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# Age of diagnosis of type 2 diabetes and associations with cardiovascular and mortality risks: Findings from the Swedish National Diabetes Registry

Sattar/Rawshani: Running title: Vascular outcomes by age of diabetes diagnosis

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## Abstract

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**Background:** Risk of cardiovascular disease (CVD) and mortality for patients with versus without type 2 diabetes mellitus (T2DM) appears to vary by age of T2DM diagnosis, but few population studies have analyzed mortality and CVD outcomes associations across the full age range.

**Methods**: Using the Swedish National Diabetes Registry (NDR), everyone with T2DM registered in the NDR between 1998, and, 2012 were included. Controls were randomly selected from the general population matched for age, sex, and county. The analysis cohort comprised 318,083 patients with T2DM matched with just under 1·6 million controls. Participants were followed from 1998 to 2013 for CVD outcomes and to 2014 for mortality. Outcomes of interest were total mortality, CV mortality, non-CV mortality, coronary heart disease, acute myocardial infarction, stroke, heart failure, and atrial fibrillation. We also examined life expectancy by age of diagnosis. We conducted the primary analyses using Cox proportional hazards models in those with no prior cardiovascular disease and repeated the work in the entire cohort.

**Results**: Over a median follow-up period of 2.52 years, T2DM patients diagnosed under 40 years or less had the highest excess risk for most outcomes relative to controls with adjusted HR [95% CI] of 2·05 [1·81 to 2·83] for total mortality, 2·72 [2·13 to 3·48] for CV related mortality, 1·95 [1·68-2·25] for non-CV mortality, 4·77 [3·86-5·89] for HF and 4·33 [3·82-4·91] for CHD. All risks attenuated progressively with each increasing decade at diagnostic age; by the time T2DM was diagnosed above 80 years, the adjusted HRs for CVD and non-CVD mortality were below one, with excess risks for other CVD outcomes substantially attenuated. Moreover, survival in those diagnosed beyond 80 was the same as controls, whereas it was beyond a decade less when T2DM was diagnosed in adolescence. Finally, HRs for most outcomes were numerically greater in younger women with T2DM.

**Conclusions**: Age at diagnosis of T2DM is prognostically important for survival and cardiovascular risks, with implications for determining timing and intensity of risk factor interventions for clinical decision making and for guideline-directed care. These observations amplify support for preventing / delaying T2DM onset in younger individuals.

**Keywords** Obesity, survival, risk factors, glycemia, heart failure.

**Clinical Perspective**

**What is new?**

- This study examined life expectancy and excess risk of CVD and death in people with type 2 diabetes across a range of ages, compared with age, sex and county-matched controls.
- All risks were highest in the patients with younger diagnosis, and risks were attenuated rapidly with increasing age at onset of type 2 diabetes.
- Developing T2DM after 80 years of age was not associated with impaired survival.
- The most pronounced excess risks were noted in women with early onset T2DM.

**What are the clinical implications?**

- Treatment target recommendations in regards to the risk factor control may need to be more aggressive in people developing diabetes at younger ages
- Many elderly with newly diagnosed type 2 diabetes but without CVD may not require aggressive management of their diabetes, so that reassessment of treatment goals in elderly might be useful.
- Diabetes screening needs for the elderly (above 80) should also be re-evaluated.

# Introduction

Given the rising prevalence of obesity, especially in younger people over the last three-four decades in high income countries,[1] type 2 diabetes mellitus (T2DM) is now more frequently diagnosed in young adults and adolescents.[2–4] This is a worrying trend since, as we[5] and others[6] have shown, these individuals have worse risk factor profiles (body mass index (BMI), lipids, and glycaemia levels) at the point of diagnosis relative to those diagnosed at older ages, as well as worse clinical outcome trajectories[5,7] over time. It is therefore likely that younger onset T2DM may pose relatively greater excess cardiovascular mortality and morbidity risks as compared with later onset T2DM. In line with this notion, having T2DM at younger ages is associated with greater losses of  expectancy[8] as well as greater mortality risks[9] relative to age-similar controls, and such losses may be related more to premature cardiovascular (CV) deaths than other causes. However, these latter studies did not compare mortality risks from the time of diagnosis and nor did they fully adjust for the impact of diabetes duration, which, is independently associated with greater CV risks. Furthermore, few prior studies have compared risks for cause-specific mortality (CV versus non-CV) at the same time as examining a wide variety of non-fatal outcomes (e.g. acute myocardial infarction, heart failure, etc.) by age of onset of T2DM. Finally, few studies have been adequately powered to allow investigation across the entire age range of age of T2DM diagnosis, which is important, given treatment and screening options at either end of the age spectrum are increasingly debated.

The aim of this study was therefore to evaluate, in relation to age at diagnosis: 1) detailed mortality and CVD mortality risks, 2) CV risks inclusive of acute myocardial infarction, stroke, and heart failure outcomes, 3) non-CV mortality risks and 4) life expectancy relative to non-diabetes counterparts. We repeated our analyses in a cohort without any prior CVD, given the clinical importance of this question, and looked at the entire cohort, and separately in both sexes.

# Methods

## DATA SOURCES

Methods used in this investigation are available to any researcher worldwide. Patient data are not readily available due to Swedish and European privacy laws. We welcome any inquiries regarding data acquisition, which is allowed under Swedish and European law (visit https://ndr.nu for more information). The Swedish National Diabetes Register (NDR), started in 1996, is a nationwide register and includes patients with diabetes (both type 1 and type 2) aged 18 and above. The data are collected by trained nurses and physicians and include information obtained in primary care and at hospital outpatient clinics. Patient data are either continuously reported via electronic patient clinical records, or registered directly online into the NDR.[10] The study was approved by the ethics review board at the University of Gothenburg. Each patient provided informed consent (verbal or written) for inclusion in the register, and more than 90% of all patients T2DM in Sweden are included.

Type 2 diabetes is defined using an epidemiologic definition: recorded type 2 diabetes in clinical records plus treatment with diet with or without the use of oral antihyperglycemic agents or treatment with oral antihyperglycemic agents with or without the use of insulin. The latter category only applied to patients who were 40 years of age or older at the time of diabetes diagnosis. The study includes all individuals with at least one record in the NDR between January 1, 1998, and December 31, 2012. For each individual with T2DM in the NDR, 5 matched controls were identified, matched for age, sex, and county, randomly selected from the general population, as reported before.[11,12] Primary analyses were performed in persons without pre-existing cardiovascular disease (CVD), including coronary heart disease (CHD), acute myocardial infarction (AMI), stroke, heart failure (HF), atrial fibrillation (AF), or dementia; analyses in the entire cohort with or without prevalent CVD were also performed. To reflect current conditions and management of T2DM, the

analysis was restricted to persons with a diabetes duration of less than ten years when first registered in the NDR.

