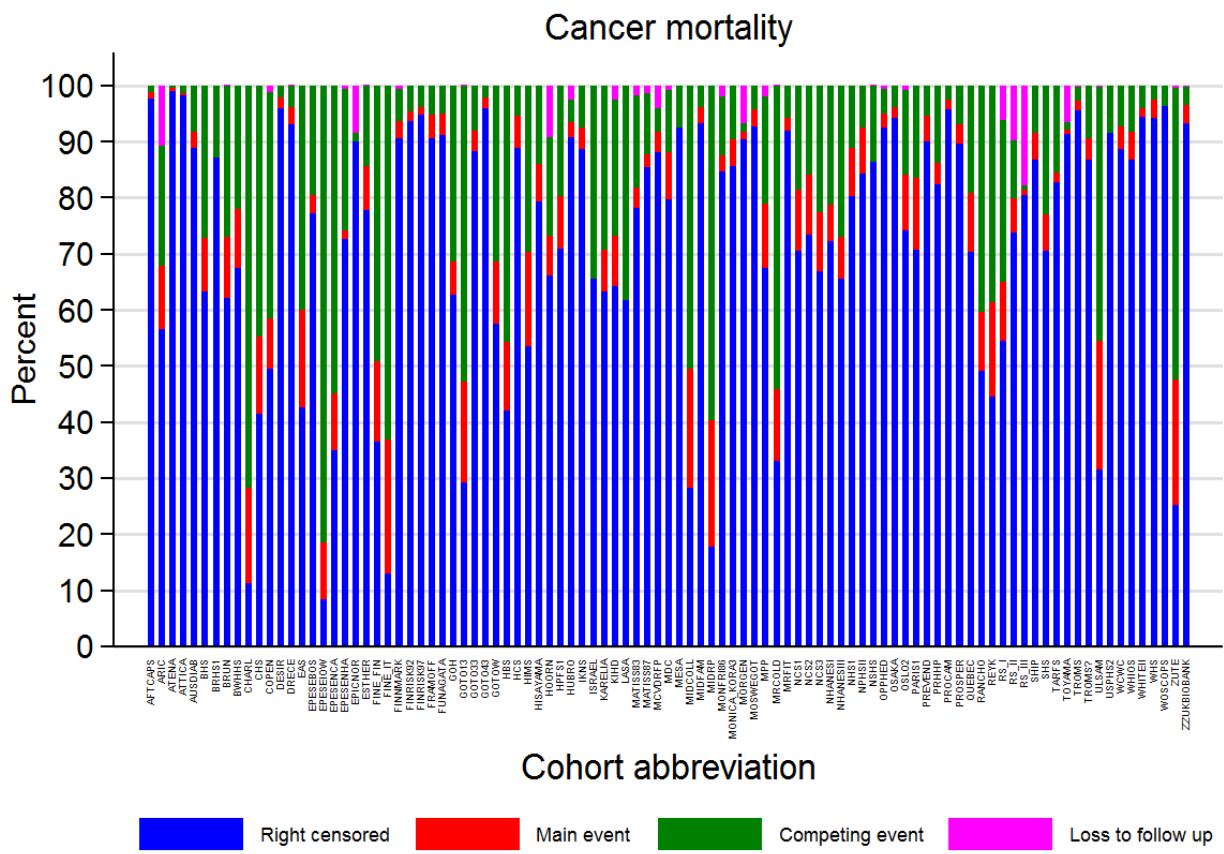
ND, No diabetes. The 6 categories of duration of diabetes correspond to: ND, <5 yrs, 5 to <10 yrs, 10 to <15 yrs, 15 to <20 yrs, and ≥20 yrs. Hazard ratios adjusted for age and sex. The reference category is no diabetes. Studies with fewer than 10 events of any outcome were excluded from the analysis of that outcome. Sizes of the boxes are proportional to the inverse of the variance of the log-transformed hazard ratios. Vertical lines represent 95% CIs.

(b) Continuous associations by sex and overall using fractional polynomial modelling



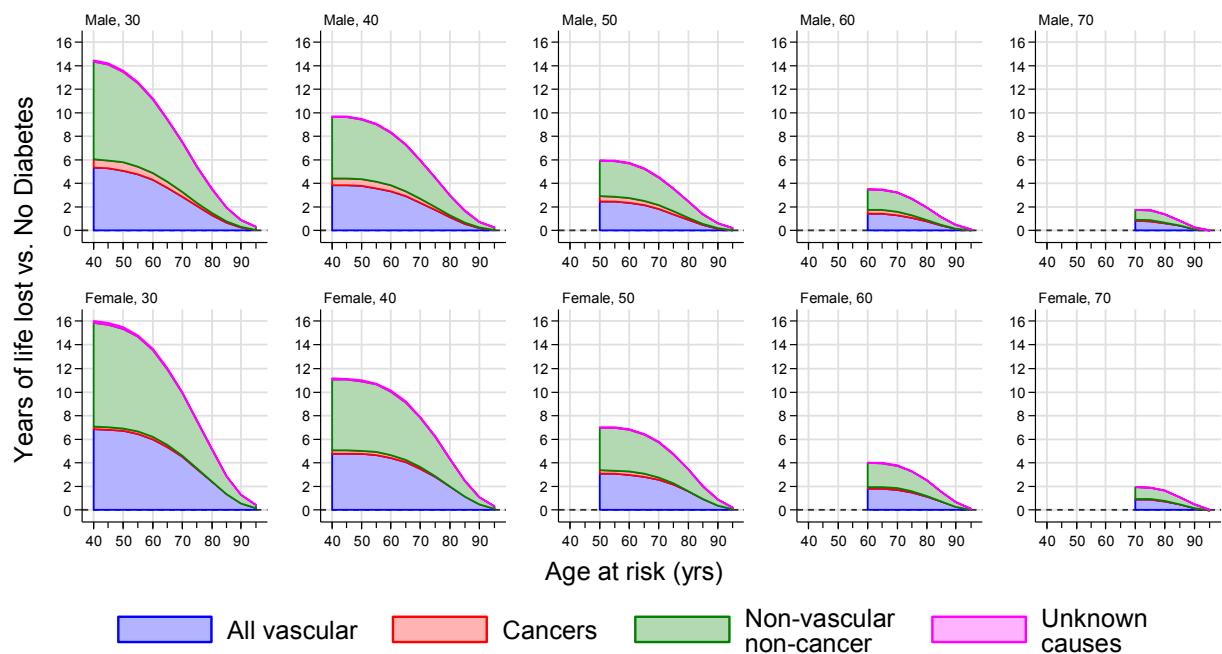
eFigure 6. Cohort specific percentages of right censoring, deaths and loss to follow up.