Information regarding coexisting conditions, CV outcomes, and deaths was retrieved from the Swedish Inpatient and Cause of Death Registries. Data linkage is virtually complete due to unique personal identification numbers, which are assigned to all Swedes from birth or immigration. Sensitivity and specificity for all outcomes have been validated in the Swedish Inpatient Register.[13]

The Longitudinal Database for Health Insurance and Labor Market studies provided information on individual incomes, country of birth, marital status, and highest educational level.

### OUTCOMES

We assessed all-cause mortality, CV mortality, AMI, stroke, CHD, hospitalization for HF, and AF. The outcomes were identified from the Inpatient Registry using the International Classification of Diseases (ICD) codes, 9$^{th}$ and 10$^{th}$ revision. The specific codes were as follows: AMI: 410 and I21; CHD: 410-414 and I20–I25; HF: 428 and I50; AF 427D, I48; Stroke: 431-434, 436, I61–I64. The codes are listed in Supplemental Table 1 (Supplemental Material, **Supplemental Table 1**).

The last date for NDR registration (i.e. inclusion) in the present analysis cohort was December 31, 2012. Patients were followed until December 31, 2013 for all outcomes, except for mortality, for which follow-up ended December 31, 2014.

## Statistical methods

The associations between age of diagnosis of T2DM and mortality as well as CV related outcomes were analyzed using Cox proportional hazards model with age as the underlying time scale. The models contain both persons with T2DM and diabetes-free matched controls coded such that the baseline hazard models the hazard function for the controls. The association between being diagnosed with diabetes at a certain age and outcomes is captured by a main effect term and the effect of living with diabetes is captured by an effect of the yearly time updated duration of

diabetes. The matched controls are persons without T2DM diagnosis (i.e. their diabetes duration equals zero) and therefore have no contribution in the model from the terms for duration of T2DM or age of T2DM diagnosis for the outcomes assessed. The persons with diabetes are modelled to get an instant increase in hazard at the date of diagnosis and have an effect of time updated duration which captures the gradual increase in hazard beyond the effect of aging shared with the controls (*please see supplement for more explanation and supplemental figures 1 and 2*). For people with diabetes, we centered diabetes duration around the population mean (2.52 years) by subtracting the mean from each individual's diabetes duration. An individual with T2DM who had 2.52 years of duration would thereafter have 0 years of duration and can therefore be compared to controls. Consequently, we estimated the excess risks in T2DM after 2.52 years of duration. Additional model details are provided in the *supplement*. The main analyses included all patients with T2DM without prior CVD, with parallel analyses repeated in the entire cohort, including those with CVD, in which case all analyses were adjusted for CVD.

A robust statistical method was developed to analyse the associations between duration of diabetes and outcomes as detailed in the supplemental section. This is based on the principle that a patient with T2DM ages differently once T2DM develops compared with a person free from T2DM.

The assumption of proportional hazard was evaluated by fitting a smoothing spline function for duration of T2DM. The best fit was achieved for log transformed duration but the choice of transformation for duration of T2DM had only a minor influence on the analyses results. Descriptive statistics were based on means and standard deviations for age and income, and absolute and relative frequencies for discrete variables.

The predicted conditional survival functions were derived from Cox regression models with T2DM vs controls as the only independent variable. Age was used as the time scale, with left censoring at age of inclusion into the analysis cohort. The conditional median survival was estimated from the middle of each age interval except 0-20 where age 15 is used and 90- where 95 is used. These analyses were

based on all persons free from prior CVD without any restriction on duration of T2DM. The estimated cumulative hazard was subsequently converted to conditional survival.

Due to the explorative nature of the study, no adjustment for multiple comparisons were made and conclusions should be based on overall patterns rather than single hypothesis tests of confidence intervals.

The statistical analysis was performed using R 3.4.0.

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# Results

*Baseline characteristics*

Data were initially analysed for 214,278 patients with T2DM without prior CVD and 1,363,612 controls matched on age, sex and county of residence, and repeated in the entire cohort when the respective numbers were 318,083 and 1,575,108. Their baseline characteristics are shown in **Table 1** (cohort without prevalent CVD) and **Supplemental Table 2** (entire cohort), respectively, and their distribution of age of T2DM diagnosis is presented in **Figure 1**, demonstrating a mean age of diagnosis of 61.79 years and a spread of ages spanning from nine to 101 years of age. By matching design, mean ages and sex distribution of cases and controls were similar for cases and controls.

Within the primary analysis subset of patients with T2DM without prior CVD, as presented in **Table 1**, patients with T2DM compared with controls had lower average income, more commonly born beyond the EU, had higher prevalence of amputation and of prior cancer, but lower prevalence of dementia at baseline. The same data in the entire cohort (Supplemental Table 2) showed similar

patterns but, more patients with T2DM had prevalent CVD, although prevalence of prior dementia remained lower.

Baseline risk factor profiles by age of diagnosis of T2DM are presented in **Table 2**. As anticipated, there was an inverse relationship between age at diagnosis of T2DM and BMI, with BMI in those diagnosed with diabetes under 40 years of age being around eight units higher than if developed diabetes in 90s (Table 2). Likewise, $HbA_{1c}$ at diagnosis declined with rising age of diabetes diagnosis, being around 5 mmol/mol (0.47%) higher in under those age <40 years compared with those 71 to 80 years of age, although $HbA_{1c}$ levels were somewhat higher in the those 91 and above. In terms of risk factors, triglyceride concentrations were higher and HDL-cholesterol levels lower in patients with younger age of diagnosis of T2DM whereas blood pressure levels rose with rising age of diagnosis (**Table 2**). Total and LDL-cholesterol were slightly higher in middle ages but declined at older ages of diagnosis, whereas LDL-C-lowering treatment was least at the extremes of age and highest in participants 61-80 years old (Table 2). Similar patterns were seen in the entire cohort (**Supplemental Table 3**).