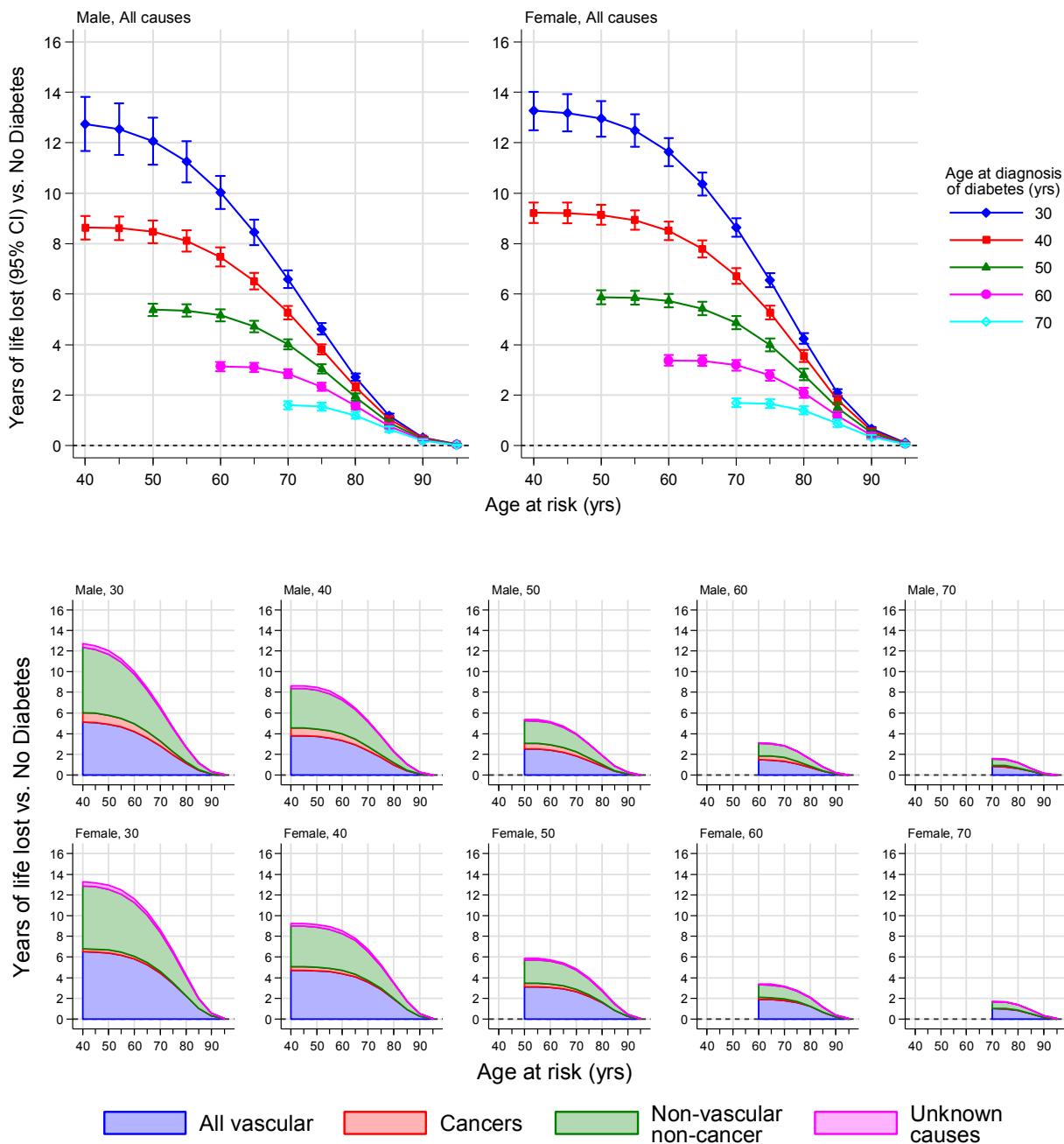
The graphs show cohort-specific percentages of participants that: (a) were still alive at the end of follow up (right censored) or (b) died of the main cause indicated on the graph title (i.e. main event) or (c) died of a different cause than one indicated (competing event) or (d) were lost to follow up.

eFigure 7. Estimated cause-specific contributions to overall reduction in life expectancy by age at diagnosis of diabetes using US 2015 death rates.