*Mortality and adverse cardiovascular outcomes*

Median follow up was 2.52 years. Overall, a total of 194,197 death events, 66,184 CV death events, 51,837 MIs, 60,346 strokes, 61,501 events of incident HF, and 83,283 incident AF events were captured for analyses. Mortality and CV outcomes over time for T2DM versus controls stratified by T2DM age of diagnosis are presented in **Figure 2** for the overall cohort and for the subset of T2DM patients without prevalent CVD at registration. There was a higher risk of all CV-related outcomes in the T2DM cohort regardless of the age of diagnosis of T2DM, with notable and consistent associations between age of diagnosis of T2DM and all outcomes analyzed, where those with T2DM diagnosed ≤40 had the highest excess relative risk for most outcomes with adjusted HRs [95% CI] in those without prior CVD for total mortality, for CV related mortality and for non-CV mortality well

above one. HRs for those diagnosed with T2DM at 40 years or less for other CVD outcomes were even higher, greatest at for HF and for CHD, as noted below:

- 2·05 [1·81 to 2·83] for total mortality
- 2·72 [2·13 to 3·48] for CV related mortality
- 1·95 [1·68-2·25] for non-CV mortality
- 4·33 [3·82-4·91] for CHD
- 3·41 [2·88-4·04] for AMI
- 3·58 [2·97-4·32] for Stroke
- 4·77 [3·86-5·89] for HF
- 1·95 [1·56-2·44] for AF

Thereafter, incremental risks generally declined with each higher decade age at diagnosis of T2DM. For participants with T2DM diagnosed at >80 years of age, adjusted relative risks reversed with most <1.0 for T2DM versus controls for all three of total mortality [0·83 (0·80-0·86)], CV mortality [0·75 (0·71-0·79)], and non-CV mortality [0·87 (0·83-0·91)] outcomes. Adjusted risks for other outcomes that include non-fatal outcomes were generally >1.0, but all HR estimates substantially attenuated compared with relative incremental risks in those diagnosed with T2DM at younger ages. In those with T2DM diagnosis age >90, the only outcome for which risk seemed to be appreciably higher for those with T2DM versus controls was stroke [HR 1·56 (1·13-2·14)]. **Figure 3** presents causes of death in each age of onset group, along with matched controls. Non-CV mortality among people with T2DM was primarily driven by external causes and cancers.

*Results stratified by sex*

When outcomes were examined separately by sex, doing so in those without all prior CVD, (Supplemental **Figure 3**), the results were broadly comparable in terms of patterns or risk by age of diagnosis although HRs were usually higher in women for most CVD-related outcomes, and particularly so for outcomes related to CHD, stroke and HF ($p<0.0001$ for sex by age interactions for

all outcomes). However, the higher excess risk in women was age-dependent, being stronger among younger individuals and not present above the age of 70.

*Results in the entire cohort*

All analyses were repeated in the entire cohort so that all participants with or without prior CVD were included with multivariable analyses additionally adjusted for baseline CVD (**Figure 2**). In this case, the main patterns of results were broadly identical to those already presented in the cohort without all prior CVD. The only minor difference noted was a slightly earlier (in terms of decade of age) attenuation to the null for mortality outcomes, whereas hazard ratios for heart failure were a little higher for the comparison of T2DM versus control.

*Median survival in those with prior CVD by age of diagnosis of type 2 diabetes*

Differences in survival analyses in individuals with versus without T2DM, stratified by age of diagnosis, were estimated (**Figure 4, supplemental Table 4**), with a median loss of life being near 12 years when T2DM was diagnosed around 15 years of age, about 6 years when diagnosed at 45 years of age, two years at 65 years of age, and no accelerated loss of life after 80 years or so. Life years lost appeared somewhat greater in younger women than in men of the same age (data available on request), although wider confidence intervals prevent meaningful comparisons.

## Discussion

In this evaluation of mortality and CVD outcomes associated with T2DM analysed by age at diagnosis using data from a national registry, younger age diagnosis is associated with higher subsequent risk for all outcomes analyzed. Younger diagnosis of T2DM was also associated with the greatest loss of life years. The risks for a range of fatal and nonfatal CVD outcomes are even more markedly elevated in those with T2DM diagnosed at a younger age, particularly for CHD and HF, where incremental relative risks approach four-five times higher than matched controls. Incremental risks associated with T2DM attenuated by age of diagnosis of T2DM, so that by the time T2DM is diagnosed above

age of 80, adjusted mortality risks are <1.0 for both CVD mortality and non-CVD mortality and excess risks for other outcomes are substantially attenuated; analysis of life-years lost with diagnosis of T2DM appears null at age >80. Finally, we show these patterns are robust whether you consider only those without prior CVD, the entire cohort with or without prior CVD, or separately in men and women in those without CVD, although there was some evidence of greater excess risks in younger women developing T2DM.

At a clinical level, our findings may offer two important considerations: i) a need to rethink risk factor treatment recommendations in those diagnosed with type 2 diabetes when under 40 years of age (an age threshold commonly considered in guidelines), and ii) a need to reassess and discuss treatment goals and aggressiveness of interventions in people diagnosed after 80 years of age, particularly in asymptomatic individuals. Whether it is cost effective to screen for diabetes or pre-diabetes to identify people suitable for diabetes prevention programs in those above 80 years of age, is also questioned by our data.

In analyses evaluating associations between age of diabetes onset and CVD risks, analyzing data from just under 8000 patients with newly diagnosed diabetes in the late 1990s,[14] and before widespread preventative statin or antihypertensive use, they found a 14-fold higher MI risk in under 45 year olds with diabetes whereas risks were fourfold higher in those diagnosed above 45 years of age compared to age-matched controls.[14] In a more recent study, prevalent diabetes at younger ages (<55) was associated with around threefold greater mortality risks, whereas such risks were null in patients with diabetes over the age of 75.[9] Data from the Emerging Risk Factor Collaboration likewise showed life years lost were significantly greater with diabetes present at younger ages, although once again this study did not examine risks by age at diagnosis.[8] More recently, using only two age groups, a Chinese study suggested a near double the risk of non-fatal cardiovascular in those with early (<40 years) versus later diagnosed type 2 diabetes,[6] whereas work from Australia showed higher mortality risk, in particular CVD mortality, in younger diagnosed diabetes patients in

study of just under three quarters of a million Australians with diabetes.[15] However, this latter study lacked access to individual controls and did not consider non-fatal outcomes. We were also able to show that a greater excess risk for CVD outcomes and mortality commonly attributed to women, seemed to be far less evident in those with older diagnosed T2DM (roughly beyond 70 years of age), a novel finding extending considerable prior work on sex differences.

The present results meaningfully extend the relevant published data by: i) evaluating the question in a large, national, contemporary cohort well characterized at baseline and with complete outcomes data capture; ii) evaluating an extensive range of all-cause mortality and CV outcomes; iii) extending analyses of age of diagnosis of T2DM into the 10$^{th}$ decade, an important asset given rising numbers of people living well beyond 80 years of age, especially in some countries like Japan. They also have the advantage over results from many prior studies by having age and sex matched controls and by adjusting for diabetes duration. Our findings are also potentially generalizable given trends in diabetes risks previously reported in Sweden seem to broadly match findings in other high income countries.

The potential mechanisms for incremental risk reductions and favorable effects on life years lost at younger ages of T2DM diagnosis warrants some discussion. From Table 2, it is notable that diabetes diagnosis at younger ages is associated with considerably higher BMI. Beyond early T2DM incidence, these patients also have worse lipid profiles and higher glycaemia levels than people developing T2DM when older.[5] While control data for BMI are lacking, population BMI in high-income countries is lower at younger ages and rises to a maximum at around 50-70 years of age,[16] suggesting that younger patients developing diabetes must be more obese than their non-diabetic counterparts. By contrast, BMI levels in older individuals developing diabetes must be closer to their counterparts without diabetes so that other risk factors related to adiposity, e.g. lipids, blood pressure, would also be less different. In other words, obesity and related risk factor perturbances more strongly accompany the development of diabetes at younger ages leading, in turn, to greater relative

increases in CVD risks. Younger patients developing diabetes also seem to smoke more and be of lower socioeconomic status, both strong independent CVD risk factors.

Why might older (>80 years of age) diagnosed diabetes patients have little or no difference in mortality rates relative to their non-diabetes counterparts? One potential is such patients are better treated for CVD risk factors than those of similar age but without diabetes. However, since non-CVD mortality is also lower in diabetes diagnosed above 81 years of age in all analyses, other factors must be at play. One possibility is that to develop diabetes at older ages requires individuals to retain their weights better than non-diabetes counterparts. A better weight retention would increase chances of developing diabetes as well keep blood pressures and other non-fatal vascular risks (e.g. cholesterol) slightly higher than controls not developing diabetes. However, some of those not developing diabetes may be at higher mortality risk because they are losing weight unintentionally due to comorbidities (e.g. dementia, **Supplemental Table 5**) that are linked to an earlier death. If this reasoning is correct, developing diabetes beyond the 9th or 10th decades of life may, in part, and in some patients, represent a part of the aging process**.** Of course, other unmeasured factors may also be at play such as better health seeking behaviour in those developing diabetes at older ages.

Irrespective of mechanisms, in stark contrast to younger patients, mortality risk in much older diagnosed diabetes patients are not meaningfully elevated compared to their non-diabetes counterparts in Sweden, and even if non-fatal risks remain marginally elevated, there was no apparent loss in life years (Figure 4). This finding needs to be replicated in other high-income countries, and if confirmed, suggests that an upper age threshold of around 80 years of diabetes or so could be helpful in diabetes screening programmes to enable better targeting of younger onset diabetes (or pre-diabetes) who have much more to lose in terms of CVD risks and years of life.

These findings hold important clinical implications for CVD clinical management and prevention guidelines as they emphasise the need to be more aggressive both in population screening for T2DM and for consideration of more intensive CV risk modification among younger/newly diagnosed

persons with T2DM. Currently, guidelines (e.g. UK Joint British Societies 3 , European Society of Cardiology CV prevention guidelines)[17,18] are less aggressive/prescriptive in management of risk factors in individuals developing diabetes under the age of 40, and this group tends to have far slower update of preventative therapies. More recently, the UK National Institutes of Clinical Excellence (NICE) guideline recommended a ten-year risk score to determine statin allocation and in this case younger patients are likely to miss out on statins simply due to their low age. These and other guidelines need reconsideration since our data show that such patients are at highest relative risk of mortality and heart failure from younger ages (so highest lifetime risks) and stand to gain most from preventative therapies (and perhaps diabetes drugs with potential heart failure prevention benefits). It is well established than earlier interventions in those at excess risk yield greater lifetime benefits.[19]

Whilst this study has many strengths, including the ability to track people from the age at diagnosis of T2DM (or within one year of this date), and to match to controls of similar age, sex, and county, risk factor capture in controls was not systematic, precluding the ability to completely account for such risk factors. These data derived exclusively from the Swedish registry comprising almost exclusively white individuals and so further studies in different countries and in more heterogeneous populations are needed. We also acknowledge that classification of diabetes types is a complicated matter. While a small percentage of the cohort may have late-onset type 1 diabetes, based on epidemiologic estimates, the vast majority would have type 2 diabetes and we believe the overall conclusion about the importance of the age of onset would not meaningfully change. Of interest, we have recently shown that age of onset for type 1 diabetes also seems to have prognostic implications for subsequent adverse clinical outcomes[20]. We also acknowledge that some controls may have developed diabetes after baseline but would anticipate this to be a minority and to not meaningfully influence the results. Finally, correction for multiple testing was not performed, and thus caution is needed with respect to the interpretation of significance tests.

In conclusion, these nationwide data suggest that the mortality and cardiovascular harm associated with T2DM differs markedly by the age of diagnosis with highest mortality and especially CHD and HF risks in those with early diagnosed T2DM, whereas a slight survival benefit (both CVD and non-CVD related) appears present in patients with T2DM >81 years at diagnosis, reflected in no loss of life years. These findings, in turn, reiterate the notion that the pathogenicity of T2DM differs markedly by age of diagnosis highlighting perhaps better than ever the importance of age as important risk stratifier in the management, screening, and preventative strategies for this chronic condition.

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## Figure Legends

**Figure 1.** Histogram of age of onset of type 2 diabetes in all those without prior cardiovascular disease.

**Figure 2.** Adjusted hazard ratios (95% CI) for patients with type 2 diabetes according to age at diagnosis, as compared with matched controls in those without prior cardiovascular disease (blue) and in the whole cohort (red). All outcomes minus atrial fibrillation and non-acute myocardial infarction coronary heart disease. The models used in the main analyses (blue) used age as the underlying time scale and includes only sex, yearly time-updated duration (which is zero for the controls who are persons who have not yet been diagnosed with diabetes), and used group, which codes for controls or different groups of persons with diabetes defined by their age at onset. The models used for the supporting analyses in the entire cohort (red) include also persons with prevalent cardiovascular disease at cohort entry additionally contain binary indicators for per index cardiovascular disease, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation and heart failure.

CVD: cardiovascular disease; CV: cardiovascular; CHD: coronary heart disease; AMI: acute myocardial infarction; HF: heart failure; CI: confidence interval.

**Figure 3.** Causes of death in relation to age at onset of Type 2 diabetes diagnosis and corresponding matched controls.

**Figure 4**. Type 2 diabetes age at diagnosis and loss of life years, in persons free from prior cardiovascular disease and without any restriction on duration of type 2 diabetes mellitus.