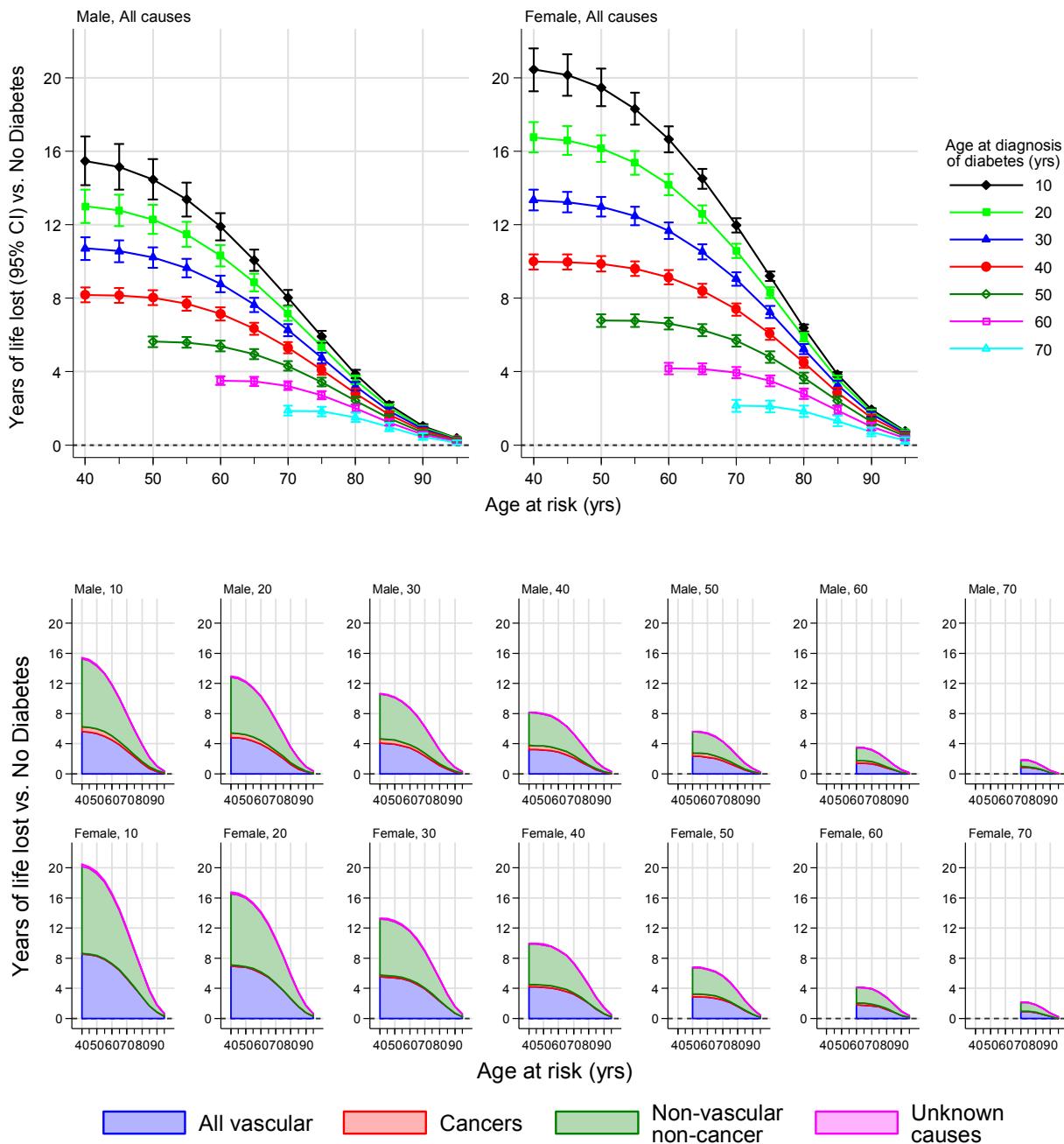
The estimates of cumulative survival from 40 years of age onwards according to age at diagnosis of diabetes were calculated by applying hazard ratios (specific to age at risk) for all-cause mortality associated with age at diagnosis of diabetes to US 2015 death rates at the age of 40 years or older.

eFigure 8. Estimated cause-specific contributions to overall reduction in life expectancy by age at diagnosis of diabetes using EU 2015 death rates.



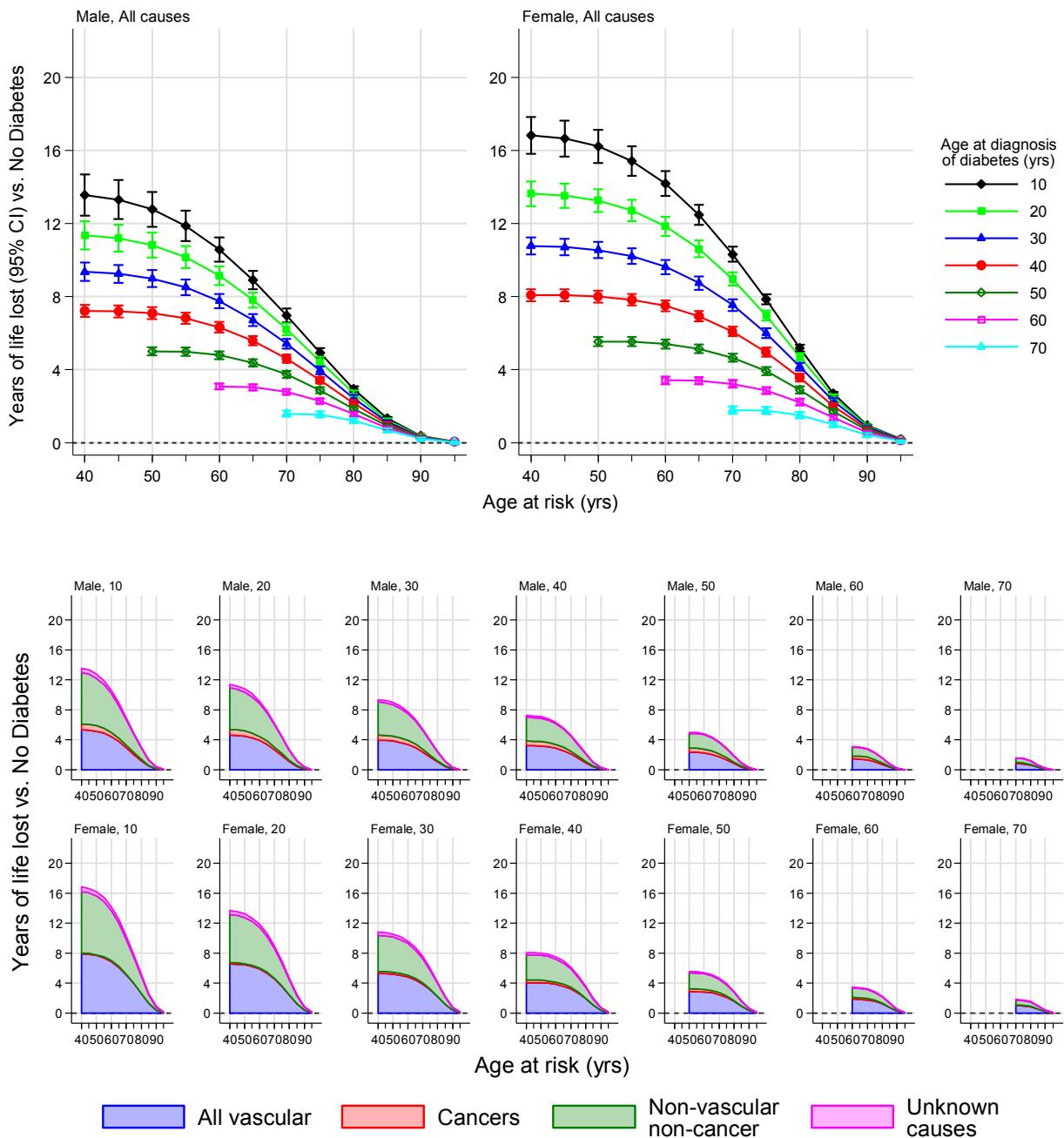
The estimates of cumulative survival from 40 years of age onwards according to age at diagnosis of diabetes were calculated by applying hazard ratios (specific to age at risk) for all-cause mortality associated with age at diagnosis of diabetes to EU 2015 death rates at the age of 40 years or older.