**Table 1. Descriptive statistics at diagnosis for type 2 diabetes with less than 10 years duration and matched controls (all those with prior cardiovascular disease taken out)**

| | Control | T2DM | p | SMD |
|---|---|---|---|---|
| n | 1363612 | 241278 | | |
| Male (%) | 737980 (54·1) | 128043 (53·1) | <0·001 | 0·021 |
| Age (mean (SD)) at onset | 62·27 (12·07) | 61·79 (12·27) | <0·001 | 0·039 |
| Education (%) | | | <0·001 | 0·217 |
| College level | 553769 (41·2) | 101970 (43·1) | | |
| Elementary school | 438516 (32·6) | 92925 (39·3) | | |
| Upper secondary school | 351308 (26·1) | 41682 (17·6) | | |
| Marital status (%) | | | <0·001 | 0·051 |
| Married | 772509 (63·2) | 130317 (60·8) | | |
| Separated | 221624 (18·1) | 40511 (18·9) | | |
| Single | 227625 (18·6) | 43393 (20·3) | | |
| Widowed | 141780 (10.4) | 27057 (11.2) | | |
| Income (mean (SD)), ksek | 206.47 (419.59) | 177.61 (244.56) | <0·001 | 0·084 |
| Country of origin (%) | | | <0·001 | 0·127 |
| EU | 35322 (2·7) | 5649 (2·5) | | |
| Nordic | 63884 (4·8) | 12234 (5·4) | | |
| RoW | 50479 (3.8) | 16994 (7.3) | | |
| Sweden | 1192599 (89·5) | 196733 (86·6) | | |
| Previous CVD (%) | 0 (0·0) | 0 (0·0) | NA | NA |
| Previous CHD (%) | 0 (0·0) | 0 (0·0) | NA | NA |

| | | | | |
|---|---|---|---|---|
| Previous AMI (%) | 0 (0·0) | 0 (0·0) | NA | NA |
| Previous Stroke (%) | 0 (0·0) | 0 (0·0) | NA | NA |
| Previous Renal (%) | 1016 (0·1) | 300 (0·1) | <0·001 | 0·016 |
| Previous HF (%) | 0 (0·0) | 0 (0·0) | NA | NA |
| Previous AF (%) | 0 (0·0) | 0 (0·0) | NA | NA |
| Previous Amputation (%) | 550 (0·0) | 312 (0·1) | <0·001 | 0·031 |
| Previous Dementia (%) | 6212 (0·5) | 388 (0·2) | <0·001 | 0·053 |
| Previous Cancer (%) | 76796 (5·6) | 14988 (6·2) | <0·001 | 0·025 |

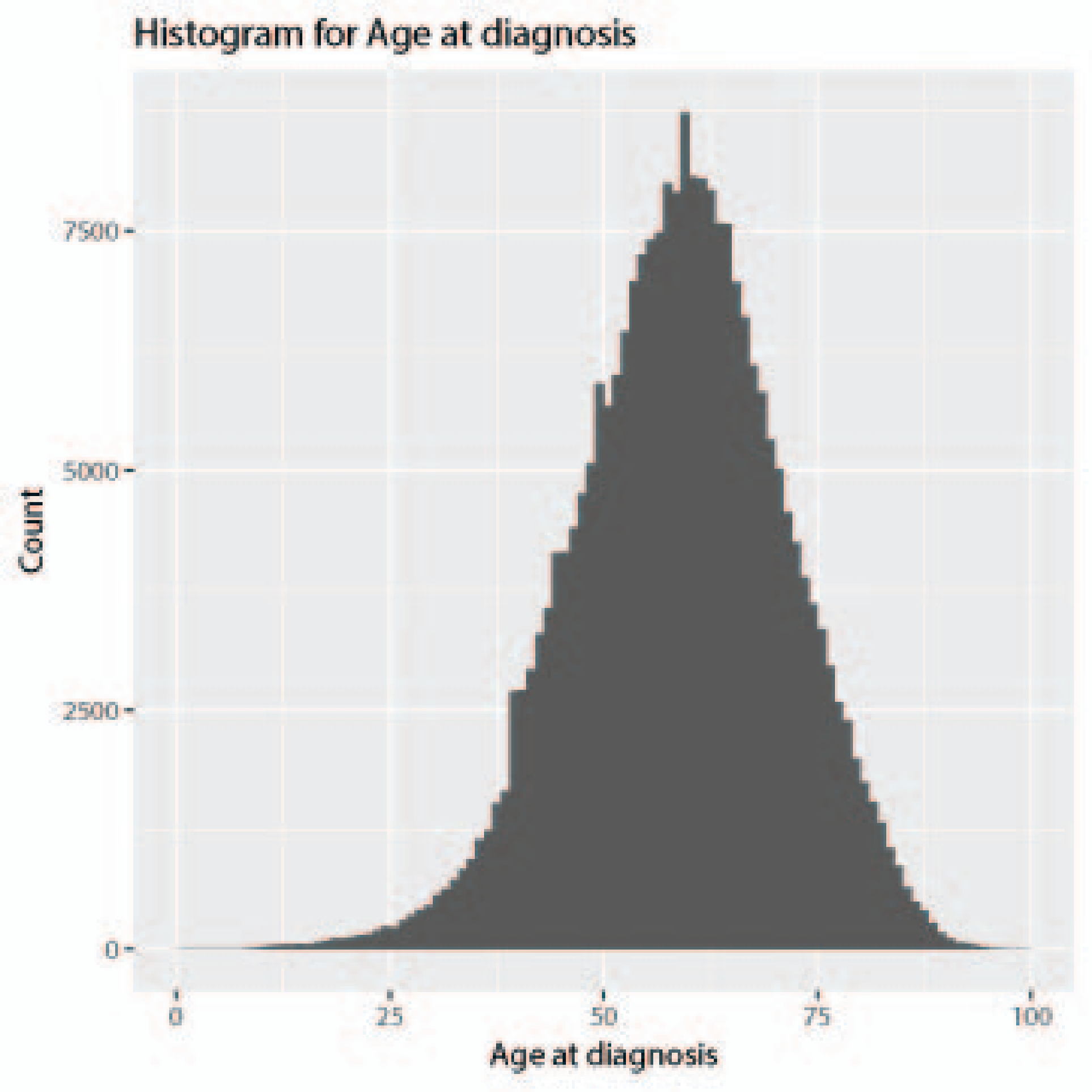
T2DM: type 2 diabetes mellitus; SMD: Standardised mean difference; SD: standard deviation; SEK: Swedish krona; EU: European Union; RoW: Rest of World; CVD: cardiovascular disease; CHD: coronary heart disease; AMI: acute myocardial infarction; HF: heart failure; AF: atrial fibrillation

**Table 2. Descriptive statistics at diagnosis for type 2 diabetes by age of diagnosis in those without prior cardiovascular disease**

| | Age at diagnosis of type 2 diabetes | | | | | | |
|---|---|---|---|---|---|---|---|
| | **40 or less** | **41 to 50** | **51 to 60** | **61 to 70** | **71 to 80** | **81 to 90** | **91 or older** |
| n | 7253 | 19490 | 34448 | 37952 | 18073 | 5213 | 236 |
| Female (%) | 3115 (42·9) | 7319 (37·6) | 13880 (40·3) | 17687 (46·6) | 11453 (63·4) | 3511 (67·4) | 171 (72·5) |
| Age – mean (SD) | 35·03 (5·37) | 46·47 (2·84) | 56·31 (2·90) | 65·50 (2·82) | 75·16 (2·85) | 84·34 (2·51) | 92·95 (1·78) |
| $HbA_{1c}$ – mean (SD) | 56·15 (19·38) | 55·99 (18·54) | 54·45 (17·55) | 52·31 (15·89) | 50·96 (14·03) | 51·65 (14·11) | 54·02 (15·19) |
| Systolic BP – mean (SD) | 127·15 (15·14) | 131·59 (15·76) | 136·97 (16·50) | 140·50 (16·82) | 144·10 (17·58) | 146·14 (18·59) | 146·67 (18·44) |
| Diastolic BP – mean (SD) | 79·48 (10·51) | 81·61 (10·18) | 81·89 (9·58) | 80·05 (9·28) | 77·87 (9·39) | 76·41 (9·67) | 75·42 (9·51) |
| Triglycerides – mean (SD) | 2·32 (1·76) | 2·27 (1·69) | 2·09 (1·42) | 1·87 (1·12) | 1·72 (0·88) | 1·68 (0·80) | 1·75 (0·92) |
| Antihypertensives – n (%) | 1305 (18) | 7016 (36) | 17913 (52) | 24289 (64) | 12651 (70) | 3753 (72) | 172 (73) |
| BMI – mean (SD) | 33·60 (7·47) | 31·95 (6·36) | 30·72 (5·47) | 30·00 (5·20) | 28·90 (4·87) | 27·34 (4·43) | 25·80 (4·21) |
| LDL cholesterol – mean (SD) | 3·07 (0·92) | 3·20 (0·96) | 3·26 (0·98) | 3·20 (0·98) | 3·16 (0·97) | 3·18 (0·94) | 3·10 (0·94) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| HDL cholesterol – | 1·06 | 1·14 | 1·23 | 1·30 | 1·38 | 1·39 | 1·48 |
| mean (SD) | (0·32) | (0·35) | (0·37) | (0·39) | (0·41) | (0·41) | (0·66) |
| Total cholesterol – | 5·14 | 5·32 | 5·41 | 5·34 | 5·32 | 5·35 | 5·28 |
| mean (SD) | (1·17) | (1·16) | (1·16) | (1·11) | (1·08) | (1·09) | (1·12) |
| Statins – n (%) | 943 | 4678 | 11023 | 14042 | 5964 | 938 | 14 |
| | (13) | (24) | (32) | (37) | (33) | (18) | (6) |
| Estimated GFR – | 107·44 | 98·04 | 90·56 | 83·17 | 73·47 | 65·53 | 58·04 |
| mean (SD)[1] | (28·13) | (27·43) | (21·78) | (21·38) | (19·99) | (18·44) | (16·65) |
| Smokers – n (%) | 1222 | 3963 | 6647 | 5064 | 1295 | 166 | 2 |
| | (22·0) | (25·1) | (23·4) | (16·3) | (8·6) | (3·9) | (1·1) |
| **Physical activity[2] – n** | | | | | | | |
| **(%)** | | | | | | | |
| No physical activity | 467 | 1366 | 2156 | 2238 | 1246 | 632 | 49 |
| | (12·1) | (12·2) | (10·8) | (9·7) | (12·1) | (21·8) | (42·6) |
| Less than | 533 | 1509 | 2453 | 2376 | 1062 | 410 | 20 |
| once/week | (13·8) | (13·4) | (12·3) | (10·3) | (10·3) | (14·1) | (17·4) |
| 1–2 times/week | 883 | 2462 | 4313 | 4559 | 2028 | 588 | 14 |
| | (22·9) | (21·9) | (21·7) | (19·8) | (19·7) | (20·3) | (12·2) |
| 3–5 times/week | 987 | 2852 | 5143 | 5686 | 2367 | 505 | 18 |
| | (25·6) | (25·4) | (25·8) | (24·7) | (23·0) | (17·4) | (15·7) |
| Daily physical | 980 | 3040 | 5855 | 8191 | 3593 | 763 | 14 |
| activity | (25·5) | (27·1) | (29·4) | (35·5) | (34·9) | (26·3) | (12·2) |

SD: standard deviation; HbA1c: hemoglobin A1C; BP: blood pressure; BMI: body mass index; LDL: low-density lipoproteins; HDL: high-density lipoproteins; GFR: glomerular filtration rate


Histogram for Age at diagnosis
7500
5000
2500
0
Count
0
25
50
75
100
Age at diagnosis

Whole cohort
No prior CVD

## Mortality

| | Whole cohort | No prior CVD |
|---|---|---|
| 91 or older | 0.68 (0.62 – 0.74) | 0.77 (0.67 – 0.88) |
| 81 to 90 | 0.74 (0.72 – 0.76) | 0.83 (0.80 – 0.86) |
| 71 to 80 | 0.86 (0.84 – 0.88) | 0.94 (0.91 – 0.96) |
| 61 to 70 | 1.05 (1.03 – 1.08) | 1.13 (1.09 – 1.16) |
| 51 to 60 | 1.28 (1.25 – 1.32) | 1.33 (1.29 – 1.38) |
| 41 to 50 | 1.63 (1.56 – 1.71) | 1.65 (1.57 – 1.74) |
| 40 or less | 1.97 (1.75 – 2.22) | 2.05 (1.81 – 2.33) |

## CV mortality

| | Whole cohort | No prior CVD |
|---|---|---|
| 91 or older | 0.65 (0.58 – 0.74) | 0.74 (0.61 – 0.90) |
| 81 to 90 | 0.68 (0.66 – 0.71) | 0.75 (0.71 – 0.79) |
| 71 to 80 | 0.79 (0.76 – 0.81) | 0.83 (0.79 – 0.87) |
| 61 to 70 | 1.01 (0.97 – 1.05) | 1.00 (0.95 – 1.06) |
| 51 to 60 | 1.35 (1.29 – 1.42) | 1.29 (1.21 – 1.38) |
| 41 to 50 | 1.87 (1.72 – 2.03) | 1.66 (1.50 – 1.84) |
| 40 or less | 2.84 (2.27 – 3.55) | 2.72 (2.13 – 3.48) |