eFigure 9. Estimated cause-specific contributions to overall reduction in life expectancy by age at diagnosis of diabetes using US 2015 death rates, including diabetes diagnosed before age 30 years.



The estimates of cumulative survival from 40 years of age onwards according to age at diagnosis of diabetes were calculated by applying hazard ratios (specific to age at risk) for all-cause mortality associated with age at diagnosis of diabetes to US 2015 death rates at the age of 40 years or older.

eFigure 10. Estimated cause-specific contributions to overall reduction in life expectancy by age at diagnosis of diabetes using EU 2015 death rates, including diabetes diagnosed before age 30 years.



The estimates of cumulative survival from 40 years of age onwards according to age at diagnosis of diabetes were calculated by applying hazard ratios (specific to age at risk) for all-cause mortality associated with age at diagnosis of diabetes to EU 2015 death rates at the age of 40 years or older.

eAppendix 1. List of ERFC study acronyms*

| Abbreviation | Full name |
|--------------|---|
| ARIC | Atherosclerosis Risk in Communities Study |
| AUSDIAB | Australian Diabetes, Obesity and Lifestyle Study |
| BHS | Busselton Health Study |
| BRUN | Bruneck Study |
| BWHHS | British Women's Heart and Health Study |
| CHARL | Charleston Heart Study |
| CHS | Cardiovascular Health Study |
| COPEN | Copenhagen City Heart Study |
| DESIR | Data from an Epidemiological Study on the Insulin Resistance Syndrome |
| DRECE | Diet and Risk of Cardiovascular Disease in Spain |
| EPESEIOW | Established Populations for the Epidemiologic Study of the Elderly Studies, Iowa |
| EPESENHA | Established Populations for the Epidemiologic Study of the Elderly Studies, New Haven |
| FINE_FIN | Finland, Italy and Netherlands Elderly Study |
| FINRISK92 | Finrisk Cohort 1992 |
| FRAMOFF | Framingham Offspring Cohort |
| GOTO13 | Goteborg Study 1913 |
| GOTOW | Population Study of Women in Göteborg, Sweden |
| HCS | Hertfordshire Cohort Study |
| HIMS | Health in Men Study |
| HOORN | Hoorn Study |
| HPFS1 | Health Professionals Follow-up Study |
| LASA | Longitudinal Aging Study Amsterdam |
| MDC | Malmö Diet and Cancer Cardiovascular Study |
| MESA | Multi-Ethnic Study of Atherosclerosis |
| MONICA_KORA3 | MONICA/KORA Augsburg Survey S3 |
| NHANESI | National Health and Nutrition Examination Survey I |
| NHS1 | Nurses' Health Study |
| PARIS1 | Paris Prospective Study I |
| PREVEND | Prevention of Renal and Vascular End Stage Disease Study |
| QUEBEC | Quebec Cardiovascular Study |
| RANCHO | Rancho Bernardo Study |
| SHIP | Study of Health in Pomerani |
| SHS | Strong Heart Study |
| TOYAMA | Toyama Study |
| TROMSØ | Tromsø Study |
| ULSAM | Uppsala Longitudinal Study of Adult Men |
| WHS | Women's Health Study |
| ZUTE | Zutphen Elderly Study |
| ATENA | Progetto CUORE |
| BRHS1 | British Regional Heart Study |
| EPICNOR | European Prospective Investigation of Cancer Norfolk Study |
| ESTHER | Epidemiologische Studie zu Chancen der Verhutung und optimierten Therapie chronischer Erkrankungen in der alten Bevölkerung |
| FINNMARK | Cohort of Norway |
| FINRISK97 | Finrisk Cohort 1997 |
| FUNAGATA | The Funagata Study |
| GOTO33 | Goteborg Study 1933 |
| GOTO43 | Goteborg Study 1943 |
| HBS | Helsinki Businessmen Study |
| HISAYAMA | Hisayama Study |
| HUBRO | Cohort of Norway |
| KARELIA | North Karelia Project |
| MCVDRFP | Monitoring of CVD Risk Factors Project |
| MIDFAM | MIDSPAN Family Study |
| MORGEN | Dutch Monitoring Project on Risk Factors for Chronic Diseases |
| MOSWEGOT | MONICA Göteborg Study |
| MPP | Malmö Preventive Project |
| MRCOLD | MRC Study of Older People |
| NHANESIII | National Health and Nutrition Examination Survey III |
| NSHS | Nova Scotia Health Survey |
| OPPHED | Cohort of Norway |
| OSLO2 | Cohort of Norway |
| RS_II | The Rotterdam Study II |
| RS_III | The Rotterdam Study III |
| TROMS | Cohort of Norway |
| USPHS2 | U.S. Physicians Health Study II |
| WHIOS | Women's Health Initiative (Observational Study) |
| AFTCAPS | Air Force/Texas Coronary Atherosclerosis Prevention Study |
| CAPS | Caerphilly Prospective Study |
| EAS | Edinburgh Artery Study |
| EPESEBOS | Established Populations for the Epidemiologic Study of the Elderly Studies, East Boston |
| EPESENCA | Established Populations for the Epidemiologic Study of the Elderly Studies, North Carolina |
| FINE_IT | Finland, Italy and Netherlands Elderly Study |
| GOH | The Glucose Intolerance, Obesity and Hypertension Study |
| IKNS | Ikawa, Kyowa, and Noichi Study |
| ISRAEL | Israeli Ischaemic Heart Disease Study |
| KIHD | Kuopio Ischaemic Heart Disease Study |
| MATISS83 | Progetto CUORE |
| MATISS87 | Progetto CUORE |
| MIDCOLL | MIDSPAN Collaborative Study |
| MIDRP | MIDSPAN Renfrew & Paisley Study |
| MRFIT | Multiple Risk Factor Intervention Trial 1 |
| NCS1 | Norwegian Counties Study 1 |
| NCS2 | Norwegian Counties Study 2 |