## Non CV mortality

| | Whole cohort | No prior CVD |
|---|---|---|
| 91 or older | 0.68 (0.59 – 0.77) | 0.78 (0.65 – 0.94) |
| 81 to 90 | 0.79 (0.76 – 0.81) | 0.87 (0.83 – 0.91) |
| 71 to 80 | 0.92 (0.90 – 0.95) | 0.99 (0.96 – 1.02) |
| 61 to 70 | 1.11 (1.08 – 1.14) | 1.18 (1.14 – 1.22) |
| 51 to 60 | 1.30 (1.25 – 1.34) | 1.37 (1.31 – 1.42) |
| 41 to 50 | 1.60 (1.52 – 1.70) | 1.69 (1.59 – 1.80) |
| 40 or less | 1.82 (1.58 – 2.09) | 1.95 (1.68 – 2.25) |

## CVD

| | Whole cohort | No prior CVD |
|---|---|---|
| 91 or older | 1.31 (1.11 – 1.54) | 1.41 (1.08 – 1.84) |
| 81 to 90 | 1.17 (1.13 – 1.21) | 1.28 (1.22 – 1.35) |
| 71 to 80 | 1.22 (1.20 – 1.25) | 1.33 (1.29 – 1.37) |
| 61 to 70 | 1.39 (1.35 – 1.42) | 1.42 (1.37 – 1.47) |
| 51 to 60 | 1.69 (1.64 – 1.74) | 1.66 (1.60 – 1.72) |
| 41 to 50 | 2.30 (2.19 – 2.42) | 2.30 (2.17 – 2.43) |
| 40 or less | 3.47 (3.09 – 3.90) | 3.52 (3.10 – 3.99) |

## CHD

| | Whole cohort | No prior CVD |
|---|---|---|
| 91 or older | 1.02 (0.87 – 1.19) | 1.26 (0.91 – 1.73) |
| 81 to 90 | 1.17 (1.14 – 1.21) | 1.42 (1.34 – 1.50) |
| 71 to 80 | 1.34 (1.31 – 1.36) | 1.52 (1.47 – 1.57) |
| 61 to 70 | 1.58 (1.55 – 1.61) | 1.70 (1.65 – 1.76) |
| 51 to 60 | 2.00 (1.95 – 2.05) | 2.07 (1.99 – 2.15) |
| 41 to 50 | 2.93 (2.82 – 3.05) | 2.99 (2.83 – 3.16) |
| 40 or less | 4.14 (3.72 – 4.61) | 4.33 (3.82 – 4.91) |

1 2 3 5 7
Hazard Ratio (95% CI)

## AMI

| | Whole cohort | No prior CVD |
|---|---|---|
| 91 or older | 1.21 (0.95 – 1.54) | 1.32 (0.88 – 1.98) |
| 81 to 90 | 1.24 (1.18 – 1.30) | 1.37 (1.28 – 1.47) |
| 71 to 80 | 1.29 (1.25 – 1.33) | 1.43 (1.37 – 1.50) |
| 61 to 70 | 1.41 (1.36 – 1.46) | 1.46 (1.40 – 1.53) |
| 51 to 60 | 1.64 (1.58 – 1.71) | 1.62 (1.54 – 1.71) |
| 41 to 50 | 2.27 (2.14 – 2.42) | 2.34 (2.17 – 2.52) |
| 40 or less | 3.35 (2.88 – 3.91) | 3.41 (2.88 – 4.04) |

1 2 3 5 7
Hazard Ratio (95% CI)

## Stroke

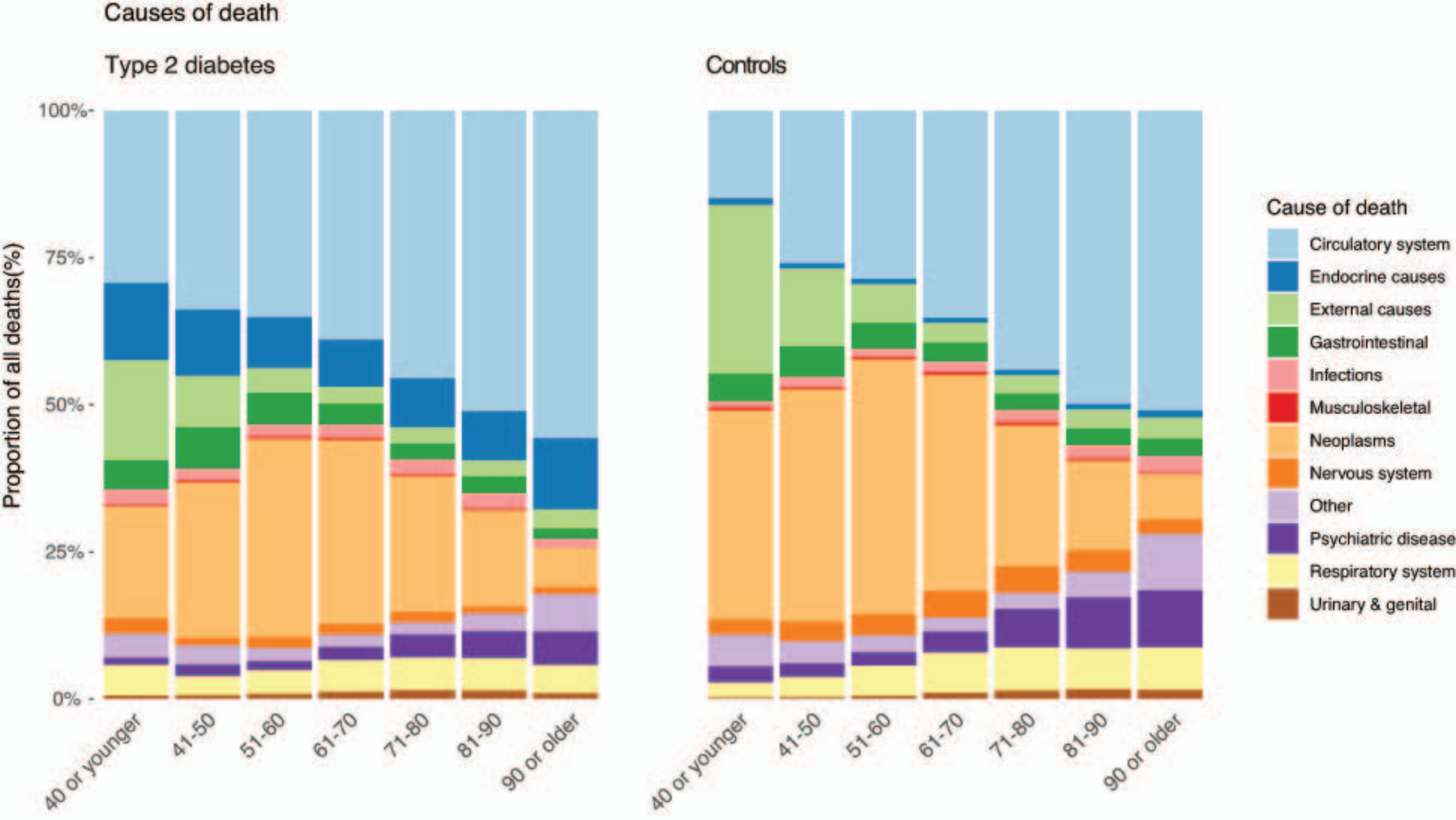
| | Whole cohort | No prior CVD |
|---|---|---|
| 91 or older | 1.43 (1.17 – 1.75) | 1.56 (1.13 – 2.14) |
| 81 to 90 | 1.11 (1.06 – 1.16) | 1.20 (1.13 – 1.28) |
| 71 to 80 | 1.17 (1.14 – 1.21) | 1.25 (1.19 – 1.30) |
| 61 to 70 | 1.36 (1.32 – 1.41) | 1.38 (1.32 – 1.44) |
| 51 to 60 | 1.72 (1.65 – 1.79) | 1.69 (1.60 – 1.79) |
| 41 to 50 | 2.29 (2.13 – 2.46) | 2.21 (2.03 – 2.40) |
| 40 or less | 3.83 (3.06 – 4.31) | 3.58 (2.97 – 4.32) |