| | |
|---------|---|
| NCS3 | Norwegian Counties Study |
| NPHSII | Northwick Park Heart Study II |
| OSAKA | Osaka Study |
| PRHHP | Puerto Rico Heart Health Program |
| PROCAM | Prospective Cardiovascular Münster Study |
| PROSPER | Prospective Study of Pravastatin in the Elderly at Risk |
| REYK | Reykjavik Study |
| RS_I | The Rotterdam Study I |
| SPEED | Speedwell Study |
| TARFS | Turkish Adult Risk Factor Study |
| WCWC | Wuerltemberg Construction Workers Cohort |
| WHITEII | Whitehall II Study |
| WOSCOPS | West of Scotland Coronary Prevention Study |

* The cohorts are listed in the same order as in eTable 1 for ease of cross-referencing.

eAppendix 2. 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.¹ 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

Hazard ratios and 95% CI for all-cause and cause-specific mortality were calculated using Cox proportional-hazards regression models. The primary analysis adjusted for age and sex only. Secondary analyses were additionally adjusted for body mass index, systolic blood pressure, medication usage (including lipid-lowering, anti-hypertensive, and diabetes drugs) and education level. Data were analysed using Stata version 13.1.

Reference List

- (1) Sudlow C, Gallacher J, Allen N et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12(3):e1001779.
- (2) UK Biobank (2007). Protocol for a large-scale prospective epidemiological resource. <http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf> (accessed 06 March 2017).

eAppendix 3. Calculation of age at diagnosis of diabetes mellitus

To enable current analysis of associations according to age at diagnosis, prospective cohorts were asked to provide further data on age at diagnosis (or duration) of prevalent diabetes and also, where available, information on incident diabetes (provided either as known age/date/time of diagnosis, or participant's diabetes status at date-stamped resurveys). Where information was provided as time duration since/prior to baseline, we calculated the age at diagnosis as age at baseline plus/minus the time duration. Where incidence information was provided as diabetes status (yes/no) at date-stamped resurveys, we estimated the age at diagnosis as the participant's age at the midpoint of two consecutive surveys in which the participant developed diabetes. We also computed an accuracy indicator as half-width of the time interval between the two surveys.

The age at diagnosis of diabetes could either have been reported at a baseline survey (i.e. prevalent diabetes) or corresponded to new diagnosis of diabetes during follow up (i.e. incident diabetes). Thus the 96 ERFC cohorts that met this criteria, could be broadly classified into three groups (**eTable 1**): (i) those that recorded both age at diagnosis of prevalent diabetes and incident diabetes (36 cohorts, 374,136 participants); (ii) those that enquired on age of diagnosis of prevalent diabetes and did not ascertain incident diabetes (29 cohorts, 300,080 participants); and (iii) those that did not enquire on age of diagnosis of prevalent diabetes but ascertained incident diabetes (31 cohorts, 234,369 participants).

eAppendix 4. Statistical methods used for estimating years of life lost

We used three pieces of information to estimate reductions in life expectancy associated with diagnosis of diabetes at a specified age (henceforth “age at diagnosis”):

- (i) age-at-risk specific hazard ratios for all-cause (and cause-specific) mortality for specified ages at diagnosis of diabetes compared to those without diabetes (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) age-at-risk specific prevalence of diabetes in the population by age at diagnosis (derived from the ERFC).

We utilised age-at-risk specific hazard ratios for mortality by age at diagnosis of diabetes, estimated from ERFC data, and published routine statistics on overall population mortality rates to estimate population survival curves by age at diagnosis of diabetes. To calculate an appropriate mortality rate for the reference group (i.e. those without diabetes at a given age-at-risk) we modelled age-at-risk specific prevalence of diabetes by age at diagnosis in ERFC data as described below. We estimated reductions in life-expectancy as differences in areas under any two survival curves compared.

Age-at-risk specific hazard ratios for mortality by age at diagnosis of diabetes 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 time-dependent variables of diabetes status (yes/no) and age at diagnosis with linear and quadratic terms for the age-at-risk variable were included in the model to obtain smoothed hazard ratios for specified ages at diagnosis of diabetes. Thus, for participant i in stratum s the log hazard rate at time t since baseline was modelled as:

$$\log(h_{si}(t)) = \log(h_{s0}(t)) + \beta_0 diab_{si} + \beta_1 agediab_{si} + \beta_2 agerisk_{si} + \beta_3 agerisk_{si}^2 + \beta_4 diab_{si} \times agerisk_{si} + \beta_5 diab_{si} \times agerisk_{si}^2 + \beta_6 agediab_{si} \times agerisk_{si} + \beta_7 agediab_{si} \times agerisk_{si}^2 \quad (1)$$

from which the age-at-risk specific hazard ratios (and 95% CIs) for mortality at specified ages at diagnosis of diabetes (30, 40, 50, 60, and 70 years) 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 year 2015 from the Center for Disease Control (CDC) WONDER online database (<https://wonder.cdc.gov/ucd-icd10.html>) (**Figure 2**), as well as for 28 EU countries during year 2015 (<http://ec.europa.eu/eurostat/data/database>). Because the mortality rates were provided only up to age-group 80-84 years and the open-ended interval of ≥ 85 years, but we desired to estimate the overall population survival curves, we used a piecewise cubic Hermite interpolation (PCHIP) method to smooth through the midpoints of 5-year age-groups and extrapolate the mortality rates to age 110 years (**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**).

$$p(\text{survival} | \text{agerisk} \geq 35) = \prod_{\text{agerisk} \geq 35} S_a \quad (2)$$