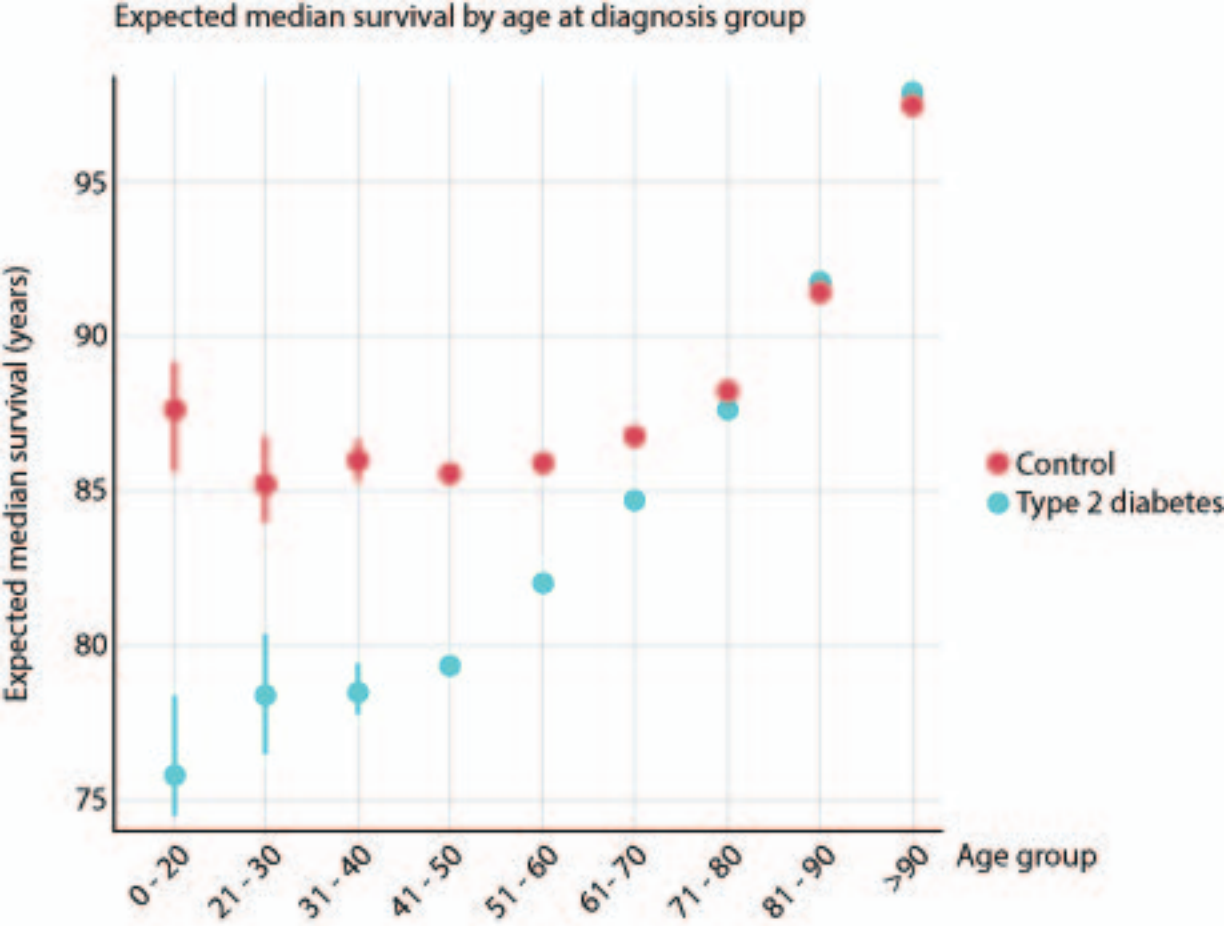
1 2 3 5 7
Hazard Ratio (95% CI)

## HF

| | Whole cohort | No prior CVD |
|---|---|---|
| 91 or older | 0.95 (0.83 – 1.09) | 1.13 (0.87 – 1.47) |
| 81 to 90 | 1.04 (1.00 – 1.07) | 1.09 (1.03 – 1.15) |
| 71 to 80 | 1.36 (1.32 – 1.39) | 1.33 (1.28 – 1.39) |
| 61 to 70 | 1.89 (1.83 – 1.94) | 1.71 (1.63 – 1.79) |
| 51 to 60 | 2.65 (2.55 – 2.75) | 2.32 (2.19 – 2.46) |
| 41 to 50 | 3.83 (3.59 – 4.09) | 3.38 (3.10 – 3.69) |
| 40 or less | 5.19 (4.35 – 6.19) | 4.77 (3.86 – 5.89) |

1 2 3 5 7
Hazard Ratio (95% CI)


Causes of death
Type 2 diabetes
Controls
Proportion of all deaths(%)
100%
75%
50%
25%
0%
40 or younger
41-50
51-60
61-70
71-80
81-90
90 or older
Cause of death
Circulatory system
Endocrine causes
External causes
Gastrointestinal
Infections
Musculoskeletal
Neoplasms
Nervous system
Other
Psychiatric disease
Respiratory system
Urinary & genital


Expected median survival by age at diagnosis group
Expected median survival (years)
95
90
85
80
75
0 - 20
21 - 30
31 - 40
41 - 50
51 - 60
61 - 70
71 - 80
81 - 90
>90
Age group
Control
Type 2 diabetes