In order to infer population mortality rates appropriate for the reference group used in our estimation of age-specific hazard ratios (i.e. those without diabetes at a given age), we used logistic regression to model the age-at-risk specific prevalence of diabetes by age at diagnosis in ERFC cohorts by sex and decade of follow up (**Figure 5**) We used the

age-specific prevalence estimates for the decade commencing in the year 2000 to infer the age-specific mortality rates appropriate for the reference group without diabetes IR_{a0} as:¹

$$IR_{a0} = \frac{IR_a}{p_{a0} + \sum_{j=1}^5 p_{aj} \times RR_{aj}} \quad (3)$$

Where IR_a is the population mortality rate for age group a , p_{aj} is the age-specific prevalence of 5 groups of diabetes age at diagnosis j , and RR_{aj} is the age-specific hazard ratio for comparison of group j versus reference group ($j = 0$). The age-specific mortality rates in each of the non-reference age at diagnosis 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 age at diagnosis-specific population survival curves (**Figure 6**). Finally, reductions in life expectancy according to age at diagnosis were estimated as difference in the areas under the survival curves for the reference group and each age at diagnosis in turn (**Figure 7**). The areas under curves were calculated by numerical integration.

eAppendix 4 References

- 1 Woloshin S, Schwartz LM, Welch HG. The risk of death by age, sex, and smoking status in the United States: putting health risks in context. J Natl Cancer Inst 2008;100(12):845-53.

eAppendix 4. Figures

Figure 1. Age-at-risk specific hazard ratios for all-cause mortality by sex and age at diagnosis of diabetes

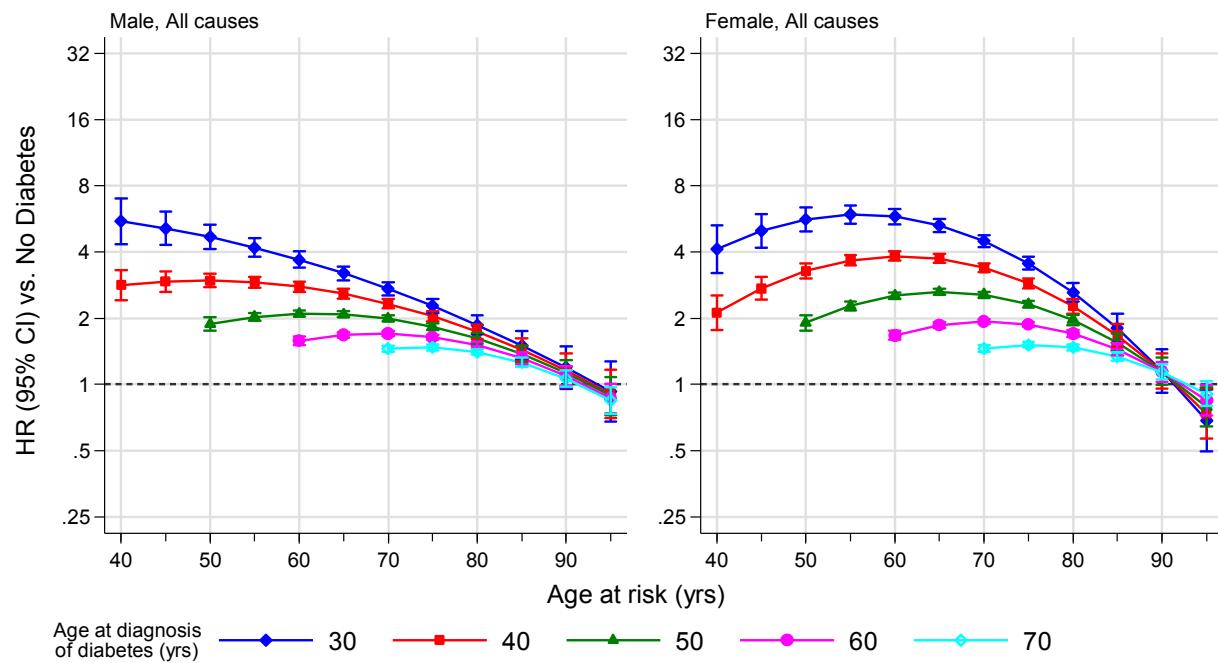
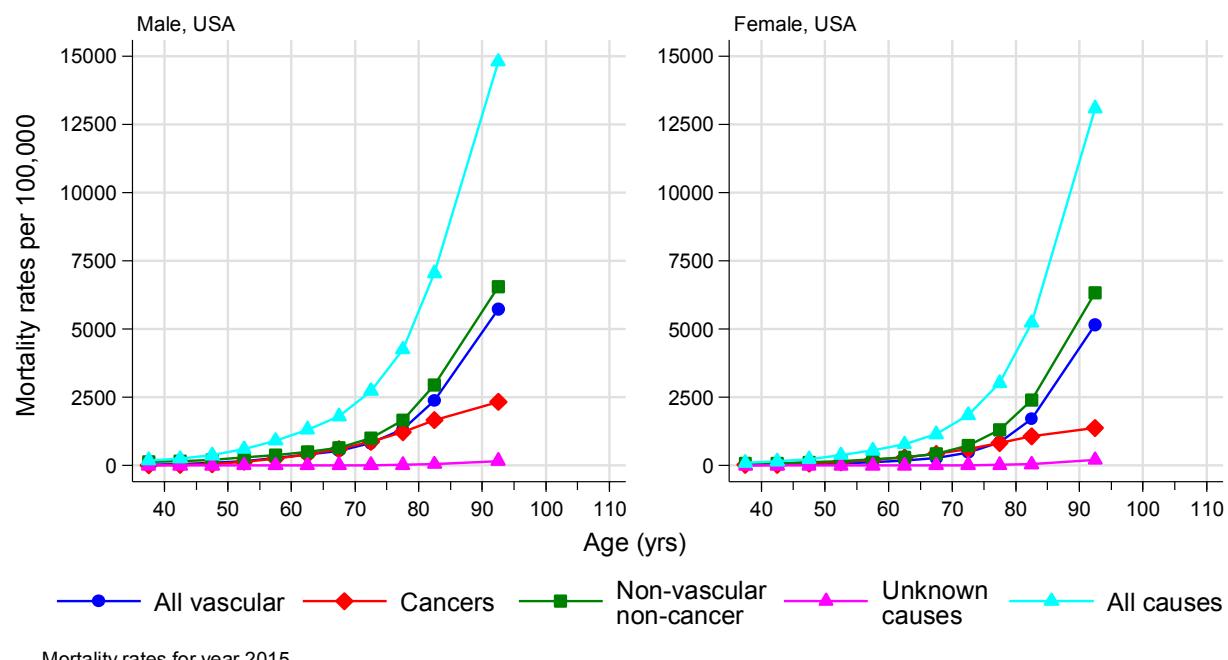


Figure 2. US population mortality rates during year 2015 downloaded from CDC WONDER online database*



* 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).

Figure 3. Assessment of adequacy of a piecewise cubic Hermite interpolation (PCHIP) method to smooth and extrapolate US population mortality rates during year 2015. Data was downloaded from CDC WONDER online database in 5-year age groups up to 80 years inclusive, and the unbounded 85 years plus category (the database's highest age group category with mortality rates estimates provided).

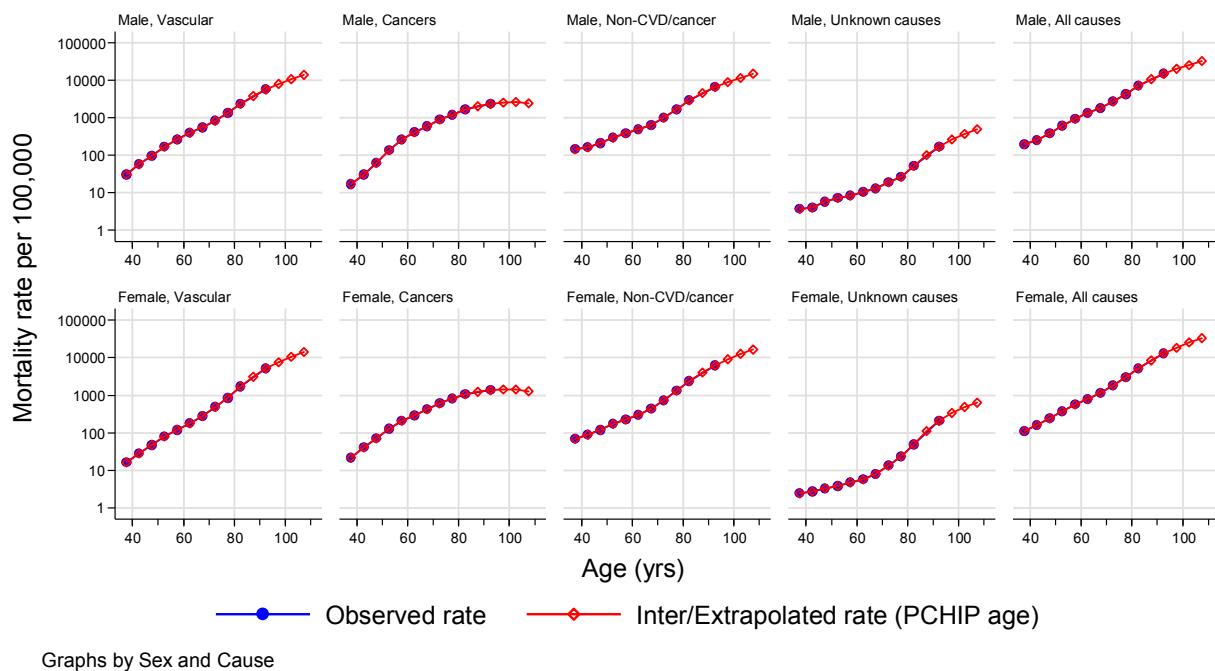


Figure 4. Derived population survival curves for all-cause and cause-specific mortality from age 35 years based on smoothed and extrapolated US population mortality rates for year 2015

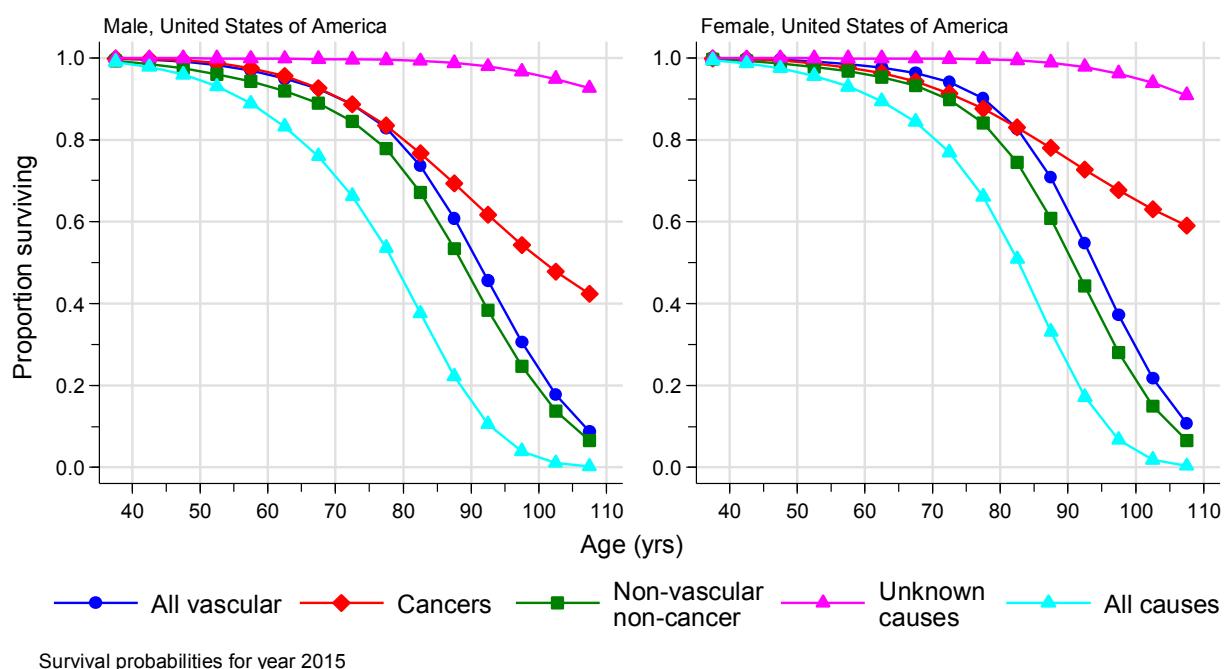


Figure 5. Modelled age-specific prevalence of diabetes in ERFC cohorts by sex and decade of recruitment and age at diagnosis.

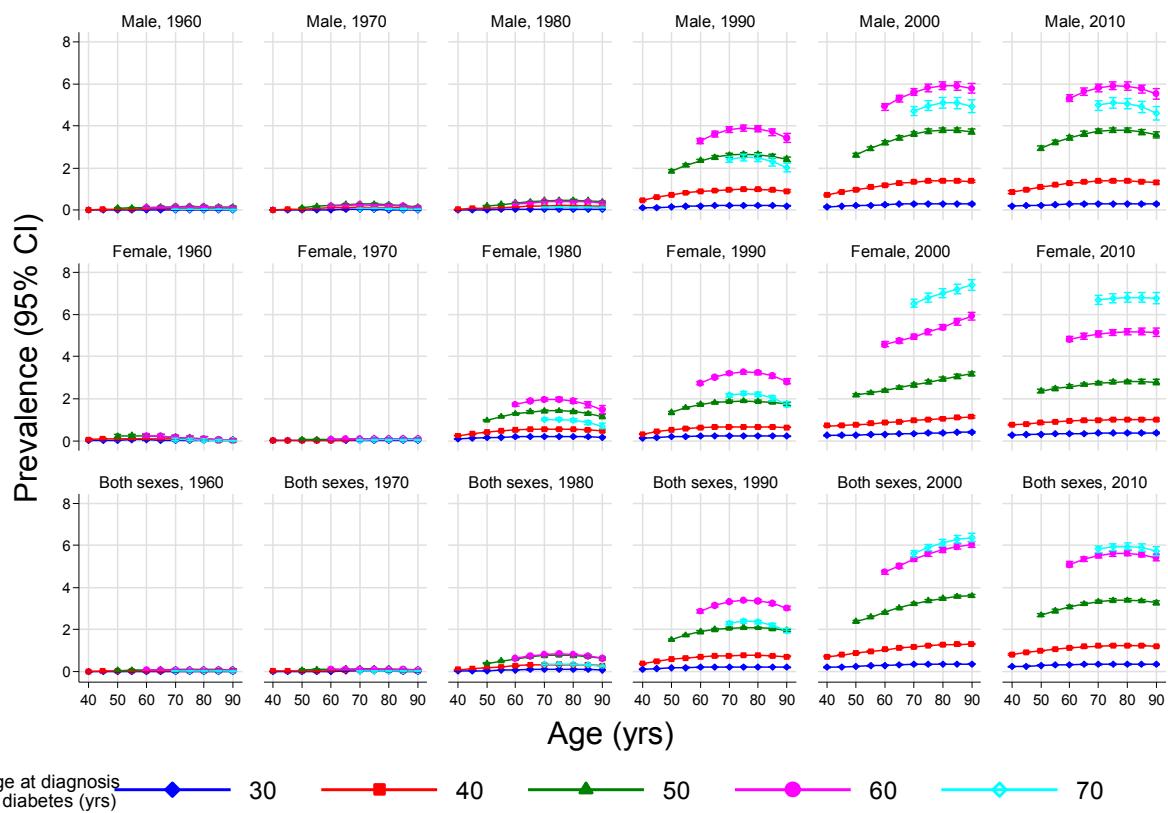


Figure 6. Inferred survival curves for US population by sex and age at diagnosis of diabetes

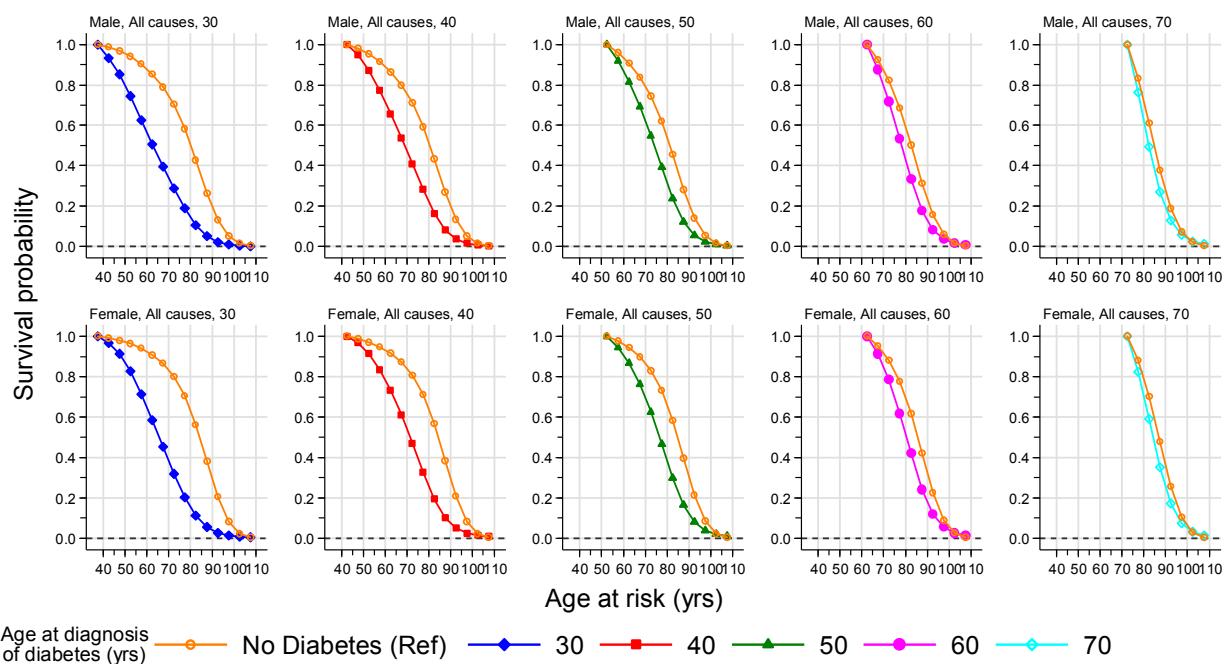


Figure 7. Estimated sex-specific reductions in life expectancy in the US population according to age at diagnosis of diabetes

